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Synthesis and biological evaluation of *N*-thia-*carba*-thymidine as an antiherpetic agent

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ABSTRACT

As a continuation of our project aimed at the search for new antiviral agents, the synthesis and biological evaluation of *N*-thia-*carba*-thymidine ((1*R*,2*S*,4*S*,5*S*)-5-methyl-1-{6-thia-4-hydroxy-5-[(hydroxy)-methyl]-bicyclo[3.1.0]hex-2-yl}-1,3-dihydropyrimidine-2,4-dione; compound **8**) was carried out employing the carbocyclic enantioenriched intermediate (1*R*,4*S*)-4-phenylmethoxy-3-[(phenylmethoxy)methyl]cyclopent-2-en-1-ol, which in turn was prepared from (3*R*,4*S*) phenylmethoxy-3-[(phenylmethoxy)methyl]-cyclopent-1-ene. The title compound resulted to be a very potent antiherpetic agent exhibiting a similar potency to acyclovir as shown. The synthetic approach to obtain this carbanucleoside required a novel strategy to introduce a thiirane group fused to a functionalized five-membered ring.

1. Introduction and background

In carbanucleosides the replacement of the oxygen atom at the furanose ring by a substituted methylene group enhances structural diversity of conventional nucleosides.[1–3] The responsible enzymes for pharmacological actions of conventional nucleosides also recognize the *carba*-analogues displaying a similar wide range of biological properties.[4,5] Nucleosides in solution exist in a dynamic equilibrium between a Northern geometry and the respective antipodal Southern geometry according to the pseudorotational cycle,[6,7] but only one single conformer is responsible for optimal molecular recognition. Conformationally locked carbanucleosides into either the *N*- or the *S*-geometry have been employed to study this preferred conformation.[8] A three-membered ring fused to the cyclopentane ring proved to be a suitable pseudosugar to fix nucleoside conformation in any of these extreme antipodes.[8] For example, a bicyclo[3.1.0]hexane template as a sugar moiety can fix the conformation to either a North ($_2$E) or a South ($_3$E) geometry, as was the case of *N*-methano-*carba*-adenosine (**1**) and *S*-methano-*carba*-adenosine (**2**), respectively.[9] The use of this bicyclic scaffold was motivated by the structure of neplanocin C (**3**), which is a naturally occurring carbanucleoside possessing an equivalent 6-oxabicyclo[3.1.0]hexane system (Fig. 1).[10]

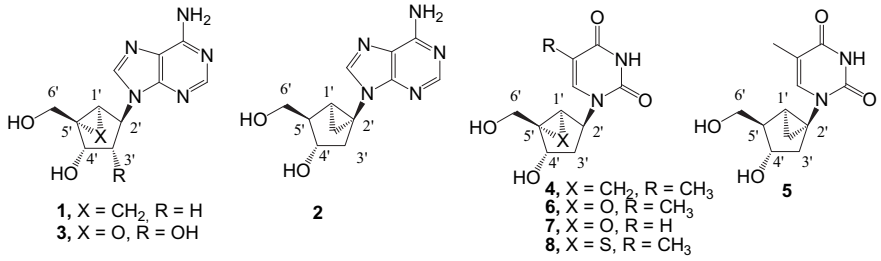

Figure 1. Chemical structure of *N*-methano-*carba*-thymidine (**4**) and structurally related carbanucleosides.

The use of bicyclo[3.1.0]hexane template has indicated that there exits a favored conformation for molecular recognition in several enzymes.[11–14] The conformationally rigid *N*-methano-*carba*-thymidine (**4**) and *S*-methano-*carba*-thymidine (**5**) constitute interesting

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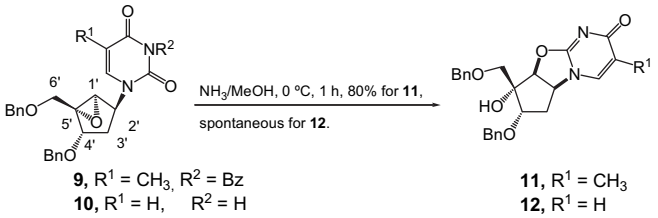
examples of unambiguous conformational preferences for enzyme–drug interaction, where only the Northern conformer is responsible for its potency against both HSV-1 and HSV-2 viruses.[15] The potency of **4** is even greater than acyclovir, a well-known antiherpetic agent.[15] It is worth pointing out that **4** and **5** exhibit opposite affinities for herpes thymidine kinase and DNA polymerases.[16]

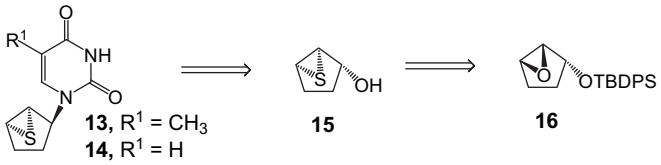
Efforts to optimize compound **4** as an antiherpetic agent has been carried out, especially at the heterocyclic base.[17] Our first approach to improve the efficacy of **4** had considered the isosteric replacement of the cyclopropyl moiety **4** by an epoxy group to produce compounds **6** and **7**. This structural variation would be benefit for molecular recognition due to the smaller size of the epoxy group. However, it was not possible to obtain the theoretical pyrimidine derivatives **6** and **7** as a consequence of an intramolecular epoxide ring opening of intermediates **9** and **10** produced by attack of enol base onto the epoxy group to give rise to **11** and **12** as illustrated in Scheme 1.[18] This spontaneous reaction had been quite unexpected bearing in mind the stability of the epoxy group in related compounds.[11,19] As epoxy groups suffer ring opening when placed adjacent to pyrimidine bases, it was thought that a thiirane group would be an attractive alternative to fix nucleoside conformation; then, compound **8** was selected as a molecular target.



Scheme 1.

2. Results and discussion

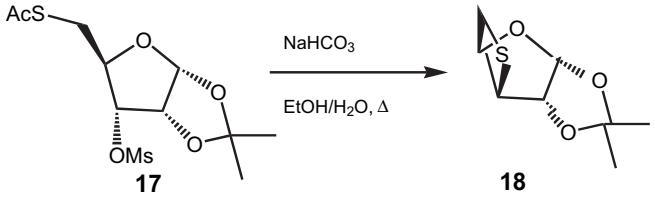
We had demonstrated, in simple models, that pyrimidine carbanucleosides built in a thiabicyclo[3.1.0]hexane system such as **13** and **14** were stable compounds where the thiirane group did not undergo ring opening (Scheme 2).[20]



Scheme 2. Retrosynthetic analysis to prepare simple pyrimidine derivatives built on a thiabicyclo[3.1.0]hexane system.

The synthesis of **13** and **14** had required a common intermediate that involved a thiirane moiety fused to a five-membered ring such as compound **15**. The preparation of a functionalized thiabycyclo[3.1.0]hexane system is not trivial from the synthetic point of view concerning, mainly, reaction yields. Most methods require an appropriate epoxide, which is converted into the corresponding thiirane, usually on treatment with potassium thiocyanate.[21] The reaction occurs with inversion of configuration as shown in the **16**→**15** transformation (Scheme 2).

The main drawback to prepare thiirane from epoxides was the low reaction yields. In this sense, we have developed a new protocol to access to this functionality based on a published procedure to synthesize four-membered thietane rings as illustrated in Scheme 3 for the conversion of **17** into **18**.[22]



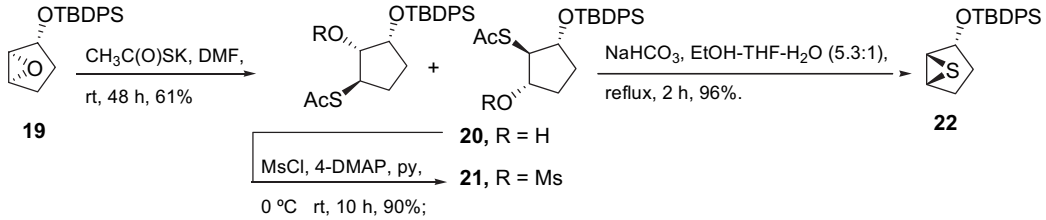
Scheme 3. Preparation of a four-membered thietane ring via S_N2 attack of a sulfide anion onto a mesylate group.

It was envisioned that a thiirane group fused to a highly functionalized five-membered ring could be prepared by the nucleophilic attack of a sulfide anion on an adjacent mesylate moiety. Therefore, we succeeded in preparing episulfide derivatives by an alternate method from **19** taken as an appropriate synthetic intermediate (Scheme 4).

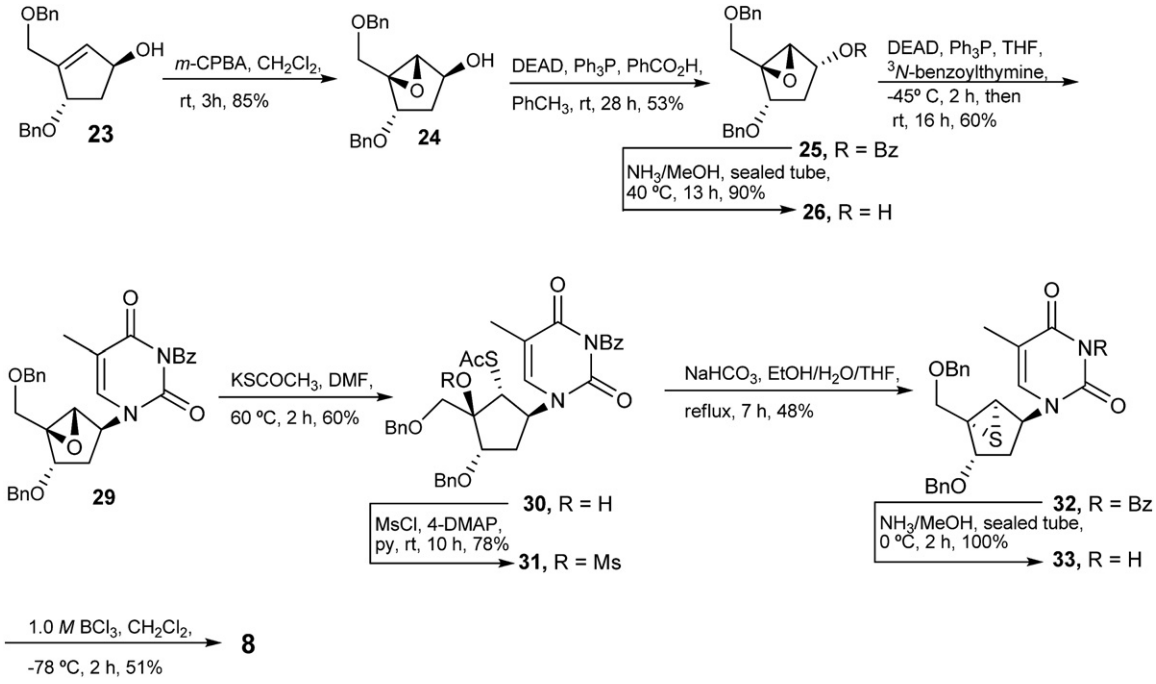
Once this method of preparation of the thiabicyclic[3.1.0]hexane system was at hand, it was possible to synthesize our target molecule. The optimized protocol based on the reaction with an epoxide with potassium thiocyanate[20] was not satisfactory as discussed below.

The synthesis of the target molecule **8** was successfully carried out employing the carbocyclic derivative (1*S*,4*S*)-4-phenylmethoxy-3-[(phenylmethoxy)methyl]cyclopent-2-en-1-ol (**23**) as a chiral advanced synthetic intermediate, which was prepared according to a published procedure.[9b] This compound, in turn, was synthesized from the readily available chiral template (3*R*,4*S*)-4-phenylmethoxy-3-[(phenylmethoxy)methyl]-cyclopent-1-ene.[23]

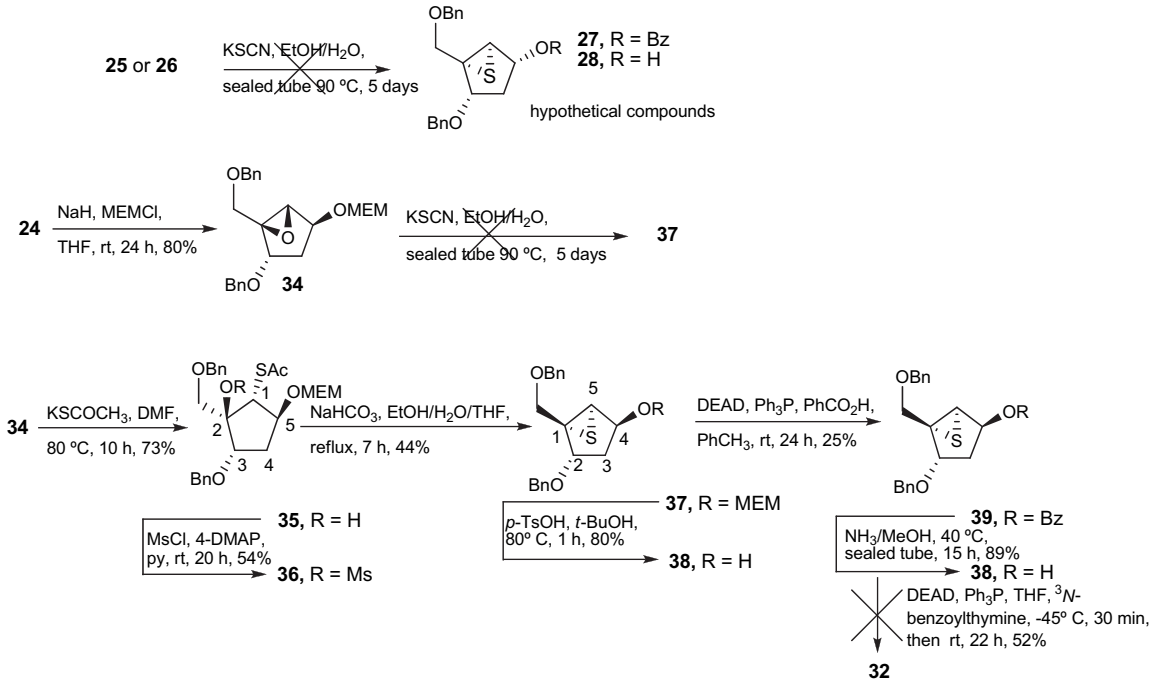
The first approach employed to access to the title compound **8** was the construction of the carbocyclic pseudosugar followed by introduction of the base. In order to have a β-epoxide, that would be a suitable precursor of an α-episulfide, cyclopentenol **23** arose as an interesting starting material. Therefore, compound **23** was reacted with *m*-chloroperbenzoic acid to afford the epoxyalcohol **24** as a single isomer. The stereochemistry of this reaction was controlled by the presence of the β free hydroxyl group at the C-1 position according to the Henbest rule.[24] The configuration of C-1 in compound **24** was inverted following a Mitsunobu esterification,[25] which gave the desired benzoyl intermediate **25** in good yield and the new epoxyalcohol **26** after ester hydrolysis (Scheme 5). Attempts to obtain the 6-thiabicyclo[3.1.0]hexane system from either **25** or **26** to produced hypothetical episulfides **27** and **28** on treatment with potassium thiocyanate were not satisfactory. In addition, the MEM-protected epoxyalcohol **34** was not able to be converted into episulfide **37** (Scheme 6).



Scheme 4.



Scheme 5.



Scheme 6.

In view of the above results, it was decided an alternate approach to prepare the 6-thiabicyclic[3.1.0]hexane system, which was previously depicted in the preparation of the simple reference model **22**. Epoxide ring opening of **34** by treatment with potassium thioacetate afforded **35** in 73% yield as a single diasteromer. In this case, α nucleophilic attack took place by the less hindered side of the molecule. ^{1}H NMR analysis was in agreement with compound **35** chemical structure. The signal assigned as H-1, which has an adjacent quaternary carbon, appeared as a doublet centered at 3.99 ppm and a coupling constant of 5.5 Hz. This signal was coupled with the peak corresponding to H-5 that was observed as a double of triplets centered at 4.23 ppm and coupling constant values of 8.3 Hz and 5.2 Hz, respectively. Peak assignment was confirmed by 2D NMR experiments (COSY and HSQC). Compound **35** was treated with mesyl chloride in pyridine in the presence of 4-(dimethylamino)pyridine to give mesylate **36** in 54% yield. In situ generation of sulfide anion by treatment with sodium bicarbonate in a refluxing mixture of ethanol–water–tetrahydrofuran followed by intramolecular attack on the

mesylate group afforded the appropriate functionalized thiabicyclo[3.1.0]hexane system **37**. ^{1}H NMR analysis indicated that not only the desired episulfide fused to five-membered ring was obtained, but also this compound adopted a rigid boat-like conformation as had been previously observed by closely related compounds where the conformational restriction was exerted by an epoxy group or a cyclopropyl moiety.[8,11–14,26] Certainly, the peak assigned as the H-5 appeared as a singlet centered at 3.30 ppm. The lack of a measurable coupling constant in this signal indicated a dihedral angle with the adjacent proton (H5–C5–C4–H4) close to 90°. In addition, the signal corresponding to H-4 was observed as a doublet suggesting once again that one of the vicinal protons had a dihedral angle (H3β–C3–C4–H4) close to 90°. Cleavage of the MEM protecting group of **37** afforded alcohol **38** in 80% yield. Attempts to invert configuration at C-4 were not satisfactory under Mitsunobu-type conditions. Certainly, treatment of compound **38** under Mitsunobu-type conditions employing benzoic acid afforded unexpectedly benzoate **39** without inversion of configuration at C-4. Certainly, ester hydrolysis of **39** afforded alcohol **38** in 89% yield, that is, the original substrate for the Mitsunobu reaction. Bearing in mind that alcohol **38**, treated with benzoic acid under Mitsunobu-type conditions, was converted into benzoate **39** with retention of configuration, it was considered that this alcohol would lead to compound **32** by treatment with the appropriate nucleophile: N^3-benzoylthymine. Unfortunately, introduction of the heterocyclic base was not satisfactory to form **32**. Then, **38** treated with diethyl azadicarboxilate, triphenylphopsphine, and N^3-benzoylthymine at −45 °C afforded a complex mixture of products. It is worth pointing out that there are many examples of Mitsunobu reactions, which under certain circumstances undergo with retention of configuration.[27]

Finally, the title compound was successfully synthesized employing the already depicted epoxyalcohol **26**. On reaction under Mitsunobu-type conditions using diethyl azadicarboxilate, triphenylphopsphine, and ^3N-benzoylthymine added at −45 °C and stirred at room temperature overnight **26** was converted into the desired N-alkylated product **29** in 60% yield. Formation of the O-alkylated derivative was not observed. This carbonucleoside precursor was reacted with potassium thioacetate to afford the sulfur-containing derivative **30**, which treated with mesyl chloride yielded **31**. On treatment with refluxing potassium bicarbonate **31** was transformed into the carbocyclic nucleoside precursor **32**, built on the desired thiabicyclo[3.1.0]hexane system. Hydrolysis of the benzoyl group at *N*-3 and cleavage of the benzyl protecting group by treatment with boron trichloride at low temperature afforded the molecular target **8**.

Biological evaluation of the title compound indicated that this compound resulted to be a very potent antiherpetic agent showing potency comparable to acyclovir, which was used as positive control. Certainly, as shown in the Table 1, compound **8** exhibited IC_{50} values of 18.1 μM and 6.5 μM against herpes simplex virus 1, F and KOS strains, respectively, while acyclovir showed IC_{50} values of 0.9 μM and 1.1 μM, respectively. In addition, this drug showed similar potency against herpes simplex virus 2 possessing IC_{50} values of 13.4 μM and 6.7 μM against HSV-2 (MS and G strains, respectively). In this case, acyclovir presented IC50 values of 6.9 μM and 0.9 μM, respectively.

Table 1
Antiviral activity against HSV-1 and HSV-2 of **8** and acyclovir. CC_{50} (cytotoxic concentration 50%): concentration required to reduce Vero cell viability by 50%. IC_{50} (inhibitory concentration 50%): concentration required to reduce plaque number of HSV-1, strains F and KOS; HSV-1 tk$^-$ strains B2006 and Field; HSV-2, strains MS and G, in Vero cells by 50%. Each value is the mean of duplicate assays ±S.D

Compound	CC_{50} (μM)	IC_{50} (μM)					
		HSV-1 strains				HSV-2 strains	
		F	KOS	B2006	Field	MS	G
8	>220	18.1±1.0	6.5±0.3	>110	>110	13.4±1.9	6.7±0.9
Acyclovir	>220	0.9±0.2	1.1±0.2	>110	>110	6.9±1.0	0.9±0.2

In summary, we succeeded in synthesizing the title compound **8**, which resulted to be a potent antiherpetic agent as expected. Although at first sight, the synthesis of **8** seemed to be straightforward, formation of a functionalized thiabicyclo[3.1.0]hexane system proved to be not trivial and was the key step for the present synthetic approach. Compound **32** is the committed synthetic precursor to access to the target molecule. The results here presented will be relevant to prepare other important carbanucleosides built in this bicyclic rigid template. Efforts aimed at preparing closely related analogues are currently being pursued in our laboratory.

3. Experimental section

3.1. General

The glassware used in air and/or moisture sensitive reactions was flame-dried and carried out under a dry argon atmosphere. Unless otherwise noted, chemicals were commercially available and used without further purification. Solvents were distilled before use. Tetrahydrofuran and toluene were distilled from sodium/benzophenone ketyl. Anhydrous *N*,*N*-dimethylformamide was used as supplied from Aldrich.

Nuclear magnetic resonance spectra were recorded using a Bruker AC-200 MHz or a Bruker AM-500 MHz spectrometers. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane. Coupling constants are reported in Hertz. ^{13}C NMR spectra were fully decoupled. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet.

High resolution mass spectra were conducted using a Bruker micrOTOF-Q II spectrometer, 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. IR spectra were recorded using a Nicolet Magna 550 spectrometer.

Column chromatography was performed with E. Merck silica gel (Kieselgel 60, 230–400 mesh). Analytical thin layer chromatography was performed employing 0.2 mm coated commercial silica gel plates (E. Merck, DC-Aluminum sheets, Kieselgel 60 F_{254}).

*3.1.1. (±)-(1SR,2RS,5RS)-tert-Butyldiphenylsilyl 6-thiabicyclo[3.1.0]-hex-2-yl ether (**22**).* A solution of compound **19** (100 mg, 0.29 mmol) in anhydrous *N*,*N*-dimethylforamide (2 mL) was treated with potassium thioacetate (675 mg, 5.9 mmol) and the mixture was stirred at room temperature for 48 h. Then, ethyl acetate (20 mL) was added, and the mixture was washed with water (2×10 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with a mixture of hexane–EtOAc (99:1) to afford 75 mg (61% yield) of compound **20** as a non separable mixture of constitutional isomers: R_f 0.49 (hexane–EtOAc, 4:1); MS (*m*/*z*, relative intensity) 399 ([M−CH_3]$^+$, 4), 357 (71), 281 (74), 199 (100), 99 (75). To a solution of compound **20** (66 mg, 0.16 mmol) in anhydrous pyridine (2 mL), cooled at 0 °C, was added dropwise mesyl chloride (0.18 ml, 2.4 mmol) in the presence of *N*,*N*-dimethylaminopyridine (10 mg, 0.08 mmol). The mixture was partitioned between methylene chloride (10 mL) and water (10 mL). The organic layer was washed with water (2×10 mL), dried (MgSO4), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing a mixture of hexane–EtOAc (19:1) to afford 60 mg (76% yield) of **21** as a mixture of isomers. R_f 0.28 (hexane–AcOEt, 4:1); MS (*m*/*z*, relative intensity) 435 ([M−$C(CH_3)_3$]$^+$, 32), 359 (19), 339 (43), 277 (100), 199 (39), 141 (24), 99 (62), 43 (52). To a solution of **21** (50 mg, 0.10 mmol) in a mixture of EtOH–THF–H_2O (5:3:1;

9 mL) was added sodium bicarbonate (17 mg, 0.20 mmol), and the reaction mixture was refluxed for 2 h. The solvent was evaporated and the residue was partitioned between water (10 mL) and methylene chloride (10 mL). The organic phase was washed with water (2×10 mL), dried ($MgSO_4$), and the solvent was evaporated. The product was purified by column chromatography (silica gel) eluting with a mixture of hexane–EtOAc (19.9:0.1) to afford 34 mg (96% yield) of pure compound **22**. Physical and spectroscopic data matched those previously published.[20]

*3.1.2. (1S,2S,4S,5R)-4-(Benzyloxy)-5-((benzyloxy)methyl)-6-oxabicyclo[3.1.0]hexan-2-ol (**24**).* To a solution of compound **23** (977 mg, 3.15 mmol) in methylene chloride (60 mL) cooled at 0 °C was added a solution of 50% of *m*-chloroperbenzoic acid (1.30 g, 3.8 mmol) in methylene chloride (100 mL). The mixture was allowed to warm to room temperature and the reaction mixture was stirred for 3 h. Then, the organic phase was washed with a saturated solution of sodium bicarbonate (3×70 mL) and water (3×70 mL). The organic layer was dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with a mixture of hexane–EtOAc (7:3) to afford 840 mg (82% yield) of pure compound **24** as a white solid: R_f 0.50 (hexane–EtOAc, 1:1); mp 74 °C; $[\alpha]_D^{25}$ +21.8 (*c* 0.9, $CHCl_3$), ^{1}H NMR(500.13 MHz, $CDCl_3$) δ 1.48 (ddd, *J*=13.9, 8.2, 5.6 Hz, 1H, H-3$_a$), 2.20 (dd, *J*=14.0, 7.8 Hz, 1H, H-3$_b$), 3.48 (d, *J*=11.5 Hz, 1H, OCHH_aBn), 3.50 (s, 1H, H-1), 4.23 (d, *J*=11.3 Hz, 1H, OCHH_bBn), 4.24 (d, *J*=6.0 Hz, 1H, H-4), 4.47 (d, *J*=11.7 Hz, 1H, OCHH_aPh), 4.52 (t, *J*=7.7 Hz, 1H, H-2), 4.55 (d, *J*=12.1 Hz, 1H, OCHH_aPh), 4.58 (d, *J*=11.7 Hz, 1H, OCHH_bPh), 4.67 (d, *J*=12.1 Hz, 1H, OCHH_bPh), 7.35–7.26 (m, 10H, aromatic protons); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 33.6 (C-3), 61.7 (C-1), 66.4 (BnOCH_2), 66.5 (C-5), 71.9 (C-2), 72.1 (PhCH_2O), 73.3 (PhCH_2O), 77.6 (C-4), 127.66 (Ph), 127.69 (Ph), 127.76 (Ph), 127.77 (Ph), 128.38 (Ph), 128.43 (Ph), 137.87 (Ph), 137.93 (Ph); MS (*m*/*z*, relative intensity) 235 ([M−Bn]$^+$, 3), 107 (21), 91 (100), 77 (11), 65 (20). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found C, 73.59; H, 6.57.

*3.1.3. (1S,2R,4S,5R)-4-(Benzyloxy)-5-((benzyloxy)methyl)-6-oxa-bicyclo[3.1.0]hexan-2-yl Benzoate (**25**).* To a solution of benzoic acid (98 mg, 0.8 mmol) and diethyl azodicarboxylate (157 μL, 1.0 mmol) in anhydrous toluene (2 mL) was added triphenylphosphine (262 mg, 1.0 mmol) under an argon atmosphere. The reaction mixture was cooled at 0 °C and a solution of **24** (163 mg, 0.5 mmol) in toluene (1 mL) was added. The reaction mixture was stirred at room temperature for 28 h. The solvent was evaporated, and the residue was purified by column chromatography (silica gel) employing a mixture of hexane–EtOAc (19:1) as eluent to afford 114 mg (53% yield) of compound **25** as a colorless oil: R_f 0.65 (hexane–AcOEt, 7:3); $[\alpha]_D^{25}$ +71.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 2.09 (m, 2H, H-3), 3.57 (d, *J*=11.4 Hz, 1H, CHH_bOBn), 3.70 (s, 1H, H-1), 4.28 (d, *J*=4.3 Hz, 1H, H-4), 4.38 (d, *J*=11.5 Hz, 1H, CHH_aOBn), 4.53 (d, *J*=11.9 Hz, 1H, PhCH_aHO), 4.56 (d, *J*=12.6 Hz, 1H, PhCH'_aHO), 4.62 (d, *J*=11.7 Hz, 1H, PhCH_bHO), 4.67 (d, *J*=12.0 Hz, 1H, PhCH'_bHO), 5.41 (d, *J*=5.5 Hz, 1H, H-2), 7.25–7.36 (m, 10H, aromatic protons), 7.39 (t, *J*=7.8 Hz, 2H, aromatic protons), 7.54 (tt, *J*=7.4, 1.2 Hz, 1H, aromatic proton), 8.00 (dd, *J*=8.3, 1.2 Hz, 2H, aromatic protons); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 34.8 (C-3), 59.7 (C-1), 66.3 (BnOCH_2), 67.6 (C-5), 71.5 (PhCH_2O), 73.3 (PhCH_2O), 73.4 (C-4), 77.0 (C-2), 127.5 (Ph), 127.5 (Ph), 127.6 (Ph), 127.7 (Ph), 128.3 (Ph), 128.3 (Ph), 128.3 (Ph), 129.8 (Ph), 129.9 (Ph), 133.1 (Ph), 138.0 (Ph), 138.1 (Ph), 165.9 (O*C*OPh); MS (*m*/*z*, relative intensity) 431 ([MH]$^+$, 2), 339 (71), 233 (49), 218 (16), 201 (16), 184 (8), 111 (24), 105 (92), 91 (100), 77 (56), 65 (33). Anal. Calcd for $C_{27}H_{26}O_5$: C, 75.33; H, 6.09. Found C, 75.31; H, 6.01.

*3.1.4. (1S,2R,4S,5R)-4-(Benzyloxy)-5-((benzyloxy)methyl)-6-oxa-bicyclo[3.1.0]hexan-2-ol (**26**).* Compound **25** (114 mg, 0.26 mmol) was treated with methanolic ammonia (10 mL, saturated at −78 °C) in a sealed tube. The reaction mixture was stirred at 40 °C for 13 h. The mixture was cooled to room temperature and the solvent was evaporated. The product was purified by column chromatography (silica gel) eluting with a mixture of hexane–EtOAc (9:1) to afford 77 mg (90% yield) of compound **26** as a white solid: R_f 0.46 (hexane–EtOAc, 1:1); mp 63–64 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.85 (m, 2H, H-3), 2.03 (d, *J*=10.9 Hz, 1H, *OH*), 3.50 (s, 1H, H-1), 3.51 (d, *J*=11.8 Hz, 1H, BnOCH_aH), 4.24 (m, 1H, H-4), 4.27 (m, 1H, H-2), 4.36 (d, *J*=11.5 Hz, 1H, BnOCH_bH), 4.54 (d, *J*=12.1 Hz, 1H, PhCH_aHO), 4.55 (d, *J*=12.1 Hz, 1H, PhCH'_aHO), 4.58 (d, *J*=11.7 Hz, 1H, PhCH_bHO), 4.63 (d, *J*=11.7 Hz, 1H, PhCH_bHO), 4.65 (d, *J*=12.1 Hz, 1H, PhCH'_aHO), 7.35–7.25 (m, 10H, aromatic protons); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 36.3 (C-3), 60.7 (C-1), 66.2 (C-2), 66.7 (C-5), 71.6 (BnOCH_2), 72.1 (PhCH_2O), 73.3 (PhCH_2O), 77.8 (C-4), 127.7 (Ph), 127.8 (Ph), 127.9 (Ph), 128.4 (Ph), 128.5 (Ph), 137.6 (Ph), 137.9 (Ph); MS (*m*/*z*, relative intensity) 235 ([M−Bn]$^+$, 33), 107 (46), 91 (100), 77 (21), 65 (41). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found C, 73.61; H, 6.90.

*3.1.5. (1S,2S,4S,5R)-5-Methyl-1-{4-(benzyloxy)-5-[(benzyloxy)methyl]-6-oxabicyclo[3.1.0]hex-2-yl}-3-(benzoyl)-1,3-dihydropyrimidine-2,4-dione (**29**).* A solution of triphenylphosphine (125 mg, 0.475 mmol) in anhydrous tetrahydrofuran (2 mL) was treated with diethyl azodicarboxylate (75 μL, 0.475 mmol) and stirred at 0 °C for 30 min. After cooling to −45 °C, a solution of N^3-benzoylthymine (88 mg, 0.38 mmol) and alcohol **26** (62 mg, 0.19 mmol) in tetrahydrofuran (1 mL) was added via cannula over 15 min. The mixture was stirred at −45 °C for 2 h. The reaction mixture was warmed to room temperature and stirred overnight. The solvent was evaporated and the residue was purified by flash chromatography using hexane–EtOAc (4:1) as eluent to give 61 mg (60% yield) of the desired N-alkylated product (compound **29**) as a colorless oil with traces of reduced DEAD: R_f 0.60 (hexane–EtOAc, 1:1); $[\alpha]_D^{23}$ +9.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.60 (ddd, *J*=13.9, 9.7, 5.2 Hz, 1H, H-3′$_a$), 1.97 (d, *J*=1.1 Hz, 3H, CH_3 at C-5), 2.33 (dd, *J*=13.8, 8.1 Hz, 1H, H-3′$_b$), 3.57 (d, *J*=11.4 Hz, 1H, BnOCH_aH), 3.67 (s, 1H, H-1′), 4.25 (d, *J*=11.4 Hz, 1H, BnOCH_bH), 4.32 (d, *J*=5.2 Hz, 1H, H-4′), 4.46 (d, *J*=11.6 Hz, 1H, PhCH_bHO), 4.57 (d, *J*=12,0 Hz, 1H, PhCH'_aHO), 4.60 (d, *J*=11.6 Hz, 1H, PhCH_bHO), 4.64 (d, *J*=12.0 Hz, 1H, PhCH'_bHO), 5.33 (ddd, *J*=9.2, 8.4, 0.8 Hz, 1H, H-2′), 7.24–7.38 (m, 10H, aromatic protons), 7.50 (m, 1H, aromatic proton), 7.57 (d, *J*=1.1 Hz, 1H, H-6), 7.64 (tt, *J*=7.4, 1.1 Hz, 2H, aromatic protons), 7.93 (dd, *J*=8.4, 1.3 Hz, 2H, aromatic protons); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 12.6 (*C*H$_3$ at C-5), 31.5 (C-3′), 54.2 (C-2′), 59.6 (C-1′), 65.2 (C-5′), 65.6 (BnOCH_2), 72.1 (PhCH_2O), 73.5 (PhCH_2O), 76.6 (C-4′), 111.6 (C-5), 127.7 (Ph), 127.7 (Ph), 127.8 (Ph), 127.9 (Ph), 128.4 (Ph), 128.5 (Ph), 129.1 (Ph), 130.4 (Ph), 131.6 (Ph), 135.0 (Ph), 136.8 (C-6), 137.3 (Ph), 137.6 (Ph), 150.0 (C-2), 162.7 (C-4), 169.0 (*C*OPh); MS (*m*/*z*, relative intensity) 538 (M$^+$, 2), 447 (3), 341 (3), 237 (7), 105 (100), 91 (82); HRMS (ESI) Calcd for ($C_{32}H_{31}N_2O_6$) [M+H]$^+$: 539.2182; found 539.2178.

*3.1.6. (1R,2R,3S,5S)-5-Methyl-1-[5-amino-3-(benzyloxy)-2-((benzyloxy)methyl)-2-hydroxy-1-acetylmercaptocyclopent-5-yl]-3-(benzoyl)-1,3-dihydropyrimidine-2,4-dione (**30**).* A solution of **29** (61 mg, 0.11 mmol) in anhydrous *N*,*N*-dimethylformamide (3 mL) was treated with potassium thioacetate (130 mg, 1.1 mmol). The mixture was stirred at 60 °C for 8 h. The reaction was quenched by addition of an aqueous saturated solution of sodium bicarbonate (5 mL). The mixture was extracted with methylene chloride (3×5 mL), and the combined organic layers were washed with water (2×5 mL), dried ($MgSO_4$), and the solvent was evaporated. The product was purified by column chromatography (silica gel) employing a mixture of hexane–EtOAc (4:1) to afford 42 mg (61% yield) of compound **30** as a colorless oil: R_f 0.49 (hexane–EtOAc,

1:1); $[\alpha]_D^{23}$ +11.5 (*c* 1.0, $CHCl_3$); ^1H NMR (500.13 MHz, $CDCl_3$) δ 1.99 (d, *J*=1.0 Hz, 3H, C*H*$_3$ at C-5), 2.21 (m, 1H, H-2′$_a$), 2.29 (s, 3H, C*H*$_3$CO), 2.41 (ddd, *J*=13.6, 9.1, 2.2 Hz, 1H, H-2′$_b$), 3.26 (s, 1H, O*H*), 3.57 (d, *J*=9.2 Hz, 1H, BnOC*H*$_a$H), 3.77 (d, *J*=9.2 Hz, 1H, BnOC*H*$_b$H), 4.03 (m, 2H, H-3′, H-5′), 4.46 (d, *J*=12.0 Hz, 1H, PhC*H*$_a$HO), 4.56 (m*AB*, 2H, PhC*H*$_2$O), 4.60 (d, *J*=12.0 Hz, 1H, PhC*H*$_b$HO), 5.21 (s, 1H, H-1′), 7.24–7.37 (m, 10H, aromatic protons), 7.48 (m, 2H, aromatic protons), 7.51 (br s, 1H, H-6), 7.62 (tt, *J*=7.5, 1.2 Hz, 1H, aromatic proton), 8.00 (d, *J*=7.3 Hz, 2H, aromatic protons); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 12.7 (*C*H$_3$), 30.2 (*C*H$_3$COS), 33.8 (C-2′), 52.7 (C-5′), 63.2 (C-1′), 69.5 (BnO*C*H$_2$), 71.2 (Ph*C*H$_2$O), 73.7 (Ph*C*H$_2$O), 82.5 (C-4′), 82.9 (C-3′), 111.7 (C-5), 127.3 (Ph), 127.7 (Ph), 127.7 (Ph), 128.0 (Ph), 128.4 (Ph), 128.5 (Ph), 129.0 (Ph), 130.7 (Ph), 131.6 (Ph), 134.8 (Ph), 137.4 (C-6), 137.7 (Ph), 150.0 (C-2), 162.7 (C-4), 169.2 (Ph*C*O), 194.8 (CH$_3$*C*OS); MS (*m*/*z*, relative intensity) 539 (M^+−SC(O)CH$_3$, 1), 435 (2), 309 (5), 217 (10), 181 (9), 127 (27), 105 (79), 91 (100). HRMS (ESI) Calcd for ($C_{34}H_{35}N_2O_7S$) $[M+H]^+$: 615.2165; found 615.2149.

*3.1.7. (1R,2R,3S,5S)-5-Methyl-1-[5-amino-3-(benzyloxy)-2-((benzyloxy)methyl)-2-methanesulfonyloxy-1-acetylmercaptocyclopent-5-yl]-3-(benzoyl)-1,3-dihydropyrimidine-2,4-dione (**31**).* To a solution of **30** (49 mg, 0.08 mmol) in anhydrous pyridine (1 mL) in the presence of 4-*N*,*N*-dimethylaminopyridine (5 mg, 0.04 mmol) was added mesyl chloride (0.19 ml, 2.4 mmol). The reaction mixture was stirred at room temperature for 6 h. Then, methylene chloride (3 mL) was added and the mixture was washed with an aqueous 1.0 N solution of hydrochloric acid (2×3 mL), an aqueous saturated solution of sodium bicarbonate (3 mL), and brine (3 mL). The organic phase was dried ($MgSO_4$), and the solvent was evaporated to afford 43 mg (78% yield) of compound **31** that was used in the next step without further purification: R_f 0.47 (hexane–EtOAc, 1:1); ^1H NMR (500.13 MHz, $CDCl_3$) δ 1.98 (d, *J*=1.0 Hz, 3H, C*H*$_3$ at C-5), 2.29 (s, 3H, C*H*$_3$CO), 2.35 (m, 2H, H-2′), 3.04 (s, 3H, SC*H*$_3$), 3.93 (d, *J*=10.2 Hz, 1H, BnOC*H*$_a$H), 4.78 (d, *J*=10.2 Hz, 1H, BnOC*H*$_b$H); HRMS (ESI) Calcd for ($C_{35}H_{37}N_2O_9S_2$) $[M+H]^+$: 693.1940; found 693.1938.

*3.1.8. (1R,2S,4S,5S)-5-Methyl-1-{4-(benzyloxy)-5-[(benzyloxy)methyl]-6-thiabicyclo[3.1.0]hex-2-yl}-3-(benzoyl)-1,3-dihydropyrimidine-2,4-dione (**32**).* To a solution of **31** (39 mg, 0.06 mmol) in 2 mL of a mixture of ethanol–tetrahydrofuran–water (5:3:1) was added sodium bicarbonate (10 mg, 0.11 mmol). The reaction mixture was refluxed for 7 h. The solvent was evaporated and the residue was partitioned between water (10 mL) and methylene chloride (10 mL). The organic phase was washed with water (2×10 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with a mixture of hexane–EtOAc (85:15) to give 15 mg (48% yield) of pure **32** as a white solid: R_f 0.52 (hexane–EtOAc, 3:2); mp 43–45 °C; ^1H NMR (500.13 MHz, $CDCl_3$) δ 1.45 (d, *J*=1.1 Hz, 1H, C*H*$_3$ at C-5), 2.02 (dd, *J*=14.6, 7.5 Hz, 1H, H-3′$_a$), 2.28 (dt, *J*=14.8, 8.1 Hz, 1H, H-3′$_b$), 3.18 (s, 1H, H-1′), 3.47 (d, *J*=9.8 Hz, 1H, BnOC*H*$_a$H), 4.30 (d, *J*=9.8 Hz, 1H, BnOC*H*$_b$H), 4.48 (d, *J*=11.2 Hz, 1H, PhC*H*$_a$HO), 4.51 (d, *J*=11.2 Hz, 1H, PhC*H*$_b$HO), 4.53 (d, *J*=12.1 Hz, 1H, PhC*H*′$_a$HO), 4.67 (d, *J*=12.1 Hz, 1H, PhC*H*′$_b$HO), 4.81 (t, *J*=8.0 Hz, 1H, H-4′), 5.23 (d, *J*=7.6 Hz, 1H, H-2′), 7.22 (dd, *J*=7.6, 1.8 Hz, 2H, aromatic protons), 7.32–7.42 (m, 8H, aromatic protons), 7.47 (d, *J*=1.4 Hz, 1H, H-5), 7.48 (m, 2H, aromatic protons), 7.64 (tt, *J*=7.5, 1.3 Hz, 1H, aromatic proton), 7.89 (dd, *J*=8.4, 1.3 Hz, 2H, aromatic protons); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 11.8 (*C*H$_3$ at C-5), 35.1 (C-3′), 44.8 (C-1′), 56.0 (C-2′), 56.1 (C-5′), 71.9 (BnO*C*H$_2$), 72.5 (Ph*C*H$_2$O), 74.0 (Ph*C*H$_2$O), 76.2 (C-4′), 111.6 (C-5), 127.8 (Ph), 128.1 (Ph), 128.3 (Ph), 128.4 (Ph), 128.6 (Ph), 128.7 (Ph), 129.1 (Ph), 130.4 (Ph), 131.6 (Ph), 135.0 (Ph), 136.5 (C-6), 137.1 (Ph), 137.9 (Ph), 149.7 (C-2), 162.6 (C-4), 169.0 (*C*OPh); MS (*m*/*z*, relative intensity) 555 (M^++1, 1), 415 (56), 308 (33), 231 (33), 204 (42), 181 (48), 160 (48), 127 (51), 105 (100). HRMS (ESI) Calcd for ($C_{32}H_{31}N_2O_5S$) $[M+H]^+$: 555.1954; found 555.1929.

*3.1.9. (1R,2S,4S,5S)-5-Methyl-1-{4-(benzyloxy)-5-[(benzyloxy)methyl]-6-thiabicyclo[3.1.0]hex-2-yl}-1,3-dihydropyrimidine-2,4-dione (**33**).* Compound **32** (15 mg, 0.027 mmol) was treated with methanolic ammonia (5 mL, saturated at −78 °C) and stirred in a sealed tube at 0 °C for 2 h. The solvent was evaporated and the residue was purified by column chromatography (silica gel) using a mixture of EtOAc–methanol (95:5) as eluent to afford 13 mg (100% yield) of pure compound **33** as a syrup: R_f 0.28 (hexane–EtOAc, 1:1); $[\alpha]_D^{23}$ −15.0 (*c* 1.0, $CHCl_3$); ^1H NMR (500.13 MHz, $CDCl_3$) δ 1.44 (d, *J*=0.9 Hz, 1H, C*H*$_3$ at C-5), 1.95 (dd, *J*=14.6, 7.6 Hz, 1H, H-3′$_a$), 2.27 (dt, *J*=14.8, 8.1 Hz, 1H, H-3′$_b$), 3.12 (s, 1H, H-1′), 3.45 (d, *J*=10.1 Hz, 1H, BnOC*H*$_a$H), 4.27 (d, *J*=9.8 Hz, 1H, BnOC*H*$_b$H), 4.46 (d, *J*=11.0 Hz, 1H, PhC*H*$_a$HO), 4.49 (d, *J*=11.2 Hz, 1H, PhC*H*$_b$HO), 4.51 (d, *J*=12.1 Hz, 1H, PhC*H*′$_a$HO), 4.65 (d, *J*=12.1 Hz, 1H, PhC*H*′$_b$HO), 4.77 (t, *J*=8.0 Hz, 1H, H-4′), 5.21 (d, *J*=7.6 Hz, 1H, H-2′), 6.09 (br s, 1H, N*H*), 7.21 (dd, *J*=7.1, 2.1 Hz, 2H, aromatic protons), 7.30–7.39 (m, 9H, aromatic protons, H-5), 7.45 (t, *J*=7.6 Hz, 1H, aromatic proton); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 11.7 (*C*H$_3$ at C-5), 35.0 (C-3′), 44.9 (C-1′), 55.8 (C-2′), 56.2 (C-5′), 71.9 (BnO*C*H$_2$), 72.5 (Ph*C*H$_2$O), 73.9 (Ph*C*H$_2$O), 76.4 (C-4′), 111.5 (C-5), 127.8 (Ph), 128.0 (Ph), 128.3 (Ph), 128.5 (Ph), 128.6 (Ph), 132.0 (Ph), 136.8 (C-6), 137.1 (Ph), 137.9 (Ph), 150.7 (C-2), 163.6 (C-4); HRMS (ESI) Calcd for ($C_{25}H_{27}N_2O_4S$) $[M+H]^+$: 451.1692; found 451.1692.

*3.1.10. (1R,2S,4S,5S)-5-Methyl-1-{4-hydroxy-5-[(hydroxy)-methyl]-6-thiabicyclo[3.1.0]hex-2-yl}-1,3-dihydropyrimidine-2,4-dione (**8**).* A solution of compound **37** (13 mg, 0.03 mmol) in anhydrous methylene chloride (3 mL) was cooled to −78 °C under argon, treated with boron trichloride (1.0 M in hexane, 3.00 mL), and stirred at −78 °C for 4 h. Methanol (4 mL) was added while the temperature was still at −78 °C, and the mixture was allowed to reach room temperature. The solvent was removed, and additional amount of methanol (6×4 mL) were added and evaporated successively. The residue was purified by column chromatography (silica gel) employing a mixture of EtOAc–methanol (49:1) as eluent to afford 4.2 mg (51% yield) of pure compound **8** as a white solid: mp 120–125 °C; $[\alpha]_D^{23}$ −12.8 (*c* 0.8, methanol); UV (MeOH) $\lambda_{máx}$ 273 nm; R_f 0.25 (EtOAc–methanol, 49:1); ^1H NMR (500.13 MHz, CD_3OD–$CDCl_3$) δ 1.85 (d, *J*=1.1 Hz, 3H, C*H*$_3$ at C-5), 1.97 (dd, *J*=14.6, 8.1 Hz, 1H, H-3′$_a$), 2.15 (dt, *J*=14.5, 7.9 Hz, 1H, H-3′$_b$), 3.21 (s, 1H, H-1′), 3.55 (d, *J*=12.0 Hz, 1H, C*H*$_a$HOH), 4.27 (d, *J*=12.0 Hz, 1H, C*H*$_b$HOH), 4.94 (d, *J*=7.7 Hz, 1H, H-2′), 4.95 (t, *J*=8.1 Hz, 1H, H-4′), 7.46 (d, *J*=1.4 Hz, 1H, H-6); ^{13}C NMR (125.77 MHz, CD_3OD–$CDCl_3$) δ 12.3 (*C*H$_3$ at C-5), 37.3 (C-3′), 46.4 (C-1′), 58.1 (C-2′), 61.0 (C-5′), 61.6 (*C*H$_2$OH), 70.3 (C-4′), 111.4 (C-5), 138.7 (C-6), 151.5 (C-2); HRMS (ESI) Calcd for ($C_{11}H_{15}N_2O_4S$) $[M+H]^+$: 271.0753; found 271.0749.

*3.1.11. (1R,2S,4S,5S)-4-((2-Methoxyethoxy)methoxy)-2-(benzyloxy)-1-((benzyloxy)methyl)-6-oxabicyclo[3.1.0]hexane (**34**).* A solution of **24** (840 mg, 2.6 mmol) in anhydrous tetrahydrofuran (15 mL) was added to 50% sodium hydride (310 mg, 6.5 mmol), previously washed with anhydrous hexane (2×2 mL) under argon. The mixture was stirred at room temperature for 1 h. Then, methoxyethyl chloromethyl ether (MEMCl; 450 μL, 3.9 mmol) was added, and the reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated and the residue was partitioned between methylene chloride (15 mL) and water (15 mL). The organic phase was dried ($MgSO_4$), and the solvent was evaporated. The product was purified by column chromatography (silica gel) employing a mixture of hexane–EtOAc (4:1) as eluent to afford 850 mg (80% yield) of compound **34** as a colorless oil: R_f 0.71 (hexane–EtOAc, 1:1); $[\alpha]_D^{23}$ +14.9 (*c* 1.9, $CHCl_3$); ^1H NMR (500.13 MHz, $CDCl_3$) δ 1.63 (ddd, *J*=13.9, 8.4, 5.5 Hz, 1H, H-3$_a$), 2.15 (dd, *J*=13.8, 7.8 Hz, 1H, H-3$_b$),

3.39 (s, 3H, OCH_3), 3.47 (d, J=11.5 Hz, 1H, BnOCH_aH), 3.57 (t, J=4.6 Hz, 2H, CH_2OCH$_3$), 3.60 (s, 1H, H-1), 3.67 (dt, J=11.3, 4.8 Hz, 1H, OCH_aHCH$_2$), 3.83 (dt, J=11.3, 4.8 Hz, 1H, OCH_bHCH$_2$), 4.22 (d, J=5.5 Hz, 1H, H-4), 4.25 (d, J=11.5 Hz, 1H, BnOCH_bH), 4.38 (dt, J=8.1, 1.0 Hz, 1H, H-2), 4.47 (d, J=11.5 Hz, 1H, PhCH_aHO), 4.54 (d, J=12.1 Hz, 1H, PhCH'_aHO), 4.59 (d, J=11.7 Hz, 1H, PhCH_bHO), 4.65 (d, J=12.1 Hz, 1H, PhCH'_bHO), 4.79 (d, J=7.1 Hz, 1H, OCH_aHO), 4.83 (d, J=7.1 Hz, 1H, OCH_aHO), 7.27–7.33 (m, 10H, aromatic protons); ^{13}C NMR (125.77 MHz, CDCl$_3$) δ 32.6 (C-3), 59.0 (OCH$_3$), 60.0 (CH_2OCH$_3$), 65.6 (C-5), 66.5 (BnOCH_2), 66.9 (C-2), 71.7 (OCH_2CH$_2$), 72.0 (PhCH_2O), 73.2 (PhCH_2O), 77.0 (C-2), 77.2 (C-4), 95.3 (OCH_2O), 127.6 (Ph), 127.7 (Ph), 127.8 (Ph), 128.4 (Ph), 128.4 (Ph), 137.97 (Ph), 138.03 (Ph); MS (m/z, relative intensity) 339 ([M−CH$_3$OCH$_2$CH$_2$OH]$^+$, 1), 105 (79), 91 (100), 89 (84). HRMS (ESI) Calcd for ($C_{24}H_{30}O_6$Na) [M+Na]$^+$: 437.1940; found 437.1921.

*3.1.12. S-(1R,2R,3S,5S)-5-((2-Methoxyethoxy)methoxy)-3-(benzyloxy)-2-((benzyloxy)methyl)-2-hydroxycyclopentyl ethanethioate (**35**).* To a solution of **34** (835 mg, 2.0 mmol) in anhydrous *N,N*-dimethylformamide (20 mL) was added potassium thioacetate (7.00 g, 60 mmol). The mixture was stirred at 60 °C for 25 h. Then, an aqueous saturated solution of sodium bicarbonate (10 mL) was added and the mixture was extracted with methylene chloride (3×15 mL). The combined organic phases were washed with water (2×5 mL), dried (MgSO$_4$), and the solvent was evaporated. The product was purified by column chromatography (silica gel) eluting with a mixture of hexane–EtOAc (4:1) to afford 850 mg (85% yield) of pure **35** as a colorless oil: R_f 0.50 (hexane–AcOEt, 1:1); $[\alpha]_D^{23}$ +14.5 (c 1.0, CHCl$_3$); ^{1}H NMR (500.13 MHz, CDCl$_3$) δ 2.12 (ddd, J=13.9, 6.5, 5.5 Hz, 1H, H-4$_a$), 2.32 (m, 1H, H-4$_b$), 2.33 (s, 3H, CH_3COS), 3.38 (s, 3H, OCH_3), 3.53 (m, 2H, CH_2OCH$_3$),3.64 (m*AB*, 2H, BnOCH_2), 3.68 (m, 2H, OCH_2CH$_2$), 3.99 (d, J=5.5 Hz, 1H, H-1), 4.02 (t, J=5.8 Hz, 1H, H-3), 4.23 (dt, J=8.3, 5.2 Hz, 1H, H-5), 4.53 (m*AB*, 2H, PhCH_2O), 4.54 (d, J=12.1 Hz, 1H, PhCH_aHO), 4.59 (d, J=12.1 Hz, 1H, PhCH_bHO), 4.71 (d, J=7.1 Hz, 1H, OCH_aHO), 4.75 (d, J=7.1 Hz, 1H, OCH_bHO), 7.27–7.34 (m, 10H, aromatic protons); ^{13}C NMR (125.77 MHz, CDCl$_3$) δ 30.2 (CH$_3$COS), 36.1 (C-4), 55.1 (C-1), 59.0 (OCH$_3$), 67.0 (CH_2OCH$_3$), 70.3 (BnOCH_2), 71.4 (PhCH_2O), 71.7 (OCH_2CH$_2$), 73.6 (PhCH_2O), 80.7 (C-5), 82.6 (C-2), 83.6 (C-3), 94.7 (OCH_2O), 127.4 (Ph), 127.5 (Ph), 127.6 (Ph), 127.6 (Ph), 128.3 (Ph), 128.3 (Ph), 137.9 (Ph), 138.3 (Ph), 196.2 (CH$_3$C(O)S); HRMS (ESI) Calcd for ($C_{26}H_{34}O_7$SNa) [M+Na]$^+$: 513.1923; found 513.1896.

*3.1.13. S-(1R,2R,3S,5S)-5-((2-Methoxyethoxy)methoxy)-3-(benzyloxy)-2-((benzyloxy)methyl)-2-methanesulfonyloxycyclopentyl ethanethioate (**36**).* To a solution of compound **35** (795 mg, 1.62 mmol) in anhydrous pyridine (15 mL) in the presence of 4-*N,N*-dimethylaminopyridine (99 mg, 0.8 mmol) cooled at 0 °C was added mesyl chloride (3.8 mL, 48.7 mmol) dropwise. The reaction mixture was stirred at room temperature for 24 h. Then, methylene chloride (30 mL) was added and the mixture was washed with an aqueous 1.0 N solution of hydrochloric acid (3×20 mL) and water (3×20 mL). The organic phase was dried (MgSO$_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing a mixture of hexane–EtOAc (3:1) as eluent to afford 448 mg (48% yield) of pure compound **36** as a yellow pale oil: R_f 0.43 (hexane–EtOAc, 1:1); $[\alpha]_D^{23}$ +15.8 (c 1.0, CHCl$_3$); ^{1}H NMR (500.13 MHz, CDCl$_3$) δ 2.12 (ddd, J=14.0, 6.6, 5.2 Hz, 1H, H-4$_a$), 2.32 (m, 1H, H-4$_b$), 2.33 (s, 3H, CH_3C(O)S), 3.04 (s, 3H, CH_3SO$_2$), 3.37 (s, 3H, OCH_3), 3.52 (distorted t, J=4.5 Hz, 2H, CH_2OCH$_3$), 3.66 (dd, J=11.2, 4.3 Hz, 1H,,BnOCH_aH), 3.70 (dd, J=11.2, 4.8 Hz, 1H, BnOCH_bHO), 3.96 (d, J=10.1 Hz, 1H, PhCH_aHO), 4.17 (d, J=10.1 Hz, 1H, PhCH_bHO), 4.26 (dt, J=8.3, 4.9 Hz, 1H, H-5), 4.53–4.58 (m, 6H, PhCH_2O, H-1, H-3), 4.59 (d, J=5.0 Hz, 1H, H-5), 4.68 (d, J=7.1 Hz, 1H, OCH_aHO), 4.73 (d, J=7.0 Hz, 1H, OCH_bHO), 7.26–7.35 (m, 10H, aromatic protons); ^{13}C NMR (125.77 MHz, CDCl$_3$) δ 30.2 (CH_3COS), 36.2 (C-4), 40.6 (CH_3SO$_2$), 52.7 (C-1), 59.0 (OCH$_3$), 67.1 (CH_2OCH$_3$), 67.6 (BnOCH$_2$), 71.7 (OCH_2CH$_2$), 72.0 (PhCH_2O), 73.6 (PhCH_2O), 81.5 (C-5), 81.9 (C-3), 94.7 (OCH_2O), 98.7 (C-2), 127.5 (Ph), 127.6 (Ph), 127.66 (Ph), 127.68 (Ph), 128.4 (Ph), 137.6 (Ph), 137.9 (Ph), 193.3 (CH$_3$C(O)S); HRMS (ESI) Calcd for ($C_{27}H_{36}NaO_9S_2$) [M+Na]$^+$: 591.1698; found 591.1679.

*3.1.14. (1S,2S,4S,5R)-4-((2-methoxyethoxy)methoxy)-2-(benzyloxy)-1-((benzyloxy)methyl)-6-thiabicyclo[3.1.0]hexane (**37**).* To a solution of **360** (448 mg, 0.8 mmol) in a mixture of ethanol–tetrahydrofuran–water (5:3:1; 16 mL) was added sodium bicarbonate (133 mg, 1.6 mmol). The reaction mixture was refluxed for 13 h. The solvent was evaporated and the residue was partitioned between water (10 mL) and methylene chloride (10 mL). The organic phase was washed with water (2×10 mL), dried (MgSO$_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with hexane–EtOAc (19:1) to afford 146 mg (43% yield) of pure compound **37** as a colorless oil: R_f 0.60 (hexane–EtOAc, 3:2); $[\alpha]_D^{23}$ +21.5 (c 0.9, CHCl$_3$); ^{1}H NMR (500.13 MHz, CDCl$_3$) δ 1.92 (ddd, J=13.8, 8.6, 5.2 Hz, 1H, H-3$_a$), 1.99 (dd, J=13.8, 7.3 Hz, 1H, H-3$_b$), 3.30 (br s, 1H, H-5), 3.37 (s, 3H, OCH_3), 3.48 (d, J=10.7 Hz, 1H, BnOCH_aH), 3.49 (m, 2H, CH_2OCH$_3$), 3.60 (ddd, J=10.9, 5.6, 3.7 Hz, 1H, OCH_aHCH$_2$), 3.73 (ddd, J=10.9, 5.7, 3.5 Hz, 1H, OCH_bHCH$_2$), 4.16 (d, J=10.8 Hz, 1H, BnOCH_bH), 4.31 (d, J=5.0 Hz, 1H, H-4), 4.49 (d, J=11.9 Hz, 1H, PhCH_aHO), 4.58 (d, J=12.1 Hz, 1H, PhCH'_aHO), 4.60 (d, J=12.0 Hz, 1H, PhCH_bHO), 4.63 (d, J=12.2 Hz, 1H, PhCH'_bHO), 4.70 (dd, J=8.5, 7.3 Hz, 1H, H-2), 4.76 (d, J=7.1 Hz, 1H, OCH_aHO), 4.78 (d, J=7.1 Hz, 1H, OCH_bHO), 7.26–7.35 (m, 10H, aromatic protons); ^{13}C NMR (125 MHz, CDCl$_3$) δ 34.0 (C-3), 45.9 (C-5), 55.6 (C-1), 59.0 (OCH$_3$), 67.0 (CH_2OCH$_3$), 71.5 (BnOCH_2), 71.6 (OCH_2CH$_2$), 72.3 (PhCH_2O), 72.8 (PhCH_2O), 77.3 (C-4), 78.2 (C-2), 94.9 (OCH_2O), 127.6 (Ph), 127.6 (Ph), 127.7 (Ph), 127.7 (Ph), 128.3 (Ph), 128.3 (Ph), 138.0 (Ph), 138.5 (Ph); HRMS (ESI) Calcd for ($C_{24}H_{31}O_5$S) [M+H]$^+$: 431.1892; found 431.1874.

*3.1.15. (1R,2S,4S,5S)-4-(Benzyloxy)-5-[(benzyloxy)methyl]-6-thiabicyclo[3.1.0]hexan-2-ol (**38**). Method A.* A solution of **37** (146 mg, 0.34 mmol) in *tert*-butanol (4 mL) was treated with *p*-toluenesulfonic acid (100 mg, 0.57 mmol) and the mixture was refluxed for 8 h. The solvent was evaporated and the residue was partitioned between an aqueous saturated solution of sodium bicarbonate (10 mL) and methylene chloride (10 mL). The aqueous layer was extracted with methylene chloride (2×10 mL), and the combined organic phases were dried (MgSO$_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with a mixture of hexane–EtOAc (19:1) to give 97 mg (83% yield) of compound **38** as a colorless oil. *Method B.* Compound **39** (21 mg, 0.047 mmol) was treated with methanolic ammonia (5 mL, saturated at −78 °C) and stirred in a sealed tube at 40 °C for 15 h. The solvent was evaporated and the residue was purified by column chromatography (silica gel) eluting with hexane–EtOAc (19:1) to give 15 mg (89% yield) of **38** as a colorless oil: R_f 0.50 (hexane–EtOAc, 3:2); ^{1}H NMR (500.13 MHz, CDCl$_3$) δ 1.92 (m, 2H, H-3), 3.09 (s, 1H, H-1), 3.44 (d, J=10.8 Hz, 1H, BnOCH_aH), 4.17 (d, J=10.8 Hz, 1H, BnOCH_bH), 4.38 (distorted d, J=3.8 Hz, 1H, H-2), 4.49 (d, J=11.9 Hz, 1H, PhCH_aHO), 4.56 (d, J=12.0 Hz, 1H, PhCH'_aHO), 4.59 (d, J=11.6 Hz, 1H, PhCH_bHO), 4.63 (d, J=12.1 Hz, 1H, PhCH'_bHO), 4.72 (t, J=7.9 Hz, 1H, H-4), 7.27–7.35 (m, 10H, aromatic protons); ^{13}C NMR (125.77 MHz, CDCl$_3$) δ 36.1 (C-3), 47.4 (C-1), 55.3 (C-5), 71.4 (BnOCH$_2$), 72.3 (PhCH$_2$O), 72.4 (C-2), 73.0 (PhCH$_2$O), 76.9 (C-4), 127.7 (Ph), 127.8 (Ph), 127.8 (Ph), 128.4 (Ph), 128.4 (Ph), 137.8 (Ph), 138.4 (Ph); HRMS (ESI) Calcd for ($C_{20}H_{23}O_3$S) [M+H]$^+$: 343.1368; found 343.1357.

*3.1.16. (1R,2S,4S,5S)-4-(Benzyloxy)-5-((benzyloxy)methyl)-6-thiabicyclo[3.1.0]hexan-2-yl benzoate (**39**).* To a solution of benzoic acid (56 mg, 0.46 mmol) and diethyl azodicarboxylate (90 μL, 0.57 mmol) in anhydrous tetrahydrofuran (1 mL) was added triphenylphosphine

(150 mg, 0.57 mmol) under an argon atmosphere. The reaction mixture was cooled at 0 °C and a solution of **38** (98 mg, 0.28 mmol) in tetrahydrofuran (1 mL) was added. The reaction mixture was stirred at room temperature for 28 h. The solvent was evaporated, and the product was purified by column chromatography (silica gel) eluting with a mixture of hexane–EtOAc (49:1) to afford 25 mg (20% yield) of compound **39** as a syrup: R_f 0.70 (hexane–AcOEt, 7:3); ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 2.15 (m, 2H, H-3), 3.33 (s, 1H, H-5), 3.46 (d, J=11.0 Hz, 1H, BnOCH_aH), 4.29 (d, J=11.0 Hz, 1H, BnOCH_bH), 4.48 (d, J=11.7 Hz, 1H, PhCH_aHO), 4.61 (d, J=11.7 Hz, 1H, PhCH_bHO), 4.64 (d, J=12.1 Hz, 1H, PhCH'_aHO), 4.68 (d, J=12.1 Hz, 1H, PhCH'_bHO), 4.86 (t, J=7.9 Hz, 1H, H-2), 5.57 (distorted t, J=2.8 Hz, 1H, H-4), 7.22–7.40 (m, 12H, aromatic protons), 7.97 (dd, J=8.2, 1.1 Hz, 2H, aromatic protons), 7.55 (tt, J=7.5, 1.0 Hz, 1H, aromatic proton); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 33.4 (C-3), 44.8 (C-5), 55.2 (C-1), 71.4 (CH_2OBn), 72.5 (OCH_2Ph), 72.8 (OCH_2Ph), 75.4 (C-4), 77.1 (C-2), 127.4 (Ph), 127.6 (Ph), 127.7 (Ph), 127.8 (Ph), 128.3 (Ph), 128.4 (Ph), 128.4 (Ph), 129.7 (Ph), 129.9 (Ph), 133.2 (Ph), 138.0 (Ph), 138.3 (Ph), 165.7 (OCOPh).

3.2. Cells and viruses

Vero (African green monkey kidney) cells were grown in Eagle's minimum essential medium (MEM) supplemented with 5% calf serum. For maintenance medium (MM), the serum concentration was reduced to 1.5%.

The following reference strains of herpes simplex virus (HSV) were used: HSV-1 strain F, HSV-1 strain KOS, HSV-2 strain G, and HSV-2 strain MS. B2006 and Field were two HSV-1 TK$^-$ strains obtained from Prof. Dr. E. De Clercq (Rega Institute, Belgium). Virus stocks were propagated and titrated by plaque formation in Vero cells.

3.3. Cytotoxicity assay

Vero cell viability was measured by the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; Sigma–Aldrich) method. Confluent cultures in 96-well plates were exposed to different concentrations of each compound, with three wells for each concentration, using incubation conditions equivalent to those used in the antiviral assays. Then 10 μL of MM containing MTT (final concentration 0.5 mg/ml) was added to each well. After 2 h of incubation at 37 °C, the supernatant was removed and 200 μL of ethanol was added to each well to solubilize the formazan crystals. After vigorous shaking, absorbance was measured in a microplate reader at 595 nm. The cytotoxic concentration 50% (CC_{50}) was calculated as the compound concentration required to reduce cell viability by 50%.

3.4. Antiviral assay

Antiviral activity was evaluated by a virus plaque reduction assay. Vero cell monolayers grown in 24-well plates were infected with about 50 PFU/well. After 1 h of adsorption at 37 °C, residual inoculum was replaced by MM containing 0.7% methylcellulose and serial two-fold dilutions of the compounds, three wells for each concentration. Acyclovir (Sigma–Aldrich, USA) was used as a reference *anti*-HSV compound. Plaques were counted after two days of incubation at 37 °C. The inhibitory concentration 50% (IC_{50}) was calculated as the compound concentration required to reduce virus plaques by 50%.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.02.092.

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