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# Synthesis of Conformationally Locked Carbocyclic Nucleosides Built on a Thiabicyclo[3.1.0]hexane System as a Pseudosugar Surrogate

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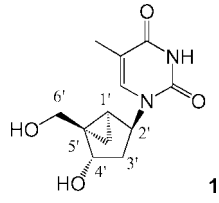
**Keywords:** 6-Thiabicyclo[3.1.0]hexane / Thiiranes / 2′,3′-Dideoxyneplanocin C / Nucleosides / Carbanucleosides

The synthesis of prototype models of purine and pyrimidine carbanucleosides built on a 6-thiabicyclo[3.1.0]hexane system as pseudosugar moiety has been investigated. These pyrimidine carbanucleosides proved to be very stable compounds, in contrast to the parent epoxy analogs, which experienced epoxide ring-opening due to intramolecular enol base attack. In addition, as the synthesis of a thiirane moiety fused to a five-membered ring is not a trivial synthetic task, validation and optimization of the existing methods for episulfide preparation were required to access the committed synthetic precursor of the title compounds: (±)-(1*RS*,2*RS*,5*SR*)-6-thiabicyclo[3.1.0]hexan-2-ol, compound **28**. 

## Introduction

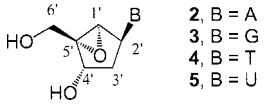
Nucleosides have been demonstrated to be a profuse source of lead drugs in the search for new antiviral and antitumor agents. The isosteric replacement of the furanose ring by a cyclopentyl moiety affords a new class of metabolically more stable nucleoside analogs known as carbocyclic nucleosides. The absence of the oxygen atom in the furanose ring enhances potential structural variations at different positions not possible with conventional nucleosides.[1,2] The carbanucleoside analog *N*-methanocarbathymidine [(1′*S*,2′*S*,4′*S*,5′*R*)-1-{4-hydroxy-5-(hydroxymethyl)bicyclo-[3.1.0]hex-2-yl}-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (**1**)] has been found to exhibit potent antiherpetic activity against the herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) (Figure 1).[3,4] The efficacy of this carbocyclic nucleoside is even greater than that exhibited by acyclovir, a well-known antiherpetic agent.[3,4]




**1**

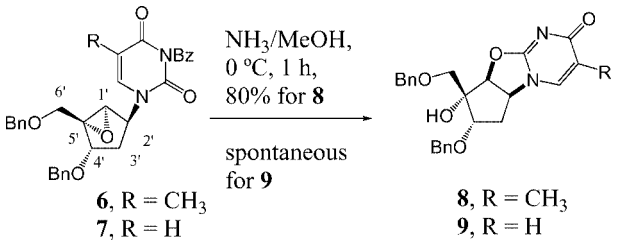
Figure 1. Chemical structure of *N*-methanocarbathymidine (**1**).

It had been considered that the isosteric replacement of the cyclopropyl moiety of **1** by an epoxy group would benefit molecular recognition as a result of the smaller size of the epoxy group. In addition, many nucleoside derivatives bearing an oxabicyclo[3.1.0]hexane system as sugar moiety exhibit important pharmacological properties.[5–12] On the basis of this idea, carbocyclic nucleosides **2**–**5** were designed, motivated not only by the potential antiviral properties of the pyrimidine derivatives, but also to enable heteroduplex stabilization studies to be carried out (Figure 2).[13] However, it was not possible to obtain the theoretical pyrimidine derivatives **4** and **5** as a consequence of intermolecular enol base attack on the epoxy group present in their synthetic intermediates **6** and **7**, which form the tricyclic structures **8** and **9**, as illustrated in Scheme 1.




**2**, B = A
**3**, B = G
**4**, B = T
**5**, B = U

Figure 2. Chemical structures of carbanucleosides built on an oxabicyclic[3.1.0]hexane system.




**6**, R = $CH_3$
**7**, R = H

**8**, R = $CH_3$
**9**, R = H

Scheme 1.

This spontaneous epoxide ring-opening reaction had been quite unexpected bearing in mind that this epoxy group proved to be a very stable functionality in similar structurally related compounds even in harsh basic condi-

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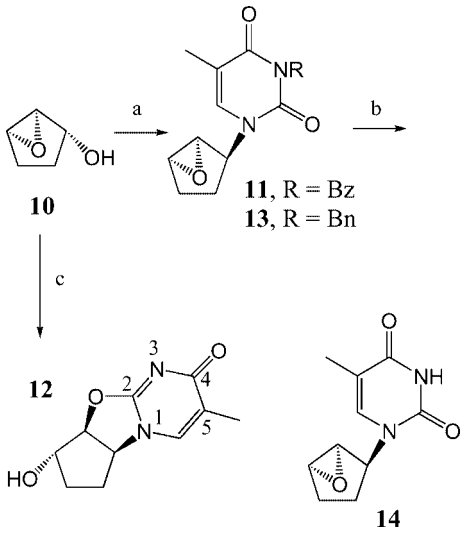
tions such as methanolic ammonia.[13–16] Therefore, this intramolecular reaction could be attributable to the relative positions of the epoxy group and the pyrimidine base rather than the lability of the epoxide.

Owing to the incompatibility of an epoxy group adjacent to a pyrimidine base, it was thought that the isosteric replacement of the cyclopropyl moiety with a thiirane group would be more appropriate. The preparation of carbanucleosides, especially pyrimidine derivatives, built on a thiabicyclo[3.1.0]hexane system is not a trivial task for a number of reasons: 1) the existing methods for the introduction of an episulfide into a five-membered ring are associated with extremely low reaction yields making them impractical from a synthetic point of view;[17–36] 2) when an epoxy group is present in the vicinity of a pyrimidine heterocyclic base, an intramolecular attack by the enol of the base takes place to produce epoxy ring-opening; 3) as epoxides and thiiranes exhibit similar chemical properties, there is also a risk of episulfide ring-opening.

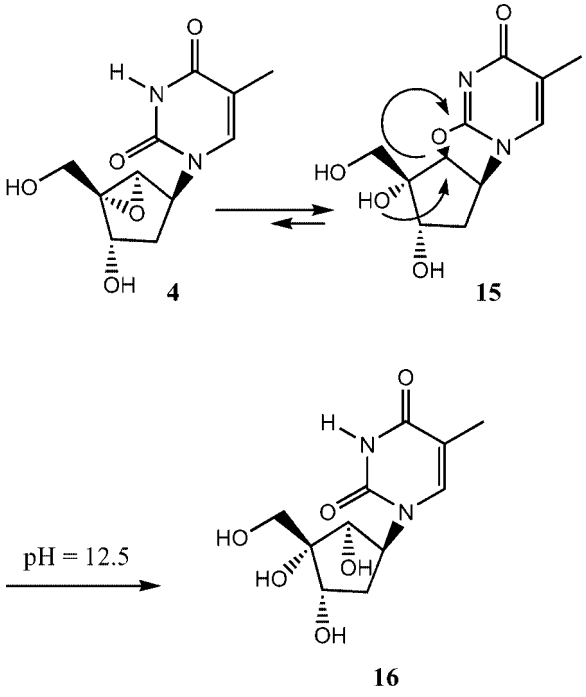



Scheme 2. Reagents and conditions: (a) $N^3$-benzoylthymine, $PPh_3$, DEAD, THF, –45 °C, 2 h → room temp., 16 h, 21% for **11**; $N^3$-benzylthymine, $PPh_3$, DEAD, THF, –45 °C, 30 min → room temp. 16 h, 26% for **13**; (b) $NH_3$/MeOH, 0 °C, 1 h 30 min, 84% from **11**; $H_2$, 1 atm, 10% Pd/C, MeOH, room temp., 48% from **13**; (c) thymine, $PPh_3$, DEAD, THF, –45 °C, 2 h → room temp., 16 h, 20%.

## Results and Discussion

In order to study the tendency for base *O*-2 nucleophilic attack on any 6-oxabicyclo[3.1.0]hexane system, a very simple model of a carbocyclic thymidine derivative was prepared, as shown in Scheme 2. (±)-*cis*-6-Oxabicyclo[3.1.0]-hexan-2-ol (**10**)[14] was used as a rigid carbocyclic ring. This compound was coupled with $N^3$-benzoylthymine[37] to give **11**, which, after ammonolysis, produced the tricyclic compound **12**. It was considered that the basic conditions employed could catalyze this transformation and, for this reason, $N^3$-benzylthymine[38] was used instead of $N^3$-benzoylthymine. The very mild conditions used for benzyl ether cleavage would not catalyze any nucleophilic attack. Therefore, epoxy alcohol **10** was treated with $N^3$-benzylthymine under Mitsunobu conditions to give **13**. Surprisingly, catalytic hydrogenation of **13** also produced **12**. Moreover, when **10** was treated with free thymine under Mitsunobu-type conditions **12** was isolated as the main product.

Molecular modelling studies of the optimized energy conformers of compounds **12** (opened ring) and **14** (the base built on the 6-oxabicyclic system) indicated that **12** is 2.88 kcal/mol more stable than the hypothetical compound **14**. The ab initio energy calculations of the optimized conformers were performed with the Gaussian 98 program employing a HF/6-31Gdp basis set.[39] An equilibrium between the open and intact epoxy group may be postulated to favor the opened-ring structure, as shown in Scheme 3. Bearing in mind that the *O*-bonded position of the base is a good leaving group and that the free hydroxy group at C-4′ can act as an intramolecular nucleophile, this equilibrium was studied by $^1H$ NMR spectroscopy at different pHs starting at neutral pH = 7.0 and ascending in order to pH = 14.0 in 0.5 pH-unit increments. Above pH = 9.0 it was possible to observe the signal corresponding to the epoxy group as a singlet centered at $\delta$ = 3.28 ppm. This effect is more noticeable at pH = 12.5. At this pH, a hydroxy ion from the medium attacked the epoxide at C-5′ to form irreversibly compound **16**.

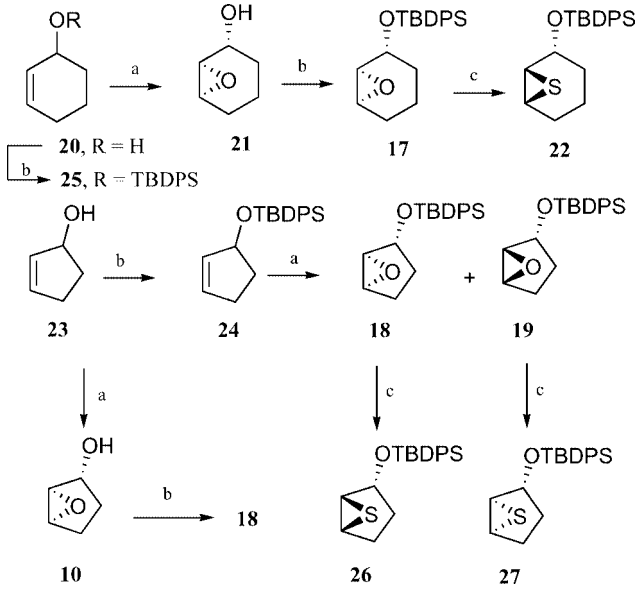



Scheme 3.

Once this incompatibility was established, the isosteric replacement of the oxygen atom by a sulfur atom was envisioned. The common precursor for the preparation of a particular thiirane ring may be either the corresponding epoxide or the corresponding alkene, the former one being favored. In order to validate a reliable method for the preparation of an episulfide attached to a five-membered ring,

it was considered that epoxides **17**–**19** would be suitable models for the preparation of the corresponding thiirane derivatives. Compound **19** is the synthetic intermediate in the preparation of simple carbanucleosides built on a thiabicyclo[3.1.0]hexane system bearing in mind that episulfide formation from an epoxide occurs with inversion of the configuration. The introduction of the silyl ether functionalities was motivated by the need to obtain aqueous hyposoluble compounds that would be easy to handle. Therefore, on treatment with *m*-chloroperbenzoic acid, cyclohexenol **20** was converted into **21** as a single diastereomer according to Henbest's rule.[40] Compound **18** was prepared starting from the already described epoxy alcohol **10** by treatment with *tert*-butylchlorodiphenylsilane. Compound **19** was prepared from cyclopentenol **23**. This compound, treated with *tert*-butylchlorodiphenylsilane, afforded the corresponding silyl ether **24**, which treated with *m*-chloroperbenzoic acid yielded **19** as the main product and a minor product, which turned out to be compound **18**. The relative stereochemistry of **19** was unambiguously established by analysis of the NMR spectra of this minor component, which matched the spectroscopic data of **18** prepared from epoxy alcohol **10**.[14] As the *tert*-butyldiphenylsilyl moiety is a bulky group, the stereochemical course of the epoxidation reaction can be explained by electrophilic attack of the epoxidizing agent on the less hindered side of the molecule (Scheme 4).

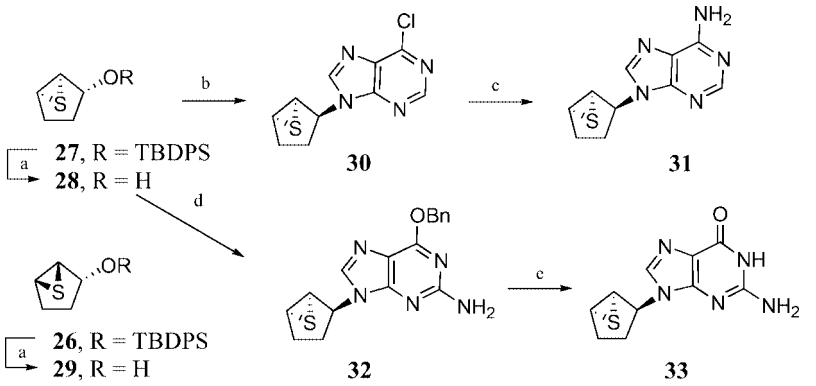



Scheme 4. Reagents and conditions: (a) MCPBA, $CH_2Cl_2$, 0 °C→room temp., 1 h, 83% for **21**; 57% for **19**; 32% for **18**; (b) imidazole, DMF, TBDPSCl, 0 °C→room temp., 6 h, 66% for **17**; 20 h, 82% for **24**; 20 h, 83% for **25**; (c) KSCN, EtOH/$H_2O$ (1:1), room temp., 72 h, 65% for **22**; reflux, 15 h, 23% for **26**; reflux, 15 h, 48% for **27**.

Once these precursors for thiirane preparation were at hand, the appropriate method to transform the epoxy group into a thiirane ring was validated. Attempts to convert compound **17** into the thiirane **22** were made under a variety of conditions, for example, by treatment with different sulfur-containing reagents such as potassium thiocyanate in water/methanol,[17,18] thiourea,[19] *N*,*N*-dimethylthioformamide,[20] ammonium thiocyanate with *tert*-butyl alcohol as a solvent in the presence of ceric ammonium nitrate[21] and ammonium thiocyanate in acetonitrile in the presence of ruthenium trichloride.[22] Another interesting method was the preparation of thiiranes via the corresponding 2-chloroalkyl 2′,4′-dinitrophenyl sulfides, which could be easily prepared from the corresponding alkene.[36] This method was not satisfactory for the preparation of **22** starting from **25**. In this case, when **25** was treated with 2,4-dinitrobenzenesulfenyl chloride a complex mixture of products was obtained instead of the desired 2-chloroethyl 2′,4′-dinitrophenyl sulfide. The best results were obtained by employing potassium thiocyanate or thiourea with good yields of 65 and 64%, respectively, while the use of either ammonium thiocyanate or *N*,*N*-dimethylthioformamide gave very low yields making these methods impractical from a synthetic point of view. In addition, *N*,*N*-dimethylformamide was an inappropriate solvent when used in combination with potassium thiocyanate because epoxide **17** could not be transformed into thiirane **22** under these reactions conditions. Therefore, it was decided to employ potassium thiocyanate as the sulfur-introducing reagent using a mixture of methanol and water as the solvent. Note that on treatment with potassium thiocyanate in methanol/water at room temperature, **17** was readily converted into **22** in a highly diastereoselective reaction. These results were in agreement with the postulated reaction mechanism[18] and with some experimental observations.[22] The introduction of an episulfide functionality into a five-membered ring required stronger reaction conditions such as higher temperatures and a longer reaction time, as expected.[18] Certainly, epoxides **18** and **19**, in independent experiments, treated with potassium thiocyanate in methanol/water under reflux for 15 h, gave the title compounds **26** and **27**, respectively, with high stereoselectivity. Once again, the reaction occurred with inversion of the configuration at the positions where the epoxy group was originally bonded (Scheme 4). The formation of products with retention of configuration was not observed in any case.

Purine carbanucleosides built on a thiabicyclo[3.1.0]hexane system were readily synthesized from the thiirane precursor **27**. Thus, this compound treated with a solution of tetrabutylammonium fluoride in tetrahydrofuran afforded the corresponding alcohol **28** in 92% yield. Analysis of the $^1$H NMR spectrum of **28** showed similar multiplicity patterns to those in the spectrum of the epoxy alcohol **10**. As an example, the signal corresponding to 2-H of **28** appeared as a doublet of triplets ($J$ = 7.9 and 3.7 Hz) centered at $\delta$ = 4.49 ppm, while the signal corresponding to 2-H of **10** also appeared as a doublet of triplets ($J$ = 8.0 and 1.2 Hz). However, the signal arising from 2-H of the diastereoisomer **29** was observed as a doublet ($J$ = 4.8 Hz) centered at $\delta$ = 4.49 ppm. Once the relative stereochemistry was confirmed, alcohol **28** was coupled with 6-chloropurine under Mitsunobu-type conditions[40] to produce the desired carbocyclic nucleoside derivative, yielding exclusively the $N^9$-alkylated

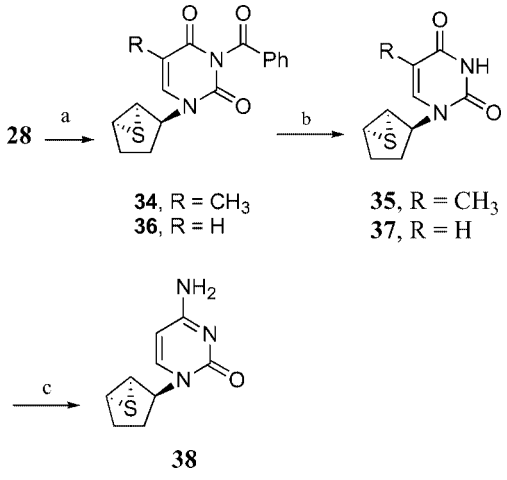
  




Scheme 5. Reagents and conditions: (a) 1.0 M $(n\text{Bu})_4\text{NF}$, THF, 0 °C→room temp., 2 h, 92% for **28**; 95% for **29**; (b) 6-chloropurine, $Ph_3P$, DEAD, THF, room temp., 24 h; (c) $NH_3$/MeOH, 70 °C, 3 h, 38% from **28**; (d) 2-amino-6-benzyloxypurine, $Ph_3P$, DEAD, THF, room temp., 24 h, 28%; (e) 1.0 M $BCl_3$ in $CH_2Cl_2$, $CH_2Cl_2$, –78 °C, 4 h, 63%.

product **30**. Treatment of **30** with methanolic ammonia gave the sulfur-containing carbocyclic analog of adenosine **31**. The presence of a thiirane group fused to a five-membered ring produced a similar effect as a cyclopropyl[41–44] or epoxy group,[13–16] fixing the pseudosugar conformation in the northern hemisphere, as deduced from the analysis of the relevant coupling constants of the $^1$H NMR spectrum. The signal corresponding to the pseudoanomeric proton (2′-H) was observed as a doublet centered at $\delta$ = 5.17 ppm with a coupling constant of 6.6 Hz, indicating that the two torsion angles between the pseudoanomeric proton and the three adjacent hydrogen atoms were close to 90°. The sulfur-containing carbocyclic analog of guanosine **33** was prepared from **28** in a Mitsunobu coupling[45–47] reaction with 2-amino-6-benzyloxypurine[41,42] to yield the carba-guanosine precursor **32**. As shown for the adenosine analog, the $N^7$-alkylated product was not detected. Benzyl ether cleavage by treatment with boron trichloride afforded compound **33** in 63% yield without affecting the thiirane group (Scheme 5).

The corresponding pyrimidine derivatives were also synthesized directly. The heterocyclic base was introduced by treatment of **28** with $N^3$-benzoylthymine[37] under Mitsunobu-type conditions at –45 °C to form **34** as a single isomer, which after benzoyl group cleavage by treatment with methanolic ammonia at 0 °C for one hour afforded compound **35**. Contrary to what was observed for pyrimidine derivatives built on the oxabicyclo[3.1.0]hexane system, which underwent epoxide ring-opening by intramolecular attack of the heterocyclic base, **35** was a stable carbanucleoside. This is a very relevant result because it will enable the design of more complex carbanucleosides bearing a thiabicyclo[3.1.0]hexane system as the pseudosugar moiety. The uridine derivative **37** was prepared following a similar approach: alcohol **28** treated with $N^3$-benzoyluracil yielded **36**, which after treatment with methanolic ammonia afforded the desired carbocyclic nucleoside **37**. This nucleoside analog was also stable on standing. The usual competition, *O*- versus *N*-alkylation,[41,42] was not observed in either of these Mitsunobu-type reactions. The cytosine target **38** was prepared from **37** via the formation of a triazole intermediate according to published methods (Scheme 6).[48]




Scheme 6. Reagents and conditions: (a) $N^3$-benzoylthymine, $Ph_3P$, DEAD, THF, –45 °C, 2 h,→room temp., 22 h, 38% or $N^3$-benzoyluracil, $Ph_3P$, DEAD, THF, –45 °C, 30 min→room temp., 48 h, 49%; (b) $NH_3$/MeOH, 0 °C, 1 h, 41% for **35** from **28**, 95% for **37** from **28**; (c) i. $POCl_3$, 1,2,4-triazole, $Et_3N$, $CH_3CN$, room temp., 36 h, ii. $NH_4OH$, dioxane, room temp., 20 h, 43%.

Unexpectedly and in contrast to the antiviral activity exhibited by the parent epoxy derivatives,[14] all title compounds were devoid of antiviral activity against herpes simplex virus types 1 and 2, and human cytomegalovirus. Antiviral activity was evaluated following standard procedures.[49]

In conclusion, the preparation of five-membered rings bearing a thiirane group was successfully carried out. Literature data indicated that the preparation of episulfides fused to a cyclopentane ring, although apparently a trivial chemical transformation, was not a simple task. In addition, with the above results at hand, it was possible to synthesize simple models of carbanucleosides built on a 6-

thiabicyclo[3.1.0]hexane system as the pseudosugar unit. The main finding of this study was the stability of these sulfur-containing carbanucleosides, which was not observed when an epoxy group was used to fix the sugar conformation. Finally, the smaller size of the thiirane moiety relative to the cyclopropyl group present in other carbanucleosides of pharmacological importance seems to be beneficial for molecular recognition. These results provide new insights into the design of new carbanucleosides.

## Experimental Section

The glassware used in air- and/or moisture-sensitive reactions was flame-dried and carried out under argon. Unless otherwise noted, chemicals were commercially available and used without further purification. NMR spectra were recorded with a Bruker AM-500 spectrometer. Chemical shifts are reported in parts per million ($\delta$) relative to tetramethylsilane. The $^1$H NMR spectra are referenced to the residual $CHCl_3$ proton of the solvent $CDCl_3$ ($\delta$ = 7.26 ppm). Coupling constants are reported in Hertz (Hz). $^{13}$C NMR spectra were fully decoupled and are referenced to the middle peak of the solvent $CDCl_3$ ($\delta$ = 77.0 ppm). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet. Low-resolution mass spectra were obtained with a VG TRIO 2 instrument at 70 eV (direct inlet). High-resolution mass spectra were recorded with a Micromass Q-Tof Ultima apparatus, which is a hybrid quadrupole time-of-flight mass spectrometer with MS/MS capability. Melting points were determined using a Fisher-Johns apparatus and are uncorrected. Column chromatography was performed with E. Merck silica gel (Kieselgel 60, 230–400 mesh). Analytical thin-layer chromatography was performed by employing 0.2 mm coated commercial silica gel plates (E. Merck, DC-Aluminium sheets, Kieselgel 60 $F_{254}$) which were visualized with 254 nm UV light or by immersion in an ethanolic solution of 5% $H_2SO_4$. Elemental analyses were performed by Atlantic Microlab, Norcross, Georgia. The results were within ±0.4% of the theoretical values except where otherwise stated.

**(±)-3-Benzoyl-5-methyl-1-[(1*RS*,2*SR*,5*SR*)-6-oxabicyclo[3.1.0]-hex-2-yl]pyrimidine-2,4(1*H*,3*H*)-dione (11):** A solution of triphenylphosphane (1.43 g, 5.45 mmol) in anhydrous tetrahydrofuran (20 mL) was treated with diethyl azodicarboxylate (0.90 mL, 5.45 mmol) and stirred at 0 °C for 20 min. After cooling to –45 °C, a solution of $N^3$-benzoylthymine (1.00 g, 4.36 mmol) and alcohol **10** (218 mg, 2.18 mmol) in tetrahydrofuran (8 mL) was added via cannula over a period of 10 min. The reaction mixture was stirred at –45 °C for 2 h and then at room temperature for 16 h. The solvent was evaporated and the residue was purified by column chromatography (silica gel) employing hexane/EtOAc (4:1) as eluent to afford 59 mg (20% yield) of pure compound **11** as a colorless oil. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 7.60–7.72 (m, 5 H, aromatic protons), 6.96 (d, $J$ = 1.1 Hz, 1 H, 6-H), 4.90 (d, $J$ = 7.3 Hz, 1 H, 2′-H), 3.77 (s, 1 H, 1′-H), 3.55 (d, $J$ = 1.8 Hz, 1 H, 5′-H), 1.95 (d, $J$ = 0.9 Hz, 3 H, $CH_3$ at C-5), 1.85–2.17 (m, 4 H, 3′-H, 4′-H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 168.8 (*C*OPh), 162.5 (C-4), 149.7 (C-2), 139.7 (Ph), 137.3 (C-6), 135.0 (Ph), 130.4 (Ph), 129.1 (Ph), 111.3 (C-5), 59.0 (C-5′), 57.8 (C-1′), 57.1 (C-2′), 28.1 (C-3′), 26.5 (C-4′), 14.3 ($CH_3$) ppm.

**(±)-3-Benzyl-5-methyl-1-[(1*RS*,2*SR*,5*SR*)-6-oxabicyclo[3.1.0]hex-2-yl]pyrimidine-2,4(1*H*,3*H*)-dione (13):** A solution of triphenylphosphane (303 mg, 1.28 mmol) in anhydrous tetrahydrofuran (20.0 mL) was treated with diethyl azodicarboxylate (0.2 mL, 1.28 mmol) under argon. The resulting mixture was stirred at 0 °C for 20 min. After cooling to –45 °C, a solution of $N^3$-benzylthymine (186 mg, 0.86 mmol) and (±)-*cis*-6-oxabicyclo[3.1.0]hexan-2-ol (**10**; 50 mg, 0.5 mmol) in tetrahydrofuran (8 mL) was added over a period of 10 min. The reaction mixture was stirred at –45 °C for 30 min and then at room temperature overnight. The reaction was quenched as described for **11** and the residue was purified by column chromatography (silica gel) eluting with hexane/EtOAc (4:1). Compound **13** was repurified by column chromatography employing $CH_2Cl_2$/$Et_2O$ (99:1) as eluent to afford 38 mg (26% yield) of pure compound **13** as a colorless oil. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 7.23–7.55 (m, 5 H, aromatic protons), 6.82 (d, $J$ = 1.5 Hz, 1 H, 6-H), 5.00 (d, $J$ = 7.3 Hz, 1 H, 2′-H), 3.76 (s, 1 H, 1′-H), 3.50 (d, $J$ = 1.8 Hz, 1 H, 5′-H), 1.94 (d, $J$ = 1.1 Hz, 3 H, $CH_3$), 1.64–2.20 (m, 4 H, 3′-H, 4′-H) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 163.1 (C-4), 151.3 (C-2), 136.8 (C-6), 135.1 (Ph), 129.1 (Ph), 128.3 (Ph), 127.5 (Ph), 110.4 (C-5), 60.3 (C-5′), 57.9 (C-1′), 56.8 (C-2′), 44.7 (Ph*C*H$_2$), 27.9 (C-3′), 26.4 (C-4′), 13.3 ($CH_3$) ppm.

**Tricyclic Compound 12**

**Method A:** Compound **11** (50 mg, 0.16 mmol) was treated with methanolic ammonia (5 mL, saturated at –78 °C) and stirred in a sealed tube at 0 °C for 30 min. The mixture was cooled to –70 °C, the tube opened and nitrogen was bubbled through it to eliminate the ammonia. The solvent was evaporated and the residue was purified by column chromatography (silica gel) eluting with EtOAc/hexane (4:1) to give 28 mg (84% yield) of pure compound **12** as a white solid.

**Method B:** A solution of compound **13** (35.1 mg, 0.12 mmol) in methanol (10 mL) in the presence of 10% Pd/C was treated with hydrogen at 1 atm. The solution was stirred at room temperature for 3 h. The mixture was filtered off and the solvent evaporated. The residue was purified by column chromatography (silica gel) eluting with $CH_2Cl_2$/methanol (19:1) to give 12.0 mg (48% yield) of pure compound **12** as a white solid.

**Method C:** A solution of triphenylphosphane (828 mg, 3.2 mmol) in anhydrous tetrahydrofuran (20.0 mL) was treated with diethyl azodicarboxylate (1.1 mL, 3.0 mmol) under argon. The resulting mixture was stirred at 0 °C for 20 min. After cooling to –45 °C, a solution of (±)-*cis*-6-oxabicyclo[3.1.0]hexan-2-ol (**10**; 126.3 mg, 1.3 mmol) in tetrahydrofuran (8 mL) and solid thymine (320 mg, 2.5 mmol) were added. The reaction mixture was stirred at –45 °C for 2 h and at room temperature overnight. The reaction was quenched as described in Method A. The product was purified by column chromatography (silica gel) employing a mixture of $CH_2Cl_2$/methanol (19:1) to produce 58 mg (21% yield) of pure **12** as white crystals: m.p. 149–152 °C. $^1$H NMR (200 MHz, $CD_3OD$): $\delta$ = 7.63 (d, $J$ = 1.1 Hz, 1 H, 6-H), 5.09 (d, $J$ = 7.1 Hz, 1 H, 1′-H), 5.01 (t, $J$ = 6.7 Hz, 1 H, 2′-H), 4.34 (d, $J$ = 3.6 Hz, 1 H, 5′-H), 2.29 (dt, $J$ = 13.2, 6.6 Hz, 1 H, 3′$_b$-H), 2.06 (dd, $J$ = 14.1, 6.6 Hz, 1 H, 3′$_a$-H), 1.93 (d, $J$ = 1.1 Hz, 3 H, $CH_3$), 1.86 (dd, $J$ = 13.9, 6.4 Hz, 1 H, 4′$_b$-H), 1.70 (m, 1 H, 4′$_a$-H) ppm. $^{13}$C NMR ($CD_3OD$): $\delta$ = 175.4 (C-4), 161.9 (C-2), 135.1 (C-6), 119.2 (C-5), 90.5 (C-1′), 76.2 (C-5′), 64.5 (C-2′), 31.60 (C-4′), 31.59 (C-3′), 13.9 ($CH_3$) ppm. $C_9H_{10}N_2O_3$: C 55.67, H 5.19; found C 55.97, H 5.32.

**(±)-5-Methyl-1-[2,3,4-trihydroxy-3-(hydroxymethyl)cyclopentyl]pyrimidine-2,4(1*H*,3*H*)-dione (16):** A 40% solution of deuteriated potassium hydroxide in deuteriated water was added to a solution of compound **15** (3 mg) in deuteriated water (0.5 mL). The pH values were increased in 0.5 units by addition of measurable volumes of KOD. The reaction was monitored by $^1$H NMR spectroscopy. When the pH value reached 12.5, **15** was irreversibly converted into **16** in an almost theoretical yield. $^1$H NMR (500.13 MHz, $D_2O$): $\delta$

= 7.32 (s, 1 H, 6-H), 5.24 (m, 1 H, 1′-H), 4.22 (t, $J$ = 7.7 Hz, 1 H), 4.06 (d, $J$ = 4.8 Hz, 1 H, 2′-H), 3.81 (d, $J$ = 12.0 Hz, 1 H, $H_b$-CHOH), 3.61 (d, $J$ = 12.0 Hz, 1 H, $H_a$-CHOH), 2.37 (m, 1 H, 5′$_a$-H), 2.09 (ddd, $J$ = 14.3, 10.5, 6.7 Hz, 1 H, 5′$_b$-H), 1.81 (s, 3 H, $CH_3$) ppm. $^{13}$C NMR (125.77 MHz, $D_2O$): $\delta$ = 166.9 (C-4), 151.9 (C-2), 141.1 (C-6), 110.6 (C-5), 82.9 (C-3′), 76.1 (C-2′), 71.9 (C-4′), 63.6 ($CH_2OH$), 56.1 (C-1′), 34.1 (C-5′), 13.6 ($CH_3$) ppm.

**(±)-(1*SR*,2*RS*,6*SR*)-7-Oxabicyclo[4.1.0]heptan-2-ol (21):** A solution of 60% *m*-chloroperbenzoic acid (6.00 g, 20.8 mmol) in dichloromethane (30 mL) was added to a solution of cyclohexenol (**20**; 1.70 g, 17.3 mmol) in dichloromethane (60 mL) at 0 °C. The mixture was stirred at room temperature for 1 h. The solvent was evaporated and the residue purified by column chromatography (silica gel) eluting with a mixture of hexane/EtOAc (9:1) to afford 1.65 g (83% yield) of pure epoxy alcohol **21** as a colorless oil. $R_f$ 0.38 (hexane/EtOAc, 4:6). $^1$H NMR (500.13 MHz, $CDCl_3$): $\delta$ = 4.00 (ddd, $J$ = 7.6, 4.9, 2.9 Hz, 1 H, 2-H), 3.34 (t, $J$ = 3.9 Hz, 1 H, 6-H), 3.30 (t, $J$ = 3.5 Hz, 1 H, 1-H), 2.59 (br. s, 1 H, OH), 1.86 (ddd, $J$ = 15.2, 9.1, 5.9 Hz, 1 H, 5$_a$-H), 1.78 (m, 1 H, 3$_a$-H), 1.55 (m, 2 H, 4-H), 1.45 (m, 1 H, 5$_b$-H), 1.25 (m, 1 H, 3$_b$-H) ppm. $^{13}$C NMR (125.77 MHz, $CDCl_3$): $\delta$ = 67.0 (C-2), 55.4 (C-1), 55.3 (C-6), 28.9 (C-3), 23.1 (C-5), 18.1 (C-4) ppm.

***tert*-Butyl(7-oxabicyclo[4.1.0]hept-2-yloxy)diphenylsilane (17):** Imidazole (2.08 g, 30.6 mmol) was added to a solution of **21** (1.74 g, 15.3 mmol) in anhydrous *N*,*N*-dimethylformamide (5.0 mL) at 0 °C. The mixture was stirred at this temperature for 10 min and then *tert*-butylchlorodiphenylsilane (4.4 mL, 16.8 mmol) was added and the mixture was stirred at room temperature for 6 h. The reaction was quenched by addition of an aqueous saturated solution of sodium chloride (50 mL). The mixture was extracted with dichloromethane (3 × 50 mL). The combined organic phases were washed with brine (2 × 30 mL), dried ($MgSO_4$) and the solvent evaporated. The product was purified by column chromatography (silica gel) eluting with hexane/EtOAc (99.5:0.5) to yield 3.56 g (66% yield) of pure compound **17** as a colorless oil. $R_f$ 0.65 (hexane/EtOAc, 4:1). $^1$H NMR (500.13 MHz, $CDCl_3$): $\delta$ = 7.75 (m, 2 H, aromatic protons), 7.70 (m, 2 H, aromatic protons), 7.41 (m, 6 H, aromatic protons), 3.98 (ddd, $J$ = 9.8, 5.1, 1.9 Hz, 1 H, 2-H), 3.14 (dist. t, $J$ = 3.4 Hz, 1 H, 6-H), 3.01 (dd, $J$ = 3.9, 1.9 Hz, 1 H, 1-H), 1.71 (m, 2 H, 3-H), 1.56 (m, 2 H, 4-H), 1.47 (m, 2 H, 5-H), 1.09 [s, 9 H, C($CH_3$)$_3$] ppm. $^{13}$C NMR (125.77 MHz, $CDCl_3$), $\delta$ = 135.8 (Ph), 134.2 (Ph), 134.1 (Ph), 129.6 (Ph), 127.6 (Ph), 127.6 (Ph), 70.3 (C-2), 55.9 (C-1), 54.6 (C-6), 27.9 (C-3), 26.9 ($CH_3$), 22.6 (C-4), 20.2 (C-5), 19.2 [($CH_3$)$_3$*C*] ppm. MS: *m*/*z* (%) = 352 (1) [M]$^+$, 295 (15), 253 (25), 217 (55), 199 (100), 183 (20), 155 (17), 139 (97), 115 (28).

***tert*-Butyldiphenyl(7-thiabicyclo[4.1.0]hept-2-yloxy)silane (22)**

**Method A:** A solution of compound **17** (203 mg, 0.57 mmol) in ethanol/water (1:1, 10 mL) was treated with potassium thiocyanate (553 mg, 5.7 mmol) and the mixture was stirred at room temperature for 72 h. Then a saturated solution of sodium chloride (5 mL) was added and the mixture was extracted with dichloromethane (2 × 30 mL). The combined organic layers were washed with brine (2 × 10 mL), dried ($MgSO_4$), and the solvent was evaporated. The product was purified by column chromatography (silica gel) eluting with hexane to afford 135 mg (65% yield) of pure **22** as a colorless oil.

**Method B:** A solution of **17** (217 mg, 0.62 mmol) in anhydrous methanol (4 mL) was treated with thiourea (83 mg, 1.1 mmol) under argon. The reaction mixture was stirred at room temperature for 5 d. The solvent was evaporated and the residue was purified by column chromatography (silica gel) employing a mixture of hexane/EtOAc (95.5:0.5) as eluent to give 144 mg (64% yield) of pure **22** as a colorless oil. $R_f$ 0.62 (hexane/EtOAc, 9:1). $^1$H NMR (500.13 MHz, $CDCl_3$): $\delta$ = 7.72–7.66 (m, 4 H, aromatic protons), 7.44–7.35 (m, 6 H, aromatic protons), 4.32 (dt, $J$ = 6.4, 1.0 Hz, 1 H, 2-H), 3.24 (ddd, $J$ = 6.4, 3.8, 2.6 Hz, 1 H, 1-H), 3.07 (dd, $J$ = 6.6, 1.1 Hz, 1 H, 6-H), 2.11 (m, 2 H, 3$_a$-H, 5$_a$-H), 1.75 (m, 1 H, 5$_b$-H), 1.48 (m, 1 H, 3$_b$-H), 1.27 (m, 2 H, 4-H), 1.10 [s, 9 H, C($CH_3$)$_3$] ppm. $^{13}$C NMR (125.77 MHz, $CDCl_3$): $\delta$ = 135.8 (Ph), 135.7 (Ph), 134.1 (Ph), 134.0 (Ph), 129.7 (Ph), 129.7 (Ph), 127.7 (Ph), 127.6 (Ph), 69.8 (C-2), 41.3 (C-1), 37.4 (C-6), 30.1 (C-3), 27.0 [C(*C*H$_3$)$_3$], 25.5 (C-5), 19.2 [*C*($CH_3$)$_3$], 14.8 (C-4) ppm. MS: *m*/*z* (%) = 368 (1) [M]$^+$, 311 (19), 279 (33), 233 (36), 199 (100), 181 (11), 155 (6), 135 (5).

**(±)-*tert*-Butyldiphenylsilyl Cyclopent-2-enyl Ether (24):** Imidazole (1.884 g, 27.7 mmol) was added to a solution of cyclopentenol **23** (1.164 g, 13.9 mmol) in anhydrous *N*,*N*-dimethylformamide (10 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min. Then *tert*-butylchlorodiphenylsilane (4.0 mL, 15.3 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 20 h. The reaction was quenched by the addition of water (50 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with an aqueous saturated solution of sodium chloride (5 × 50 mL), dried ($MgSO_4$) and the solvent evaporated. The residue was purified by column chromatography (silica gel) employing a mixture of hexane/EtOAc (99.5:0.5) as eluent to afford 3.654 g (82% yield) of pure compound **24** as a colorless oil: $R_f$ 0.85 (hexane/EtOAc, 9:1). $^1$H NMR (500.13 MHz, $CDCl_3$): $\delta$ = 7.69 (m, 4 H, aromatic protons), 7.37 (m, 6 H, aromatic protons), 5.84 (ddt, $J$ = 5.7, 2.3, 1.2 Hz, 1 H, 2-H), 5.64 (dq, $J$ = 5.8, 2.0 Hz, 1 H, 3-H), 4.90 (m, 1 H, 1-H), 2.45 (m, 1 H, 4$_b$-H), 2.13 (m, 1 H, 4$_a$-H), 2.05 (dddd, $J$ = 13.1, 8.6, 7.4, 3.6 Hz, 1 H, 5$_b$-H), 1.78 (dddd, $J$ = 13.3, 8.9, 5.4, 4.4 Hz, 1 H, 5$_a$-H), 1.06 [s, 9 H, C($CH_3$)$_3$] ppm. $^{13}$C NMR (125.77 MHz, $CDCl_3$): $\delta$ = 135.79 (Ph), 135.77 (Ph), 134.7 (Ph), 134.6 (Ph), 133.7 (Ph), 133.5 (C-2), 129.5 (C-3), 127.50 (Ph), 127.51 (Ph), 79.0 (C-1), 33.5 (C-5), 30.9 (C-4), 27.0 [C-(*C*H$_3$)$_3$], 19.0 [*C*($CH_3$)$_3$] ppm. MS: *m*/*z* (%) = 265 (23) [M – *t*Bu]$^+$, 200 (24), 199 (100), 77 (14).

**(±)-*tert*-Butyldiphenylsilyl Cyclohex-2-enyl Ether (25):** Imidazole (710 mg, 10.4 mmol) was added to a solution of 2-cyclohexenol (512 mg, 5.2 mmol) in anhydrous *N*,*N*-dimethylformamide (10 mL) at 0 °C as described for the preparation of **24**. The product was purified by column chromatography (silica gel) eluting with hexane to afford 1.45 g (83% yield) of pure **25** as a colorless oil: $R_f$ 0.80 (hexane/EtOAc, 19:1). $^1$H NMR (500.13 MHz, $CDCl_3$): $\delta$ = 7.69 (m, 4 H, aromatic protons), 7.34–7.42 (m, 6 H, aromatic protons), 5.69 (ddt, $J$ = 10.0, 3.6, 1.1 Hz, 1 H, 3-H), 5.59 (dq, $J$ = 10.1, 2.3 Hz, 1 H, 2-H), 4.23 (m, 1 H, 1-H), 2.02 (m, 1 H, 4$_b$-H), 1.90 (m, 1 H, 4$_a$-H), 1.77 (m, 1 H, 5$_b$-H), 1.68 (m, 2 H, 5$_a$-H, 6$_b$-H), 1.46 (m, 1 H, 6$_a$-H), 1.06 [s, 9 H, C($CH_3$)$_3$] ppm. $^{13}$C NMR (125.77 MHz, $CDCl_3$): $\delta$ = 135.87 (Ph), 135.84 (Ph), 134.7 (Ph), 130.8 C-2), 129.47 (Ph), 129.46 (Ph), 129.2 (C-3), 127.5 (Ph), 67.2 (C-1), 32.2 (C-6), 27.0 [C(*C*H$_3$)$_3$], 25.0 (C-4), 19.4 (C-5), 19.2 [*C*($CH_3$)$_3$] ppm.

**(±)-(1*RS*,2*RS*,3*RS*)-*tert*-Butyldiphenylsilyl 6-Oxabicyclo[3.1.0]-hex-2-yl Ether (19) and (±)-(1*RS*,2*SR*,3*RS*)-*tert*-Butyldiphenylsilyl 6-Oxabicyclo[3.1.0]hex-2-yl Ether (18):** A solution of 60% *m*-chloroperbenzoic acid (3.63 g, 12.6 mmol) in dichloromethane (50 mL) was added dropwise to a solution of compound **24** (3.39 g, 10.5 mmol) in dichloromethane (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 24 h. Then the organic phase was washed with an aqueous saturated solution of sodium hydrogencarbonate (3 × 50 mL), water (2 × 50 mL) and then dried ($MgSO_4$). The solvent was evaporated and the residue was purified

by column chromatography (silica gel) eluting with a mixture of hexane/EtOAc (99:1) to give 2.044 g (57% yield) of epoxide **19** and 1.130 g (32% yield) of **18** as white solids. Compound **19**: $R_f$ 0.65 (hexane/EtOAc, 9:1); m.p. 70–71 °C. $^1$H NMR (500.13 MHz, $CDCl_3$): $\delta$ = 7.66 (m, 4 H, aromatic protons), 7.40 (m, 6 H, aromatic protons), 4.36 (d, $J$ = 5.2 Hz, 1 H, 2-H), 3.52 (d, $J$ = 2.0 Hz, 1 H, 1-H), 3.27 (d, $J$ = 2.4 Hz, 1 H, 5-H), 1.92 (m, 2 H, 4-H), 1.57 (ddd, $J$ = 13.7, 7.6, 1.9 Hz, 1 H, $3_b$-H), 1.45 (m, 1 H, $3_a$-H), 1.08 [s, 9 H, $C(CH_3)_3$] ppm. $^{13}$C NMR (125.77 MHz, $CDCl_3$): $\delta$ = 135.69 (Ph), 135.68 (Ph), 134.0 (Ph), 133.9 (Ph), 129.8 (Ph), 129.7 (Ph), 127.71 (Ph), 127.69 (Ph), 73.1 (C-2), 58.5 (C-1), 56.9 (C-6), 29.6 (C-3), 26.9 [$C(CH_3)_3$], 25.3 (C-4), 19.2 [$C(CH_3)_3$] ppm. MS: $m/z$ (%) = 338 (1) $[M]^+$, 281 (100), 239 (16), 199 (87), 183 (34), 139 (14). Compound **18**: $R_f$ 0.48 (hexane/EtOAc, 9:1); m.p. 53–54 °C. $^1$H NMR (500.13 MHz, $CDCl_3$): $\delta$ = 7.76 (m, 2 H, aromatic protons), 7.70 (m, 2 H, aromatic protons), 7.41 (m, 6 H, aromatic protons), 4.22 (dt, $J$ = 7.6, 1.4 Hz, 1 H, 2-H), 3.28 (d, $J$ = 3.0 Hz, 1 H, 1-H), 3.18 (dd, $J$ = 2.8, 1.4 Hz, 1 H, 5-H), 2.01 (m, 1 H, $4_a$-H), 1.61 (m, 1 H, $4_b$-H), 1.47 (m, 2 H, 3-H), 1.08 [s, 9 H, $C(CH_3)_3$] ppm. $^{13}$C NMR (125.77 MHz, $CDCl_3$): $\delta$ = 135.7 (Ph), 135.7 (Ph), 134.0 (Ph), 133.9 (Ph), 129.7 (Ph), 129.7 (Ph), 127.7 (Ph), 127.6 (Ph), 74.8 (C-2), 58.4 (C-1), 54.9 (C-6), 26.8 [$C(CH_3)_3$], 26.2 (C-3), 25.5 (C-4), 19.2 [$C(CH_3)_3$] ppm. MS: $m/z$ (%) = 281 (17) $[M - {}^tBu]^+$, 203 (100), 199 (35), 185 (21), 141 (31), 105 (21).

**(±)-(1*SR*,2*RS*,5*RS*)-*tert*-Butyldiphenylsilyl 6-Thiabicyclo[3.1.0]-hex-2-yl Ether (26):** A solution of potassium thiocyanate (2.70 g, 27.8 mmol) in water (5 mL) was added to a solution of **18** (940 mg, 2.8 mmol) in ethanol (15 mL). The mixture was treated as described for the preparation of **27**. The product was purified by column chromatography (silica gel) eluting with hexane/EtOAc (99.5:0.5) to yield 227 mg (23% yield) of pure **26** as a colorless oil and 220 mg of unreacted starting material: $R_f$ 0.75 (hexane/EtOAc, 9:1). $^1$H NMR (500.13 MHz, $CDCl_3$): $\delta$ = 7.68 (m, 4 H, aromatic protons), 7.42 (m, 6 H, aromatic protons), 4.51 (d, $J$ = 4.6 Hz, 1 H, 2-H), 3.41 (t, $J$ = 3.8 Hz, 1 H, 1-H), 3.13 (d, $J$ = 4.3 Hz, 1 H, 5-H), 2.27 (dddd, $J$ = 13.8, 10.7, 7.5, 3.4 Hz, 1 H, $3_b$-H), 1.99 (dd, $J$ = 13.4, 7.3 Hz, 1 H, $4_b$-H), 1.77 (dddd, $J$ = 13.7, 11.0, 7.3, 4.6 Hz, 1 H, $3_a$-H), 1.54 (dd, $J$ = 13.4, 7.7 Hz, 1 H, $4_a$-H), 1.09 [s, 9 H, $C(CH_3)_3$] ppm. $^{13}$C NMR (125.77 MHz, $CDCl_3$): $\delta$ = 135.8 (Ph), 135.7 (Ph), 134.1 (Ph), 134.1 (Ph), 129.7 (Ph), 129.6 (Ph), 127.7 (Ph), 127.6 (Ph), 74.2 (C-2), 44.9 (C-1), 39.5 (C-6), 26.9 [$C(CH_3)_3$], 26.3 (C-4), 26.2 (C-5), 19.2 [$C(CH_3)_3$] ppm. MS: $m/z$ (%) = 354 (2) $[M]^+$, 297 (44), 200 (18), 199 (100), 99 (24).

**(±)-(1*SR*,2*SR*,5*RS*)-*tert*-Butyldiphenylsilyl 6-Thiabicyclo[3.1.0]-hex-2-yl Ether (27):** A solution of potassium thiocyanate (3.94 g, 40.6 mmol) in water (7 mL) was added to a solution of compound **19** (1.35 g, 4.06 mmol) in ethanol (20 mL) and the reaction mixture was refluxed for 15 h. The solvent was evaporated almost to dryness and the mixture was partitioned between an aqueous saturated solution of sodium chloride (20 mL) and dichloromethane (30 mL). The aqueous phase was extracted with dichloromethane (2 × 30 mL). The combined organic layers were washed with brine (2 × 10 mL), dried ($MgSO_4$) and the solvent evaporated. The residue was purified by column chromatography (silica gel) eluting with hexane/EtOAc (99.5:0.5) to afford 690 mg (48% yield) of pure compound **27** as a colorless oil: $R_f$ 0.8 (hexane/EtOAc, 9:1). $^1$H NMR (500.13 MHz, $CDCl_3$): $\delta$ = 7.77 (m, 2 H, aromatic protons), 7.70 (m, 2 H, aromatic protons), 7.42 (m, 6 H, aromatic protons), 4.45 (ddt, $J$ = 7.5, 3.5, 0.8 Hz, 1 H, 2-H), 3.13 (dd, $J$ = 4.5, 3.2 Hz, 1 H, 1-H), 3.08 (t, $J$ = 4.1 Hz, 1 H, 5-H), 1.99 (m, 1 H, $3_b$-H), 1.71 (m, 2 H, $3_a$-H, $4_b$-H), 1.57 (m, 1 H, $4_a$-H), 1.09 [s, 9 H, $C(CH_3)_3$] ppm. $^{13}$C NMR (125.77 MHz, $CDCl_3$): $\delta$ = 135.8 (Ph), 135.7 (Ph), 134.12 (Ph), 134.06 (Ph), 129.7 (Ph), 129.6 (Ph), 127.7 (Ph), 127.6 (Ph), 74.2 (C-2), 44.9 (C-1), 39.5 (C-6), 26.9 [$C(CH_3)_3$], 26.3 (C-4), 26.2 (C-5), 19.2 [$C(CH_3)_3$] ppm. MS: $m/z$ (%) = 355 (1) $[M + 1]^+$, 321 (21), 297 (70), 219 (100), 199 (45), 185 (26).

**(±)-(1*RS*,2*RS*,5*SR*)-6-Thiabicyclo[3.1.0]hexan-2-ol (28):** A 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran (3.8 mL, 3.8 mmol) was added to a solution of **27** (0.69 g, 1.95 mmol) in anhydrous tetrahydrofuran (150 mL) at 0 °C under argon. The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue was purified by column chromatography (silica gel) eluting with a mixture of hexane/$CH_2Cl_2$ (4:1) to afford 201 mg (92% yield) of pure compound **28** as a white solid: $R_f$ 0.25 ($CH_2Cl_2$); m.p. 42–45 °C. $^1$H NMR (500.13 MHz, $CDCl_3$): $\delta$ = 4.49 (dt, $J$ = 7.9, 3.7 Hz, 1 H, 2-H), 3.53 (t, $J$ = 3.9 Hz, 1 H, 1-H), 3.36 (t, $J$ = 3.9 Hz, 1 H, 5-H), 2.10 (dd, $J$ = 13.6, 7.6 Hz, 1 H, $3_b$-H), 1.86 (m, 2 H, $3_a$-H, $4_a$-H), 1.44 (m, 1 H, $4_b$-H) ppm. $^{13}$C NMR (125.77 MHz, $CDCl_3$): $\delta$ = 73.3 (C-2), 46.7 (C-1), 41.5 (C-5), 27.0 (C-3), 26.7 (C-4) ppm. MS: $m/z$ (%) = 116 (94) $[M]^+$, 98 (61), 97 (100), 83 (54), 72 (25), 71 (33).

**(±)-(1*SR*,2*RS*,5*RS*)-6-Thiabicyclo[3.1.0]hexan-2-ol (29):** A solution of **26** (270 mg, 0.58 mmol) in anhydrous tetrahydrofuran (15 mL) was treated with a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran (1.2 mL, 1.2 mmol) under argon at 0 °C as described for the preparation of **28**. The residue was purified by column chromatography (silica gel) eluting with a mixture of hexane/$CH_2Cl_2$ (1:4) to afford 67 mg (95% yield) of epi alcohol **29** as a colorless oil: $R_f$ 0.25 (hexane/EtOAc, 4:1). $^1$H NMR (500.13 MHz, $CDCl_3$): $\delta$ = 4.49 (d, $J$ = 4.8 Hz, 1 H, 2-H), 3.42 (t, $J$ = 3.9 Hz, 1 H, 1-H), 3.20 (d, $J$ = 4.3 Hz, 1 H, 5-H), 2.19 (dddd, $J$ = 13.9, 10.8, 7.6, 3.3 Hz, 1 H, $3_b$-H), 2.04 (dd, $J$ = 13.8, 7.6 Hz, 1 H, $3_a$-H), 1.93 (dddd, $J$ = 14.0, 10.9, 7.7, 4.8 Hz, 1 H, $4_b$-H), 1.54 (dd, $J$ = 14.0, 7.6 Hz, 1 H, $4_a$-H) ppm. $^{13}$C NMR (125.77 MHz, $CDCl_3$): $\delta$ = 74.5 (C-2), 43.0 (C-1), 40.8 (C-5), 28.6 (C-3), 26.8 (C-4) ppm.

**(±)-6-Chloro-9-[(1*RS*,2*SR*,5*SR*)-6-thiabicyclo[3.1.0]hex-2-yl]-purine (30):** A suspension of 6-chloropurine (247 mg, 1.6 mmol) and triphenylphosphane (603 mg, 2.3 mmol) in anhydrous tetrahydrofuran (2.0 mL) was treated with diethyl azodicarboxylate (DEAD; 0.18 mL, 1.13 mmol) at 0 °C under argon. The mixture was stirred at 0 °C for 10 min. Then a solution of **28** (116 mg 1.0 mmol) in tetrahydrofuran (2.0 mL) was added and the reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated and the residue was purified by column chromatography (silica gel) employing a mixture of hexane/EtOAc (17:3) as eluent to afford 41 mg of pure compound **30** as a white solid and 313 mg of the same compound with traces of reduced DEAD: $R_f$ 0.74 (EtOAc/methanol, 19:1); m.p. 145–148 °C. UV (methanol): $\lambda_{max}$ = 265 nm. $^1$H NMR (500.13 MHz, $CDCl_3$): $\delta$ = 8.76 (s, 1 H, 2-H), 8.11 (s, 1 H, 8-H), 5.38 (d, $J$ = 6.2 Hz, 1 H, 2′-H), 3.69 (t, $J$ = 3.5 Hz, 1 H, 5′-H), 3.48 (d, $J$ = 4.1 Hz, 1 H, 1′-H), 2.48 (m, 2 H, 3′-H), 2.35 (dt, $J$ = 13.0, 6.0 Hz, 1 H, $4'_b$-H), 1.91 (dt, $J$ = 12.2, 6.7 Hz, 1 H, $4'_a$-H) ppm. $^{13}$C NMR (125.77 MHz, $CDCl_3$): $\delta$ = 152.0 (C-2), 151.4 (C-4), 151.3 (C-6), 142.9 (C-8), 131.8 (C-5), 58.2 (C-2′), 41.5 (C-1′), 41.1 (C-5′), 28.2 (C-4′), 27.3 (C-3′) ppm. MS: $m/z$ (%) = 253 (9) $[M + 1]^+$, 219 (54), 155 (100), 119 (10), 97 (51). $C_{10}H_9ClN_4S$: C 47.52, H 3.59, Cl 14.03, N 22.17, S 12.69; found C 47.65, H 3.83, Cl 14.05, N 21.63, S 12.16.

**(±) 9-[(1*RS*,2*SR*,5*SR*)-6-thiabicyclo[3.1.0]hex-2-yl]purin-6-yl-amine (31):** Compound **30** (310 g, mmol) was treated with a saturated solution of methanolic ammonia (5 mL) in a sealed tube at 70 °C for 4 h. The mixture was cooled to –78 °C, the tube was

opened and nitrogen was bubbled through it to eliminate the ammonia. The product was purified by column chromatography (silica gel) eluting with EtOAc/methanol (19:1) to give 77 mg (38% yield from **28**) of pure **31** as a white solid: $R_f$ 0.27 (EtOAc/methanol, 19:1); m.p. 194–196 °C. UV (methanol): $\lambda_{max}$ = 261 nm. $^1$H NMR (500.13 MHz, [D$_6$]DMSO): $\delta$ = 8.17 (s, 1 H, 2-H), 8.15 (s, 1 H, 8-H), 7.21 (br. s, 2 H, NH$_2$), 5.17 (d, $J$ = 6.6 Hz, 1 H, 2′-H), 3.72 (dist. t, $J$ = 3.6 Hz, 1 H, 5′-H), 3.62 (d, $J$ = 3.9 Hz, 1 H, 1′-H), 2.51 (m, 1 H, 3′$_b$-H), 2.20 (m, 1 H, 3′$_a$-H), 2.13 (dd, $J$ = 13.6, 7.9 Hz, 1 H, 4′$_b$-H), 1.85 (dd, $J$ = 13.6, 8.0 Hz, 1 H, 4′$_a$-H) ppm. $^{13}$C NMR (125.77 MHz, [D$_6$]DMSO): $\delta$ = 156.2 (C-6), 152.6 (C-2), 149.3 (C-4), 138.9 (C-8), 119.0 (C-5), 56.6 (C-2′), 42.9 (C-1′), 42.3 (C-5′), 27.8 (C-4′), 26.3 (C-3′) ppm. MS: $m/z$ (%) = 233 (15) [M]$^+$, 200 (30), 136 (100), 99 (31). HRMS (ESI): calcd. for $C_{10}H_{12}N_5S$ [MH$^+$]: 234.0810; found 234.0813. $C_{10}H_{11}N_5S$: C 51.48, H 4.75, N 30.02, S 13.74; found C 51.45, H 4.67, N 30.17, S 13.65.

**(±)-9-[(1*RS*,2*SR*,5*SR*)-6-Thiabicyclo[3.1.0]hex-2-yl]-6-(benzyloxy)purin-2-ylamine (32):** A suspension of 2-amino-6-(benzyloxy)-purine (873 mg, 3.6 mmol) and triphenylphosphane (1.18 g, 4.5 mmol) in anhydrous tetrahydrofuran (10 mL) cooled to 0 °C was treated with diethyl azodicarboxylate (0.71 mL, 4.5 mmol) under argon. The mixture was stirred at 0 °C for 10 min. Then a solution of **28** (210 mg, 1.8 mmol) in tetrahydrofuran (2.0 mL) was added and the reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated and the residue was purified by column chromatography (silica gel) eluting with a mixture of hexane/EtOAc (3:1) to afford 174 mg (28% yield) of pure **32** as a white solid: $R_f$ 0.74 (hexane/EtOAc, 1:9); m.p. 165–167 °C. $^1$H NMR (500.13 MHz, CDCl$_3$): $\delta$ = 7.59 (s, 1 H, 8-H), 7.50 (d, $J$ = 7.4 Hz, 2 H, aromatic protons), 7.35 (dist. t, $J$ = 7.3 Hz, 2 H, aromatic protons), 7.30 (dist. t, $J$ = 7.3 Hz, 1 H, aromatic proton), 5.57 (s, 2 H, OC$H_2$Ph), 5.14 (d, $J$ = 6.3 Hz, 1 H, 2′-H), 4.88 (s, 2 H, NH$_2$), 3.59 (t, $J$ = 3.2 Hz, 1 H, 5′-H), 3.42 (d, $J$ = 4.1 Hz, 1 H, 1′-H), 2.37 (m, 2 H, 4′-H), 2.28 (m, 1 H, 3′$_b$-H), 1.83 (m, 1 H, 3′$_a$-H) ppm. $^{13}$C NMR (125.77 MHz, CDCl$_3$): $\delta$ = 161.1 (C-6), 159.2 (C-2), 153.8 (C-4), 136.7 (Ph), 136.4 (C-8), 128.4 (Ph), 128.3 (Ph), 128.0 (Ph), 115.7 (C-5), 68.0 (O$CH_2$Ph), 56.6 (C-2′), 41.6 (C-1′), 41.4 (C-5′), 28.1 (C-4′), 26.9 (C-3′) ppm. MS: $m/z$ (%) = 339 (8) [M]$^+$, 240 (9), 135 (7), 99 (65), 91 (100). $C_{17}H_{17}N_5OS\cdot\frac{1}{4}H_2O$: C 59.37, H 5.13, N 20.36, S 9.32; found C 59.40, H 5.02, N 20.46, S 9.27.

**(±)-2-Amino-9-[(1*RS*,2*SR*,5*SR*)-6-thiabicyclo[3.1.0]hex-2-yl]-1,9-dihydropurin-6-one (33):** A solution of **32** (32 mg, 0.1 mmol) in anhydrous dichloromethane (10 mL) was cooled to –78 °C under argon and treated with boron trichloride (1.0 M in dichloromethane, 0.75 mL). The reaction mixture was stirred at –78 °C for 4 h, after which time methanol (4.0 mL) was added while maintaining the same temperature. The mixture was then warm to room temperature and the solvent was evaporated to dryness. Methanol (6×4 mL) was added and evaporated after each addition. The residue was purified by column chromatography (silica gel) employing a mixture of CHCl$_3$/methanol (9:1) as eluent to afford 16 mg (63% yield) of pure compound **33** as a white solid: $R_f$ 0.30 (CHCl$_3$/methanol, 9:1); m.p. >280 °C. $^1$H NMR (500.17 MHz, [D$_6$]DMSO): $\delta$ = 10.63 (s, 1 H, NH), 7.73 (s, 1 H, 8-H), 6.54 (s, 2 H, NH$_2$), 4.92 (d, $J$ = 6.5 Hz, 1 H, 2′-H), 3.70 (t, $J$ = 3.8 Hz, 1 H, 5′-H), 3.55 (d, $J$ = 4.3 Hz, 1 H, 1′-H), 2.42 (m, 1 H, 4′$_b$-H), 2.12 (m, 2 H, 3′$_b$-H, 4′$_a$-H), 1.82 (m, 1 H, 3′$_a$-H) ppm. $^{13}$C NMR (125.77 MHz, [D$_6$]-DMSO): $\delta$ = 156.7 (C-6), 153.5 (C-2), 150.8 (C-4), 134.9 (C-8), 116.6 (C-5), 55.9 (C-2′), 42.6 (C-1′), 42.2 (C-5′), 27.6 (C-4′), 26.2 (C-3′) ppm.

**(±)-3-Benzoyl-5-methyl-1-[(1*RS*,2*SR*,5*SR*)-6-thiabicyclo[3.1.0]-hex-2-yl]pyrimidine-2,4(1*H*,3*H*)-dione (34):** Diethyl azodicarboxylate (0.44 mL, 2.8 mmol) was added to a solution of triphenylphosphane (735 mg, 2.8 mmol) in anhydrous tetrahydrofuran (5 mL) at 0 °C under argon. The resulting mixture was stirred at 0 °C for 10 min. Then the mixture was cooled to –45 °C and a suspension of $N^3$-benzoylthymine (515 mg, 2.24 mmol) and **28** (130 mg, 1.12 mmol) in tetrahydrofuran (8 mL) was added dropwise through a cannula over a 10 min period. The reaction mixture was stirred at –45 °C for 2 h and at room temperature for 22 h. The solvent was evaporated and the residual was purified by column chromatography (silica gel) eluting with a mixture of hexane/EtOAc (3:1) to afford the desired product, which was further purified by column chromatography (silica gel) employing hexane/$CH_2Cl_2$ (2:3) to afford 138.6 mg (38% yield) of compound **34** as a white solid: $R_f$ 0.87 (AcOEt); m.p. 185–186 °C. UV (methanol): $\lambda_{max}$ = 280 nm. $^1$H NMR (500.13 MHz, CDCl$_3$): $\delta$ = 7.92 (dq, $J$ = 4.2, 1.2 Hz, 2 H, aromatic protons), 7.65 (dist. t, $J$ = 7.7 Hz, 1 H, aromatic proton), 7.50 (dist. t, $J$ = 7.7 Hz, 2 H, aromatic protons), 7.05 (d, $J$ = 1.1 Hz, 1 H, 6-H), 5.09 (d, $J$ = 7.2 Hz, 1 H, 2′-H), 3.63 (t, $J$ = 3.5 Hz, 1 H, 5′-H), 3.33 (d, $J$ = 4.0 Hz, 1 H, 1′-H), 2.35 (m, 2 H, 4′-H), 2.25 (m, 1 H, 3′$_b$-H), 1.97 (d, $J$ = 1.1 Hz, 3 H, CH$_3$ at C-5), 1.78 (q, $J$ = 6.7 Hz, 1 H, 3′$_a$-H) ppm. $^{13}$C NMR (125.77 MHz, CDCl$_3$): $\delta$ = 168.9 (C-4), 162.6 (*C*OPh), 149.6 (C-2), 137.0 (C-6), 135.0 (Ph), 131.7 (Ph), 130.4 (Ph), 129.1 (Ph), 111.2 (C-5), 60.1 (C-2′), 42.3 (C-5′), 41.7 (C-1′), 28.9 (C-4′), 27.3 (C-3′), 12.7 (CH$_3$ at C-5) ppm. MS: $m/z$ (%) = 328 (16) [M]$^+$, 295 (17), 231 (17), 105 (100), 77 (60). $C_{17}H_{16}N_2O_3S$: C 62.18, H 4.91, N 8.53, S 9.76; found C 61.85, H 5.34, N 8.11, S 9.17.

**(±)-5-Methyl-1-[(1*RS*,2*SR*,5*SR*)-6-thiabicyclo[3.1.0]hex-2-yl]pyrimidine-2,4(1*H*,3*H*)-dione (35):** Compound **34** (123 mg, mmol) was treated with methanolic ammonia (5 mL, saturated at –78 °C) and stirred in a pressure vessel at 0 °C for 1 h. The solvent was evaporated and the residue was purified by column chromatography (silica gel) using hexane/EtOAc (7:3) as eluent to afford 92.4 mg (41% from **28**) of **35** as a white solid: $R_f$ 0.67 (AcOEt); m.p. 197–198 °C. UV (methanol): $\lambda_{max}$ = 272 nm. $^1$H NMR (500.13 MHz, [D$_6$]-DMSO): $\delta$ = 11.27 (s, 1 H, NH), 7.29 (d, $J$ = 1.1 Hz, 1 H, 6-H), 4.94 (d, $J$ = 7.4 Hz, 1 H, 2′-H), 3.70 (t, $J$ = 3.8 Hz, 1 H, 5′-H), 3.47 (d, $J$ = 4.3 Hz, 1 H, 1′-H), 2.38 (m, 1 H, 4′$_b$-H), 2.07 (m, 2 H, 3′$_b$-H, 4′$_a$-H), 1.79 (d, $J$ = 0.9 Hz, 3 H, CH$_3$ at C-5), 1.68 (dd, $J$ = 14.1, 8.1 Hz, 1 H, 3′$_a$-H) ppm. $^{13}$C NMR (125.77 MHz, [D$_6$]-DMSO): $\delta$ = 163.9 (C-4), 150.9 (C-2), 138.0 (C-6), 109.3 (C-5), 58.6 (C-2′), 43.8 (C-5′), 42.6 (C-1′), 28.5 (C-4′), 26.5 (C-3′), 12.2 (CH$_3$ at C-5) ppm. MS: $m/z$ (%) = 224 (23) [M]$^+$, 191 (9), 148 (8), 127 (38), 99 (100). HRMS (ESI): calcd. for $C_{10}H_{13}N_2O_2S$ [MH$^+$]: 225.0700; found 225.0698. $C_{10}H_{12}N_2O_2S$: C 53.55, H 5.39, N 12.49, S 14.30; found C 53.52, H 5.51, N 12.21, S 14.08.

**(±)-3-Benzoyl-1-[(1*RS*,2*SR*,5*SR*)-6-thiabicyclo[3.1.0]hex-2-yl]pyrimidine-2,4(1*H*,3*H*)-dione (36):** Diethyl azodicarboxylate (0.40 mL, 2,5 mmol) was added to a solution of triphenylphosphane (656 mg, 2.5 mmol) in anhydrous tetrahydrofuran (5 mL) at 0 °C under argon. The resulting mixture was stirred at 0 °C for 10 min. Then the mixture was cooled to –45 °C and a suspension of $N^3$-benzoyluracil (432 mg, 2 mmol) and **28** (116 mg, 1 mmol) in tetrahydrofuran (8 mL) was added dropwise through a cannula over a 10 min period. The reaction mixture was stirred at –45 °C for 30 min and at room temperature for 2 d. The solvent was evaporated and the residue was purified by column chromatography (silica gel) eluting with a mixture of hexane/EtOAc (3:1). The product was repurified by column chromatography (silica gel) eluting with hexane/$CH_2Cl_2$ (1:1) to afford 154 mg (49% yield) of pure **36** as a white solid: $R_f$ 0.50 (hexane/EtOAc, 3:7); m.p. 151–153 °C. UV (methanol): $\lambda_{max}$ = 256 nm. $^1$H NMR (500.13 MHz, CDCl$_3$): $\delta$ = 7.94 (dd, $J$ = 8.4 Hz, 1.2 Hz, 2 H, aromatic protons), 7.66 (tt, $J$ = 7.5, 1.2 Hz, 1

H, aromatic proton), 7.51 (m, 2 H, aromatic protons), 7.24 (d, $J$ = 8.1 Hz, 1 H, 6-H), 5.84 (d, $J$ = 8.1 Hz, 1 H, 5-H), 5.11 (d, $J$ = 7.3 Hz, 1 H, 2′-H), 3.61 (t, $J$ = 3.6 Hz, 1 H, 5′-H), 3.33 (d, $J$ = 4.1 Hz, 1 H, 1′-H), 2.38 (m, 1 H, 4′$_b$-H), 2.28 (m, 2 H, 3′$_b$-H, 4′$_a$-H), 1.79 (dd, $J$ = 14.4, 7.1 Hz, 1 H, 3′$_a$-H) ppm. $^{13}$C NMR (125.77 MHz, $CDCl_3$): $\delta$ = 168.6 (CO), 161.8 (C-4), 149.6 (C-2), 141.0 (C-6), 135.2 (Ph), 131.4 (Ph), 130.5 (Ph), 129.2 (Ph), 102.6 (C-5), 60.3 (C-2′), 42.0 (C-5′), 41.4 (C-1′), 28.7 (C-4′), 27.3 (C-3′) ppm. MS: $m/z$ (%) = 314 (14) $[M]^+$, 281 (18), 103 (100), 77 (50).

**(±)-1-[(1*RS*,2*SR*,5*SR*)-6-Thiabicyclo[3.1.0]hex-2-yl]pyrimidine-2,4(1*H*,3*H*)-dione (37):** Compound **36** (104 mg, 0.33 mmol) was treated with methanolic ammonia (5 mL, saturated at –78 °C) and stirred in a pressure vessel at 0 °C for 1 h. The solvent was evaporated and the product was purified by column chromatography (silica gel) employing a mixture of hexane/EtOAc (3:2) as eluent to afford 66 mg (95% yield) of pure compound **37** as a white solid: $R_f$ 0.30 (hexane/EtOAc, 1:9); m.p. 154–156 °C. UV (methanol): $\lambda_{max}$ = 266 nm. $^1$H NMR (500.13 MHz, $CDCl_3$): $\delta$ = 9.05 (s, 1 H, NH), 7.14 (d, $J$ = 8.1 Hz, 1 H, 6-H), 5.74 (dd, $J$ = 8.0, 1.5 Hz, 1 H, 5-H), 5.13 (d, $J$ = 7.3 Hz, 1 H, 2′-H), 3.60 (t, $J$ = 3.4 Hz, 1 H, 5′-H), 3.29 (d, $J$ = 4.1 Hz, 1 H, 1′-H), 2.37 (ddt, $J$ = 14.4, 9.3, 7.7 Hz, 1 H, 4′$_b$-H), 2.26 (m, 2 H, 3′$_b$-H, 4′$_a$-H), 1.72 (m, 1 H, 3′$_a$-H) ppm. $^{13}$C NMR (125.77 MHz, $CDCl_3$): $\delta$ = 162.9 (C-4), 150.6 (C-2), 141.1 (C-6), 102.7 (C-5), 59.6 (C-2′), 42.0 (C-5′), 41.5 (C-1′), 28.7 (C-4′), 27.2 (C-3′) ppm. MS: $m/z$ (%) = 210 (43) $[M]^+$, 177 (22), 134 (27), 113 (58), 99 (100). $C_9H_{10}N_2O_2S$: C 51.41, H 4.79, N 13.32, S 15.25; found C 51.25, H 4.83, N 13.17, S 15.16.

**(±)-4-Amino-1-[(1*RS*,2*SR*,5*SR*)-6-thiabicyclo[3.1.0]hex-2-yl]pyrimidin-2(1*H*)-one (38):** Triethylamine (296 μL, 3.88 mmol) was added to a stirred mixture of 1,2,4-triazole (155 mg, 2.25 mmol), phosphorus oxychloride (44 μL, 0.867 mmol) and anhydrous acetonitrile (2.0 mL) under argon. Compound **37** (52 mg, 0.45 mmol) dissolved in acetonitrile (1.0 mL) was added to this mixture, and the reaction mixture was stirred at room temperature for 36 h. An additional amount of triethylamine (204 μL, 1.47 mmol) and water (54 μL, 3.0 mmol) was added and the mixture was stirred for 10 min more before removing the solvent. The residue was partitioned between dichloromethane (50 mL) and an aqueous saturated solution of sodium hydrogencarbonate (50 mL) and the organic layer was separated. The aqueous layer was extracted further with dichloromethane (2 × 50 mL) and the combined organic extract was dried ($MgSO_4$) and the solvent evaporated. The residue was dissolved in dioxane (10 mL) and stirred with ammonium hydroxide ($d$ = 0.9, 1.0 mL) at room temperature overnight. The solvent was evaporated and the product was purified by column chromatography (silica gel) eluting with EtOAc/methanol (19:1) to afford 21 mg (43% yield) of pure **38** as a white solid: $R_f$ 0.25 (EtOAc/methanol, 4:1); m.p. 162 °C (decomp.). UV (methanol): $\lambda_{max}$ = 277 nm. $^1$H NMR (500.13 MHz, [D$_6$]DMSO): $\delta$ = 7.45 (d, $J$ = 7.5 Hz, 1 H, 6-H), 7.06 (br. s, 2 H, $NH_2$), 5.69 (d, $J$ = 7.3 Hz, 1 H, 5-H), 4.98 (d, $J$ = 7.1 Hz, 1 H, 2′-H), 3.67 (t, $J$ = 3.6 Hz, 1 H, 5′-H), 3.38 (d, $J$ = 4.1 Hz, 1 H, 1′-H), 2.29 (m, 1 H, 4′$_b$-H), 2.06 (m, 2 H, 3′$_b$-H, 4′$_a$-H), 1.59 (m, 1 H, 3′$_a$-H) ppm. $^{13}$C NMR (125.77 MHz, $CDCl_3$): $\delta$ = 165.5 (C-4), 155.5 (C-2), 142.8 (C-6), 93.8 (C-5), 58.9 (C-2′), 43.4 (C-5′), 43.1 (C-1′), 28.2 (C-4′), 26.6 (C-3′) ppm. MS: $m/z$ (%) = 209 (14) $[M]^+$, 176 (43), 112 (71), 99 (27), 97 (25), 44 (100).

**Supporting Information** (see also the footnote on the first page of this article): Copies of the $^1$H and $^{13}$C NMR spectra for representative compounds described in this work and copies of the elemental analyses for the title compounds.

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[49] Antiviral activity was evaluated by two methods: reduction of virus plaque formation for HSV-1 and HSV-2, and inhibition of the cytopathic effect (CPE) for HCMV. In the plaque reduction assay, Vero cell monolayers grown in 24 well plates were infected with about 50 PFU (plaque forming units) of virus per well in the absence or presence of various concentrations of the compounds. After adsorption for 1 h, residual inoculum was replaced by MEM containing 0.7% methylcellulose and the corresponding dose of compound. Plaques were counted after 2 d of incubation at 37 °C. The antiviral activity was calculated as the percentage reduction of virus plaque formation in treated cultures with respect to untreated control cultures. The values obtained represent the mean of two independent experiments with duplicate determinations for each concentration. Acyclovir was used as a positive control with an $ID_{50}$ of 0.16 μM. The anti-HCMV activity was determined by a cytopathic effect reduction assay. Briefly, PH monolayers were infected in quadruplicate with HCMV at a multiplicity of infection of 0.1 in the absence or presence of various concentrations of the compounds. Cell controls were included in each experiment. After 7 d of incubation at 37 °C, the cytopathic effect was examined under an inverted microscope.

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