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# Synthesis of Novel Bi-, Tri-, and Tetracyclic Nucleosides by Reaction of a Common Cyclic Enamine Derived from TSAO-T with Nucleophiles

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We report here the efficient regio- and stereoselective synthesis of new polycyclic nucleosides using a common cyclic enamine (**7**) as the starting material. In fact, the reaction of **7**, easily prepared by reaction of 5′-*O*-Tosyl TSAO-T under basic nonnucleophilic conditions (potassium carbonate), with different classes of nucleophiles, for example, nitrogen-, oxygen-, sulfur-, and carbon-based nucleophiles, or with amino acids afforded, with total regio- and stereoselectivity, new bi-, tri-, and tetracyclic nucleosides. This straighforward route represents an original and unambiguously regio- and stereoselective pathway to these compounds. Some of these polycyclic nucleosides may be useful intermediates for a second series of reactions that may lead to the generation of structurally new nucleosides.

## Introduction

The design and synthesis of bicyclic nucleosides has been of great importance in recent years. Because of the decrease in the conformational freedom that these compounds present, they have been used, as monomers, to synthesize antisense oligonucleotides with enhanced affinities for complementary RNA or DNA sequences[1−7] and have been used in studies aimed to probe the conformational preferences of some receptors and enzymes involved in the metabolism or polymerization of nucleosides and nucleotides.[8,9] On the other hand, a great diversity of bicyclic nucleosides have been synthesized for potential antiviral activity.[10−15] Consequently, the design and synthesis of bicyclonucleosides remains a

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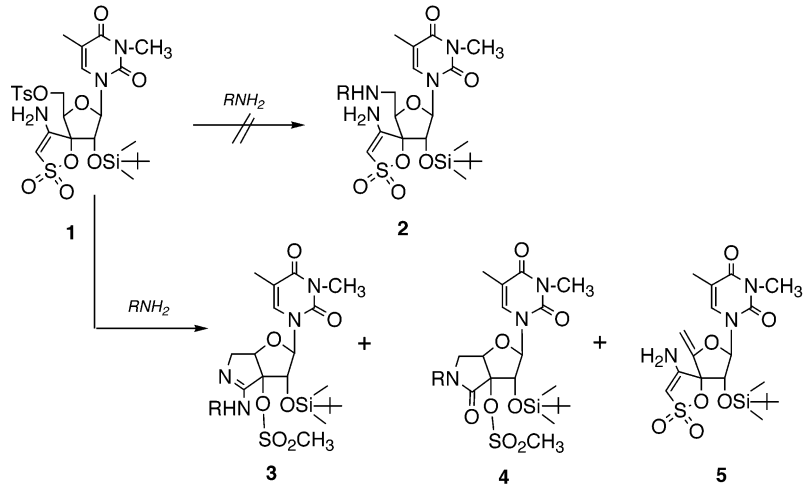
**SCHEME 1. Reaction of 5′-*O*-Tosyl TSAO-m$^3$T 1 with Alkylamines**




challenging field of research with great potential from medicinal and synthetic points of view.

Our research goal during the last few years has been the synthesis of hypermodified nucleosides as potential anti-HIV agents.[16−18] In this context, we have developed a family of potent and specific inhibitors of HIV-1 reverse transcriptase.[19,20] The prototype of this family is the thymine derivative TSAO-T (**1**; Figure 1).

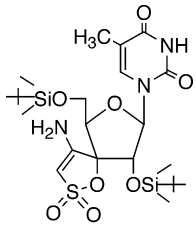



**FIGURE 1.** Structure of TSAO-T (**1**).

As a part of our program to develop novel analogues of TSAO-T with an improved activity/toxicity profile, we were interested in the replacement of the 5′-TBDMS group by alkylamines (Scheme 1). For the synthesis of the 5′-alkylamino-substituted TSAO derivatives, we designed a synthetic route that involved the nucleophilic attack of the 5′-*O*-Tosyl TSAO-m$^3$T **1** derivative by different alkylamines. This reaction did not lead to the expected 5′-alkylamino derivative **2**. Instead, new classes of highly functionalized bicyclic nucleosides **3** and **4**,[21] together with the 4′,5′-didehydro nucleoside **5**, were obtained.[21,22]

Formation of the bicyclic nucleosides was explained by the attack of the alkylamine at the C-4″ carbon atom of the 3-*N*-methyl thymine cyclic enamine **6** (Figure 2).[21]

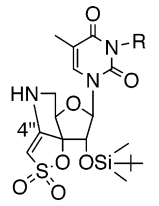



**FIGURE 2.** Structure of cyclic enamines **6** and **7**.

This was demonstrated by the isolation and subsequent treatment of **6** with different alkylamines to afford, in high yields, the new bicyclic nucleosides.[21] Therefore, the cyclic enamine **6** could be considered as a versatile intermediate useful for obtaining bicyclic nucleosides in high yield.

To consider this second synthetic strategy as a general and efficient approach for the synthesis of new bicyclic nucleosides, we decided to investigate the reaction of the nonmethylated thymine cyclic enamine **7** (Figure 2) with different classes of nucleophiles. Our results are described in this paper.

## Results

**Chemistry.** The cyclic enamine **7** was prepared following the method previously reported for enamine **6**.[21]

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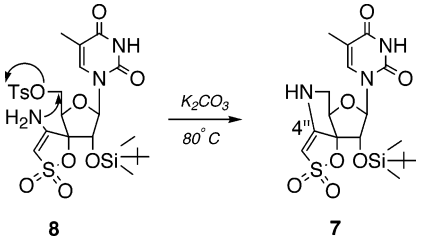
Thus, treatment of 5′-*O*-Tosyl TSAO-T **8**[23] under basic nonnucleophilic conditions (potassium carbonate), to avoid further reactions with the nucleophile, afforded the cyclic compound **7** in 70% yield (Scheme 2).

**SCHEME 2. Synthesis of Cyclic Enamine 7**

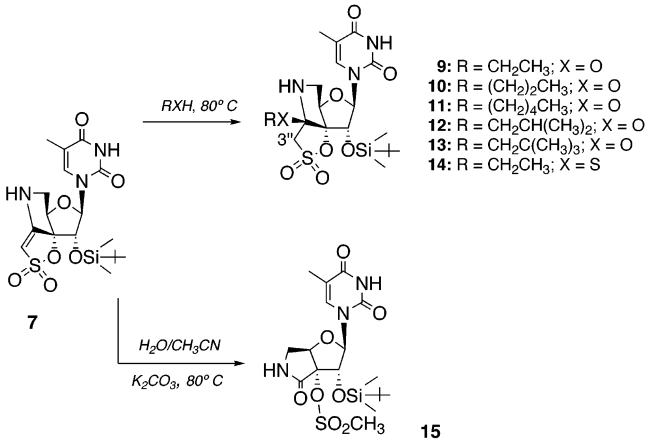



Formation of the cyclic enamine **7** could be explained by an intramolecular attack of the 4″-amino group of the spiroaminooxathiole dioxide ring to the 5′-tosyl moiety[21] (Scheme 2).

With the cyclic enamine **7** in hand, our next objective focused on exploring its reactivity toward various nucleophiles, for example, oxygen-, sulfur-, carbon-, and nitrogen-based nucleophiles. Its reaction with amino acids was also investigated.

First, we studied the reaction of **7** with (thio)alcohols. Thus, treatment of **7**, under reflux with ethanol as the nucleophile, gave the tricyclic nucleoside **9** (70%), resulting from the nucleophilic attack of the alcohol to the C-4″ carbon atom (Scheme 3). A similar reaction of **7** with

**SCHEME 3. Reaction of 7 with Alcohols and Water**




different primary alcohols such as propanol, pentanol, isobutyl alcohol, and neopentanol gave the corresponding tricyclic derivatives **10**−**13** in high yields (60−83%; Scheme 3). However, reaction with *tert*-butyl alcohol or phenol as the nucleophiles only gave the unaltered starting compound **7**.

The presence of an AB system with signals at $\delta$ 3.73 and 3.98 ($J_{gem}$ = 13.9 Hz) in the $^1$H NMR spectrum of **9** was crucial for the identification of this compound. In the gradient heteronuclear multiple-bond correlation (gHMBC) experiment (Figure 3A), a long-range correlation between the H-5′ protons ($\delta$ 3.18 and 3.44) and the C-4″ carbon ($\delta$ 97.7) was observed as corresponds to a cyclized

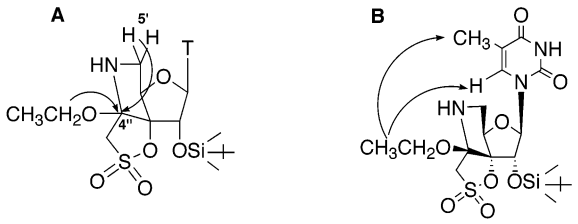



**FIGURE 3.** (A) gHMBC NMR correlations, indicated by arrows. (B) Relevant NOEs, indicated by arrows.

structure. In addition, a correlation was observed between the $CH_2$ protons of the $OCH_2CH_3$ moiety and the C-4″ carbon.

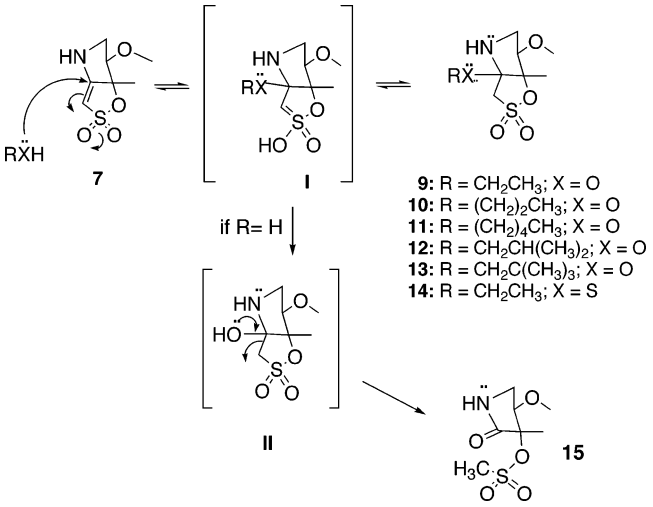
The stereochemistry of the new stereogenic center created on C-4″ was established as *S* on the basis of NOE difference experiments. Thus, irradiation of the signal at $\delta$ 1.26, corresponding to the methyl group of the $OCH_2CH_3$ moiety, caused the enhancement of the signals of the protons of the nucleobase H-6 and $CH_3$-5 (Figure 3B), indicating that these protons and the ethanol group were at the same upper side of the furanose ring. Semiempirical calculations (using the Hyperchem package[24]) indicated that compound **9** ($E$ = −325.28 kcal mol$^{-1}$) is more stable than its respective *R* isomer ($E$ = −299.24 kcal mol$^{-1}$) by 26 kcal mol$^{-1}$ in the gas phase.

Reaction of **7** with ethanethiol afforded the tricyclic nucleoside **14** in 80% yield (Scheme 3).

Next, we studied the reaction of **7** with water. Reaction of **7** with a 1:1 mixture of acetonitrile and water in the presence of potassium carbonate afforded the bicyclic nucleoside **15** (68% yield), in which a $\gamma$-lactam ring was fused to the ribose moiety (Scheme 3).

The experimental results shown above with alcohols, thioethanol, or water could be explained (Scheme 4) by

**SCHEME 4. Proposed Mechanism for the Reaction of 7 with Alcohols and Water**




the attack of the nucleophile at the C-4″ carbon atom of the spiroaminooxathiole dioxide to give intermediate **I**; a proton transfer at the next step would give the tricyclic derivatives **9**−**14**. With water, formation of intermediate **II** and subsequent ring opening may occur to give the

(23) Ingate, S.; Pérez-Pérez, M. J.; De Clercq, E.; Balzarini, J.; Camarasa, M. J. *Antiviral Res.* **1995**, *27*, 281.

(24) HyperChem TM. *Windows Molecular Modelling System,* Release 5.1; HyperCube: Waterloo, Ontario, Canada, 1997.

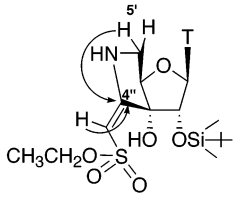
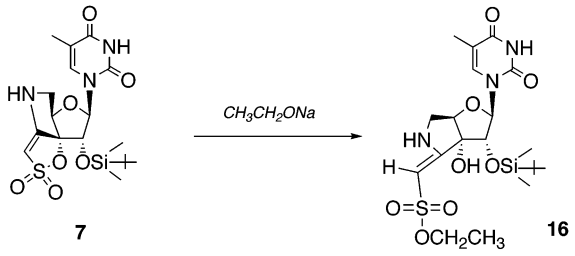


**FIGURE 4.** gHMBC NMR correlations, indicated by arrows.

bicyclic nucleoside **15**, in which a $\gamma$-lactam ring appeared fused to the original ribose moiety.

Next, we decided to investigate the reaction between **7** and a more nucleophilic compound such as sodium ethoxide (Scheme 5).

**SCHEME 5. Reaction of 7 with Sodium Ethoxide**



In this reaction, carried out at room temperature, we found that a new product (**16**) completely unrelated (as determined by $^1$H NMR) to the bicyclic nucleosides previously mentioned (**9**−**15**) was formed in 72% yield. The $^1$H and $^{13}$C NMR data of this compound revealed the presence of an (*E*)-vinylsulfonate moiety, together with an OH attached at the C-3′ position. In the gHMBC experiment (Figure 4), the absence of long-range correlations between the $OCH_2CH_3$ protons and the nucleoside carbons, together with the correlations observed between the H-5′ ($\delta$ 3.72 and 3.90) and H-3″ protons ($\delta$ 4.76) with the C-4″ carbon ($\delta$ 163.3), allowed the unambiguous assignment of **16** as a cyclized structure. In this reaction, it seems that the sodium ethoxide attacks at the sulfur of the $SO_2$ group instead of at the C-4″ carbon. This behavior has been previously observed in the reaction of sodium methoxide with other spiro derivatives of carbohydrates.[25]

The stereochemistry of the double bond of the vinylsulfonate moiety was established as *E* on the basis of NOE difference experiments.

To prepare more functionalized derivatives from a common starting compound, we decided to synthesize the tricyclic nucleoside **17** (Scheme 6). Thus, reaction of **7** with sodium cyanide afforded the tricyclic nucleoside **17** in 75% yield (Scheme 6). This compound could be considered a very versatile intermediate for the synthesis of substituted tricyclic nucleosides by transforming the cyano moiety into an amide, carboxylic ester, amine, or other functional group.

Hydrolysis of the cyano group was effectively carried out,[26] using phase transfer conditions, by treatment of

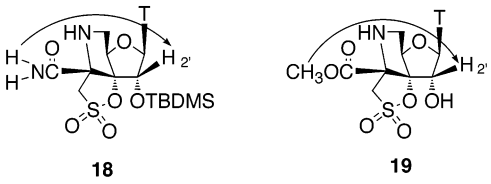


**FIGURE 5.** Relevant NOEs, indicated by arrows.

**17** with aqueous sodium hydroxide and hydrogen peroxide to furnish the carboxamide **18** in 65% yield (Scheme 6).

Alcoholysis of the cyano group, by reaction of **17** with a saturated solution of HCl in MeOH, afforded the methoxycarbonyl derivative **19** in 60% yield (Scheme 6). Under these reaction conditions, concomitant deprotection of the 2′-*O*-*tert*-butyldimethylsilyl group was observed.

Assignment of the absolute configuration at the C-4″ position of the cyano derivative **17** was indirectly determined as *S* on the basis of NOE experiments carried out on the amide **18** and methyl ester **19** tricyclic derivatives (Figure 5). Thus, irradiation of the signal at $\delta$ 7.46 (compound **18**), corresponding to one of the protons of the $CONH_2$ moiety, and the signal at $\delta$ 3.86 (compound **19**), corresponding to the $CH_3$ of the methyl ester moiety, causes an enhancement of the signal for the H-2′ proton, indicating that all of these protons are located on the same upper face of the molecule. The absolute configurations for **18** and **19** were assumed to be the same as those of the corresponding cyano derivative **17** because no epimerization was expected in the transformation of this group.

Catalytic hydrogenation of the CN group of **17** to generate the corresponding amine derivative **20** (Scheme 7) was attempted in methanol using 10% Pd/C as a catalyst. Initially, the reaction was carried out at room temperature and at atmospheric hydrogen pressure. However, under these conditions, the starting compound **17** remained unchanged, even upon prolonged reaction times. When the reaction was performed at 40 °C, the expected amine derivative **20** was not obtained; instead, the tetracyclic compound **21** was formed in 56% yield (Scheme 7). Assignment of the structure of tetracyclic nucleoside **21** was not obvious; this was achieved by $^1$H and $^{13}$C NMR spectroscopy using mono- and bidimensional techniques (gHMBC and gradient heteronuclear single-quantum coherence).

The formation of compound **21** could be explained as follows (Scheme 8). The first step would be the catalytic hydrogenation of the cyanide group to give the amine **20** that was not isolated. According to the literature,[27] alcohols may serve as carbonyl precursors to carry out the reductive alkylation of an amine in the presence of a reducing agent. Thus, we assume that reductive alkylation of **20** by methanol used as the solvent may occur to give imine **22**. Once compound **22** is formed, an intramolecular attack of the NH of the pyrrolidine ring to the carbon of the imino moiety would give compound **21**.

This extremely easy attack suggests that the NH of the pyrrolidine moiety has a pronounced nucleophilic character; this was proved when compound **7** was sub-

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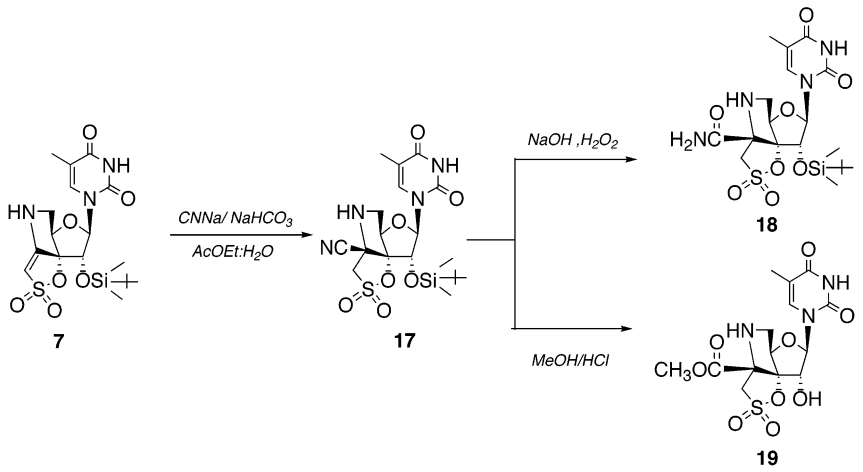
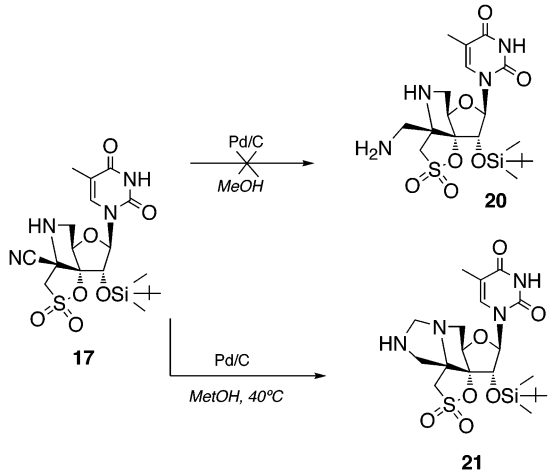
**SCHEME 6. Synthesis of Tricyclic Nucleosides 17−19**




**SCHEME 7. Synthesis of the Tetracyclic Nucleoside 21**




jected to reactions with compounds that contain carbonyl carbons. Thus, reaction of **7** with dimethyl malonate afforded compound **23** (55% yield; Scheme 9), and reaction of **7** with 4-*p*-methoxyphenylisocyanate afforded the ureido derivative **24** with a 58% yield.

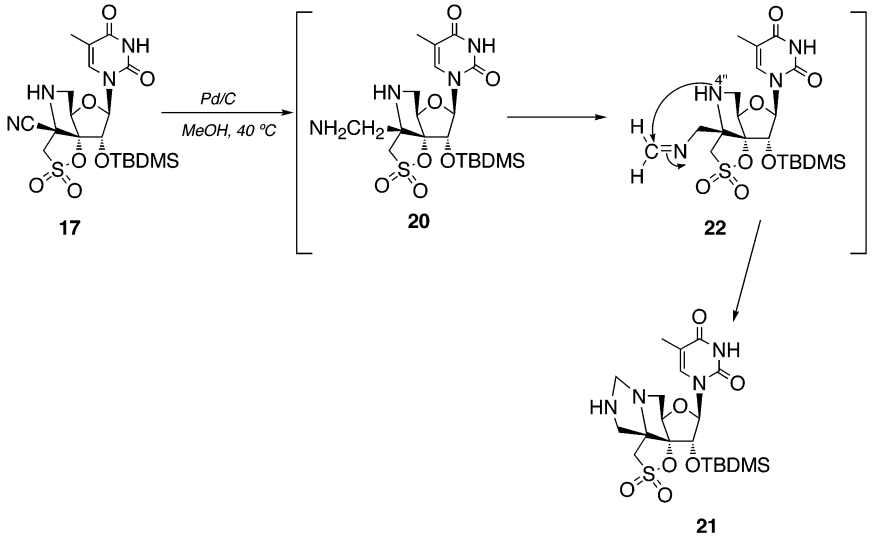
The presence of the carbonyl group directly attached to the NH in compounds **23** and **24** was unambiguously determined by the strong downfield shift ($\delta$ 2.03) of the signal corresponding to the H-3″ proton with respect to the same signal in the starting compound **7**.

Next, we focused on the reaction of the cyclic enamine **7** with primary and secondary amines. When **7** was reacted with an excess of a primary amine (propyl- or isopropylamine; Scheme 10), the bicyclic nucleosides **25** (65% yield) and **26** (63% yield) were obtained. A similar treatment of **7** with a secondary amine such as dimethylamine (2 M in THF) afforded the bicyclic nucleoside **27** in 69% yield (Scheme 10). As was previously proposed,[21] formation of these compounds could be explained by the attack of the amine to the C-4″ carbon atom of the spiroaminooxathiole ring followed by ring opening.

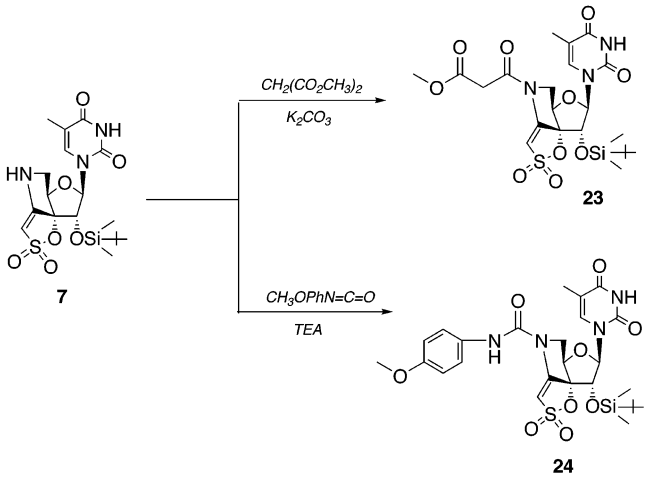
Finally, we investigated the reaction of **7** with the benzyl or methyl ester derivatives of the following amino acids: L-valine [H-(L)-Val-OBn·HCl], L-alanine [H-(L)-Ala-OBn·HCl], and L-glycine [H-(L)-Gly-OMe·HCl]. The reaction, carried out in the presence of triethylamine (TEA), afforded the bicyclic nucleosides **28**−**30** in good yields (60−63%; Scheme 11).

The presence of the (*E*)-vinylsulfonamide moiety was unambiguously determined by $^1$H and $^{13}$C NMR data. The

**SCHEME 8. Proposed Mechanism for the Synthesis of 21**

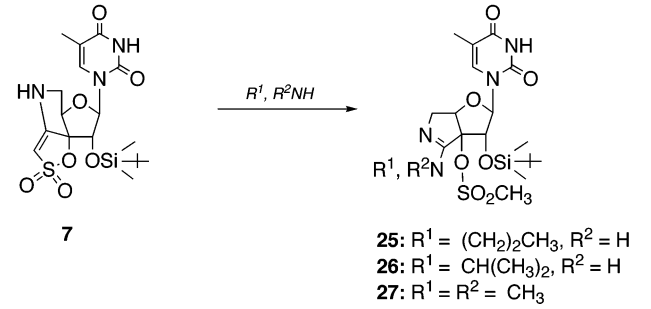


**SCHEME 9. Synthesis of 23 and 24**



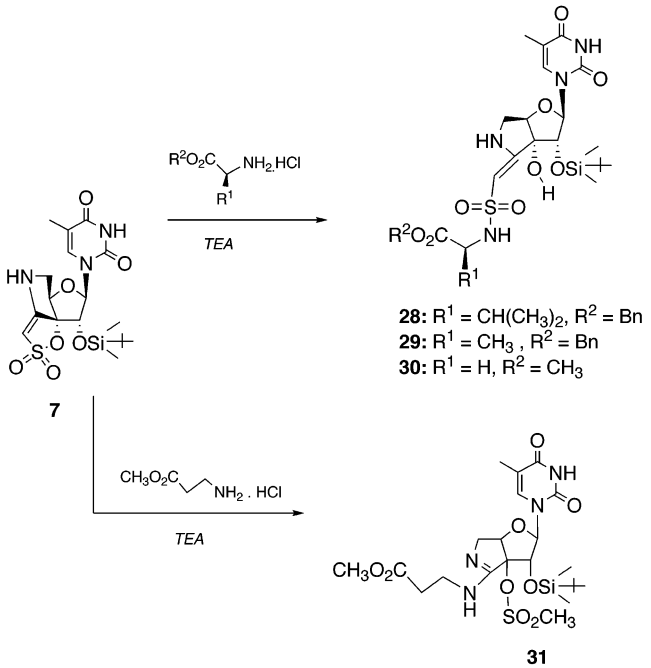

stereochemistry of this moiety was established as *E* on the basis of NOE difference experiments.

**SCHEME 10. Reaction of 7 with Amines**




Contrary to the reaction with amines (Scheme 10), in this reaction the compounds resulting from the nucleophilic attack of the α-amino acid to the C-4″ position were not detected; instead, the α-amino acid attacked at the sulfur of the $SO_2$ group. An explanation for such behavior might be that the attack of the amino group present in the α-amino acid to the C-4″ position is hindered for steric reasons. Therefore, we reasoned that insertion of a methylene group between the amino and the α carbon of the amino acid would enable the attack of the amino acid to the C-4″ position, and this was indeed the case. Thus, the reaction of **7** and a *β*-amino acid such as *β*-L-alanine afforded compound **31** exclusively, resulting from the attack of the amino acid to the C-4″ position (Scheme 11). Compound **31** was similar to the compounds (**25**−**27**; Scheme 10) obtained from the reaction of **7** with primary and secondary amines.

**SCHEME 11. Reaction of 7 with Amino Acids**




## Conclusions

The work presented here clearly shows the potential of the cyclic enamine **7** for the regio- and steroselective synthesis of new highly functionalized polycyclic nucleosides, with different molecular skeletons. These very stable compounds were very efficiently obtained (high yields and easy purifications) by a one-step reaction of cyclic enamine **7** with different nucleophiles. In addition, the highly functionalized bicyclic nucleosides obtained from **7** have different sites of potential reactivity that enable the possibility of performing a second, third, and so forth series of reactions that may lead to the synthesis of new highly functionalized nucleosides with medicinal or synthetic applications.

The compounds described herein are currently being evaluated for antiviral activity. In addition, some molecular modeling is in progress in order to rationalize our results.

## Experimental Section

The names of some polycyclic nucleosides in this section are given according to the von Baeyer nomenclature. However, for easy comparison, the assignments of the signals of the NMR spectra follow standard carbohydrate/nucleoside numbering (i.e., the furanose skeleton numbered 1′−5′), with the thymine moiety having the highest priority.

**5′,*N*$^{4''}$-Cyclo{1-[2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-*β*-D-ribofuranosyl]thymine}-3′-spiro-5″-(4″-amino-1″,2″-oxathiole-2″,2″-dioxide) (7).** To a solution of 5′-*O*-Tosyl TSAO-T **8**[23] (0.30 g, 0.50 mmol) in dry acetonitrile (5 mL) was added potassium carbonate (0.08 g, 0.58 mmol). The solution was refluxed for 6 h and evaporated to dryness. The residue was dissolved in ethyl acetate (20 mL) and washed with water (2 × 20 mL). The organic layer was dried ($Na_2SO_4$), filtered, and evaporated to dryness. The residue was purified by CCTLC on the chromatotron [hexane/ethyl acetate (1:2)] to give 0.07 g (70%) of **7** as a white foam. $^1$H NMR [300 MHz, $(CD_3)_2CO$] *δ*: 1.87 (s, 3H), 3.92 (dd, 1H, $J_{5'a,5'b}$ = 10.8 Hz), 4.06 (m, 1H), 4.94 (dd, 1H, $J_{4',5'a}$ = 5.7 Hz, $J_{4',5'a}$ = 8.9 Hz), 5.14 (d, 1H), 5.64 (s, 1H), 5.98 (d, 1H, $J_{1',2'}$ = 8.9 Hz), 6.65 (bs, 1H), 7.69 (s, 1H), 10.51 (bs, 1H). $^{13}$C NMR [75 MHz, $(CD_3)_2CO$] *δ*: 12.1, 54.4, 74.1, 80.9, 88.6, 93.7, 111.9, 138.2, 157.2, 163.8, 168.8. MS (ES+) *m/z*: 458.1 $(M + H)^+$. Anal. Calcd for $C_{18}H_{27}N_3O_7SSi$: C, 47.25; H, 5.95; N, 9.18. Found: C, 47.55; H, 5.65; N, 9.58.

**5′,*N*$^{4''}$-Cyclo{1-[2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-*β*-D-ribofuranosyl]thymine}-3′-spiro-5″-(4″-amino-4″*S*-ethoxy-1″,2″-oxathiolane-2″,2″-dioxide) (9).** A solution of **7** (0.2 g, 0.46 mmol) in ethanol (6 mL) was heated in a sealed tube at 80 °C for 16 h. After evaporation of the solvent, the residue was purified by CCTLC on the chromatotron [hexane/

ethyl acetate (1:2)] to give 0.15 g (70%) of **9** as a white foam. $^1$H NMR [300 MHz, $(CD_3)_2CO$] $\delta$: 1.26 (t, 3H, $J$ = 7.1 Hz), 1.85 (s, 3H), 3.18 (m, 1H), 3.44 (m, 1H), 3.57 (m, 1H), 3.73 (d, 1H, $J$ = 13.9 Hz), 3.83 (t, 1H), 3.90 (m, 1H), 3.98 (d, 1H), 4.62 (dd, 1H, $J_{4',5'a}$ = 4.3 Hz, $J_{4',5'b}$ = 6.1 Hz), 4.94 (d, 1H), 6.02 (d, 1H, $J_{1',2'}$ = 6.8 Hz), 7.48 (s, 1H), 10.15 (bs, 1H). $^{13}$C NMR [75 MHz, $(CD_3)_2CO$] $\delta$: 12.4, 15.6, 49.4, 54.7, 60.9, 72.1, 85.4, 92.2, 97.7, 99.5, 111.8, 137.5, 152.3, 166.2. MS (ES+) *m/z*: 526.2 (M + Na)$^+$. Anal. Calcd for $C_{20}H_{33}N_3O_8SSi$: C, 47.70; H, 6.60; N, 8.34. Found: C, 47.61; H, 6.55; N, 8.69.

**General Procedure for the Synthesis of Bicyclic Nucleosides 10−14.** To a solution of **7** (0.2 g, 0.46 mmol) in dry acetonitrile (10 mL) was added the corresponding (thio)alcohol (2.15 mmol). The reaction was heated at 80 °C for 18−24 h. After evaporation of the solvent, the residue was purified by CCTLC on the chromatotron [hexane/ethyl acetate (1:2)]. The analytical and spectroscopic data of the isolated products are indicated below for each reaction.

**5′,*N*$^{4''}$-Cyclo{1-[2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-β-D-ribofuranosyl]thymine}-3′-spiro-5″-(4″-amino-4″*S*-propyloxy-1″,2″-oxathiolane-2″,2″-dioxide) (10).** According to the general procedure, **7** was treated with propanol (0.4 mL, 2.15 mmol) to give 0.13 g (60%) of **10** as a white foam. $^1$H NMR [300 MHz, $(CD_3)_2CO$] $\delta$: 0.98 (t, 3H, $J$ = 7.6 Hz), 1.66 (m, 2H), 1.83 (s, 3H), 3.18 (m, 1H), 3.44 (m, 1H), 3.46 (m, 1H), 3.60 (d, 1H, $J$ = 13.9 Hz), 3.80 (m, 3H), 3.97 (d, 1H), 4.63 (dd, 1H, $J_{4',5'a}$ = 4.2 Hz, $J_{4',5'b}$ = 5.9 Hz), 4.93 (d, 1H), 6.01 (d, 1H, $J_{1',2'}$ = 6.5 Hz), 7.41 (s, 1H), 10.21 (bs, 1H). $^{13}$C NMR [75 MHz, $(CD_3)_2CO$] $\delta$: 10.1, 11.3, 22.7, 50.2, 56.1, 65.5, 71.2, 84.5, 91.0, 92.7, 99.7, 112.4, 135.1, 151.3, 165.3. MS (ES+) *m/z*: 540.2 (M + Na)$^+$. Anal. Calcd for $C_{21}H_{35}N_3O_8SSi$: C, 48.72; H, 6.81; N, 8.12. Found: C, 48.85; H, 6.95; N, 8.05.

**5′,*N*$^{4''}$-Cyclo{1-[2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-β-D-ribofuranosyl]thymine}-3′-spiro-5″-(4″-amino-4″*S*-pentyloxy-1″,2″-oxathiolane-2″,2″-dioxide) (11).** Following the general procedure, **7** was treated with pentanol (0.2 mL, 2.15 mmol) to give 0.18 g (79%) of **11** as a white foam. $^1$H NMR [300 MHz, $(CD_3)_2CO$] $\delta$: 0.90 (t, 3H, $J$ = 6.9 Hz), 1.39, 1.66 (m, 6H), 1.94 (s, 3H), 3.16 (m, 1H), 3.50 (m, 2H), 3.77 (t, 1H), 3.85 (m, 1H), 4.62 (dd, 1H, $J_{4',5'a}$ = 4.1 Hz, $J_{4',5'b}$ = 5.9 Hz), 4.92 (d, 1H), 6.01 (d, 1H, $J_{1',2'}$ = 6.5 Hz), 7.49 (s, 1H), 10.22 (bs, 1H). $^{13}$C NMR [75 MHz, $(CD_3)_2CO$] $\delta$: 12.5, 14.3, 23.1, 29.8, 49.7, 54.9, 64.7, 71.1, 84.9, 91.7, 98.7, 99.3, 111.1, 136.1, 151.3, 163.9. MS (ES+) *m/z*: 568.2 (M + Na)$^+$. Anal. Calcd for $C_{23}H_{39}N_3O_8SSi$: C, 50.62; H, 7.20; N, 7.70. Found: C, 50.25; H, 6.85; N, 7.35.

**5′,*N*$^{4''}$-Cyclo{1-[2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-β-D-ribofuranosyl]thymine}-3′-spiro-5″-(4″-amino-4″*S*-isobutyloxy-1″,2″-oxathiolane-2″,2″-dioxide) (12).** According to the general procedure, **7** was treated with isobutyl alcohol (0.2 mL, 2.15 mmol) to give **12** (0.16 g, 72%) as a white foam. $^1$H NMR [300 MHz, $(CD_3)_2CO$] $\delta$: 0.98, 1.00 (d, 6H), 1.84 (s, 3H), 1.85 (m, 1H), 3.18 (dd, 1H), 3.19 (dd, 1H), 3.30 (dd, 1H), 3.54 (dd, 1H, $J$ = 6.5 Hz, $J$ = 8.9 Hz), 3.64 (d, 1H, $J$ = 13.7 Hz), 3.83 (t, 1H), 3.98 (d, 1H), 4.63 (dd, 1H, $J_{4',5'a}$ = 4.0 Hz, $J_{4',5'b}$ = 6.0 Hz), 4.95 (d, 1H), 6.01 (d, 1H, $J_{1',2'}$ = 6.2 Hz), 7.35 (s, 1H), 10.12 (bs, 1H). $^{13}$C NMR [75 MHz, $(CD_3)_2CO$] $\delta$: 12.6, 19.2, 19.3, 25.7, 48.9, 54.8, 70.9, 72.0, 85.0, 91.9, 98.3, 98.9, 111.3, 145.1, 150.9, 163.5. MS (ES+) *m/z*: 554.2 (M + Na)$^+$. Anal. Calcd for $C_{22}H_{37}N_3O_8SSi$: C, 49.70; H, 7.01; N, 7.90. Found: C, 50.25; H, 6.85; N, 7.35.

**5′,*N*$^{4''}$-Cyclo{1-[2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-β-D-ribofuranosyl]thymine}-3′-spiro-5″-(4″-amino-4″*S*-neopentyloxy-1″,2″-oxathiolane-2″,2″-dioxide) (13).** Following the general procedure, **7** was treated with neopentanol (6 mL) to give **13** (0.2 g, 83%) as a white foam. $^1$H NMR [300 MHz, $(CD_3)_2CO$] $\delta$: 1.00 (s, 3H), 1.95 (s, 3H), 3.17 (m, 1H), 3.22 (d, 1H), 3.54 (m, 1H, $J_{5'a,5'b}$ = 12.2 Hz), 3.57 (d, 1H, $J$ = 8.8 Hz), 3.84 (t, 1H), 4.62 (dd, 1H, $J_{4',5'a}$ = 4.1 Hz, $J_{4',5'b}$ = 6.2 Hz), 4.99 (d, 1H), 5.75 (s, 2H), 6.00 (d, 1H, $J_{1',2'}$ = 6.3 Hz), 7.52 (s, 1H), 10.21 (bs, 1H). $^{13}$C NMR [75 MHz, $(CD_3)_2CO$] $\delta$: 12.4, 29.2, 32.1, 49.0, 54.3, 65.5, 70.9, 84.9, 91.4, 98.1, 99.4, 111.5, 136.0, 151.4, 163.9. MS (ES+) *m/z*: 568.2 (M + Na)$^+$. Anal. Calcd for $C_{23}H_{39}N_3O_8SSi$: C, 50.62; H, 7.20; N, 7.70. Found: C, 50.35; H, 6.75; N, 7.95.

***N*$^{4''}$-Cyclo{1-[2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-β-D-ribofuranosyl]thymine}-3′-spiro-5″-(4″-amino-4″*S*-ethylthio-1″,2″-oxathiolane-2″,2″-dioxide) (14).** According to the general procedure, **7** was treated with ethanethiol (0.160 mL) to give 0.178 g (80%) of **14** as a white foam. $^1$H NMR [300 MHz, $(CD_3)_2CO$] $\delta$: 1.34 (t, 3H), 1.85 (s, 3H), 2.93 (q, 2H), 3.18 (m, 1H), 3.50 (m, 1H), 3.72 (t, 1H), 3.80 (d, 1H, $J$ = 13.9 Hz), 4.18 (d, 1H), 4.65 (dd, 1H, $J_{4',5'a}$ = 5.1 Hz, $J_{4',5'b}$ = 6.1 Hz), 4.82 (d, 1H), 6.02 (d, 1H, $J_{1',2'}$ = 7.3 Hz), 7.55 (s, 1H), 10.41 (bs, 1H). $^{13}$C NMR [75 MHz, $(CD_3)_2CO$] $\delta$: 13.1, 16.3, 19.2, 49.7, 54.9, 70.9, 92.1, 97.3, 99.1, 111.9, 132.9, 151.8, 163.2. MS (ES+) *m/z*: 542.3 (M + Na)$^+$. Anal. Calcd for $C_{20}H_{33}N_3O_7S_2Si$: C, 46.22; H, 6.40; N, 8.09. Found: C, 46.52; H, 6.30; N, 8.12.

**(1*R*,3*R*,4*R*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-mesyloxy-6-oxo-3-(thymin-1′-yl)-7-aza-2-oxabicyclo[3.3.0]octane (15).** To a solution of **7** (0.05 g, 0.11 mmol) in a mixture of acetonitrile/water (1:1; 4 mL) was added potassium carbonate (0.02 g, 0.12 mmol). The reaction was refluxed for 10 h and evaporated to dryness. The residue was dissolved in ethyl acetate (20 mL) and washed with water (2 × 20 mL). The organic layer was dried ($Na_2SO_4$), filtered, and evaporated to dryness to give, after purification by CCTLC on the chromatotron [hexane/ethyl acetate (1:1)], 0.035 g (68%) of **15** as a white foam. $^1$H NMR [300 MHz, $(CD_3)_2CO$]) $\delta$: 1.93 (s, 3H), 3.24 (s, 3H), 3.44 (m, 1H), 3.85 (dd, 1H, $J_{4',5'a}$ = 6.6 Hz, $J_{5'a,5'b}$ = 11.0 Hz), 4.48 (d, 1H), 5.01 (d, 1H), 6.00 (d, 1H, $J_{1',2'}$ = 7.1 Hz), 7.46 (bs, 1H), 7.69 (s, 1H), 10.20 (bs, 1H). $^{13}$C NMR [75 MHz, $(CD_3)_2CO$] $\delta$: 12.7, 41.6, 46.7, 76.2, 81.6, 88.5, 91.0, 122.2, 136.6, 152.1, 164.4, 171.1. MS (ES+) *m/z*: 477.2 (M + H)$^+$. Anal. Calcd for $C_{18}H_{29}N_3O_8SSi$: C, 45.46; H, 6.15; N, 8.84. Found: C, 45.69; H, 6.55; N, 8.69.

**(1*R*,3*R*,4*R*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-[1-(*E*)-(ethoxysulfonyl)methylene]-5-hydroxy-3-(thymin-1′-yl)-7-aza-2-oxabicyclo[3.3.0]octane (16).** To a solution of **7** (0.1 g, 0.21 mmol) in dry acetonitrile (4 mL) was added sodium ethoxide (0.042 g, 0.63 mmol), and the resulting solution was stirred at room temperature for 5 min. The solution was treated with (5%) HCl until the pH was neutral and then concentrated to dryness. The residue was dissolved in ethyl acetate (20 mL) and washed with brine (2 × 20 mL). The organic layer was dried ($Na_2SO_4$), filtered, evaporated to dryness, and purified by CCTLC on the chromatotron [hexane/ethyl acetate (1:2)] to give 0.075 g (72%) of **16** as a white foam. $^1$H NMR [300 MHz, $(CD_3)_2CO$] $\delta$: 1.27 (t, 3H, $J$ = 7.1 Hz), 1.84 (s, 3H), 3.72 (dd, 1H, $J_{4',5'a}$ = 2.7 Hz, $J_{5'a,5'b}$ = 11.7 Hz), 3.90 (dd, 1H, $J_{4',5'b}$ = 6.2 Hz), 4.02 (q, 2H), 4.58 (d, 1H), 4.60 (dd, 1H), 4.76 (s, 1H), 4.91 (s, 1H), 6.01 (d, 1H, $J_{1',2'}$ = 6.1 Hz), 7.03 (bs, 1H), 7.54 (s, 1H), 10.14 (bs, 1H). $^{13}$C NMR [75 MHz, $(CD_3)_2CO$] $\delta$: 12.9, 13.4, 47.8, 54.7, 75.9, 80.8, 81.7, 83.0, 88.2, 109.1, 134.8, 152.5, 163.3, 164.4. MS (ES+) *m/z*: 504.2 (M + H)$^+$. Anal. Calcd for $C_{20}H_{33}N_3O_8SSi$: C, 47.70; H, 6.60; N, 8.34. Found: C, 47.79; H, 6.75; N, 8.69.

**5′,*N*$^{4''}$-Cyclo{1-[2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-β-D-ribofuranosyl]thymine}-3′-spiro-5″-(4″-amino-4″*S*-cyano-1″,2″-oxathiolane-2″,2″-dioxide) (17).** A mixture of **7** (0.20 g, 0.43 mmol), sodium cyanide (0.07 g, 0.86 mmol), sodium bicarbonate (0.022 g, 0.43 mmol), ethyl acetate (4 mL), and water (2 mL) was stirred vigorously at room temperature for 10 h. The organic phase was separated, and the aqueous phase was washed with ethyl acetate (2 × 15 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The residue was chromatographed by CCTLC on the chromatotron [dichloromethane/methanol (30:1)] to give 0.156 g (75%) of **17** as a white foam. $^1$H NMR [300 MHz, $(CD_3)_2CO$] $\delta$: 1.86 (s, 3H), 3.35 (m, 1H), 3.58 (m, 1H), 3.94 (d, 1H, $J$ = 13.9 Hz), 4.18 (t, 1H), 4.25 (d, 1H, H-3″b), 4.71 (dd, 1H, H-4′, $J_{4',5'a}$ = 5.0 Hz, $J_{4',5'b}$ = 6.2 Hz), 4.85 (d, 1H, H-2′), 5.90 (d, 1H, H-1′, $J_{1',2'}$ = 6.1 Hz), 7.63 (s, 1H, H-6), 10.26 (bs, 1H, NH-3). $^{13}$C NMR [75 MHz,

$(CD_3)_2CO$] $\delta$: 12.0, 49.3, 52.7, 67.3, 76.1, 85.6, 90.6, 96.5, 111.4, 117.7, 135.7, 158.2, 162.3. MS (ES+) *m/z*: 485.6 $(M + H)^+$. Anal. Calcd for $C_{19}H_{28}N_4O_7SSi$: C, 47.09; H, 5.82; N, 11.56. Found: C, 47.49; H, 5.75; N, 11.45.

**5′,*N*$^{4''}$-Cyclo{1-[2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-β-D-ribofuranosyl]thymine}-3′-spiro-5″-(4″-amino-4″*S*-carbamoyl-1″,2″-oxathiolane-2″,2″-dioxide) (18).** To a solution of **17** (0.150 g, 0.31 mmol) in dichloromethane was added 30% hydrogen peroxide (0.147 mL, 1.24 mmol), tetrabutylammonium hydrogen sulfate (0.021 g, 0.06 mmol), and 0.5 M aqueous sodium hydroxide (0.750 mL, 0.34 mmol). The reaction mixture was stirred at room temperature for 2 h. Water (20 mL) and dichloromethane (10 mL) were then added. The organic layer was separated, washed with brine (10 mL), and dried ($Na_2SO_4$). The solvent was removed under reduced pressure, and the residue was purified by CCTLC on the chromatotron [dichloromethane/methanol (20:1)] to give 0.11 g (65%) of **18** as a white foam. $^1$H NMR [300 MHz, $(CD_3)_2CO$] $\delta$: 1.85 (s, 3H), 3.30 (d, 1H, $J_{5'a,5'b}$ = 11.7 Hz), 3.45 (d, 1H), 3.67 (t, 1H), 3.68 (d, 1H, $J$ = 13.9 Hz), 4.35 (d, 1H), 4.64 (dd, 1H, $J_{4',5'a}$ = 4.6 Hz), 4.65 (d, 1H), 5.88 (d, 1H, $J_{1',2'}$ = 6.6 Hz), 7.42 (s, 1H), 7.46 (bs, 1H), 8.20 (bs, 1H), 10.26 (bs, 1H). $^{13}$ C NMR [75 MHz, $(CD_3)_2CO$] $\delta$: 12.0, 49.0, 54.6, 75.2, 77.3, 85.1, 89.1, 95.7, 112.0, 135.4, 151.2, 163.7, 172.3. MS (ES+) *m/z*: 503.1 $(M + H)^+$. Anal. Calcd for $C_{19}H_{30}N_4O_8SSi$: C, 45.40; H, 6.02; N, 11.15. Found: C, 45.56; H, 5.45; N, 11.69.

**5′,*N*$^{4''}$-Cyclo[1-(5′-deoxy-β-D-ribofuranosyl)thymine]-3′-spiro-5″-(4″-amino-4″*S*-methoxycarbonyl-1″,2″-oxathiolane-2″,2″-dioxide) (19).** Compound **17** (0.1 g, 0.20 mmol) was treated with a saturated solution of HCl in MeOH (2 mL) at room temperature for 5 h and then evaporated to dryness. The residue was purified by CCTLC on the chromatotron [dichloromethane/methanol (10:1)] to give 0.05 g (60%) of **19** as a white foam. $^1$H NMR [300 MHz, $(CD_3)_2CO$] $\delta$: 1.83 (s, 3H), 3.30 (d, 1H), 3.40 (d, 1H), 3.43 (t, 1H), 3.63 (d, 1H, $J$ = 14.6 Hz), 3.86 (s, 3H), 4.16 (d, 1H), 4.22 (d, 1H), 4.74 (dd, 1H, $J_{4',5'a}$ = 2.2 Hz, $J_{4',5'b}$ = 5.1 Hz), 5.23 (d, 1H, $J$ = 7.6 Hz), 5.98 (d, 1H, $J_{1',2'}$ = 7.8 Hz), 7.45 (s, 1H), 10.11 (bs, 1H). $^{13}$C NMR [75 MHz, $(CD_3)_2CO$] $\delta$: 12.4, 49.9, 54.1, 54.9, 74.3, 79.9, 86.3, 88.7, 99.0, 112.0, 137.2, 151.2, 163.2, 170.1. MS (ES+) *m/z*: 404.0 $(M + H)^+$. Anal. Calcd for $C_{14}H_{17}N_3O_9S$: C, 41.69; H, 4.25; N, 10.42. Found: C, 41.75; H, 4.55; N, 10.59.

**(1*R*,5*S*,11*R*,13*R*,14*R*)-14-(*tert*-Butyldimethylsilyloxy)-3,3-dioxo-13-(thymin-1′-yl)-7,9-diaza-2,12-dioxa-3-thiatetracyclo[9.3.3$^{1,5}$.0.0$^{5,9}$]tetradecane (21).** A solution of **17** (0.1 g, 0.20 mmol) in methanol (10 mL) containing Pd/C (10%; 0.020 g) was hydrogenated at 30 psi and 40 °C for 6 h. The reaction mixture was filtered, and the filtrate was evaporated to dryness, under reduced pressure. The residue was purified by CCTLC on the chromatotron [dichloromethane/methanol (10:1)] to give 0.06 g (56%) of **21** as a white amorphous solid. $^1$H NMR [300 MHz, $(CD_3)_2CO$] $\delta$: 1.83 (s, 3H), 3.05 (dd, 1H, $J_{5'a,5'b}$ = 12.4 Hz), 3.36 (d, 1H, $J$ = 11.2 Hz), 3.47 (d, 1H, $J$ = 13.8 Hz), 3.62 (d, 1H), 3.67 (d, 1H), 3.69 (d, 1H), 3.83 (d, 1H, $J$ = 7.5 Hz), 4.02 (d, 1H), 4.70 (dd, 1H, $J_{4',5'a}$ = 4.0 Hz, $J_{4',5'b}$ = 5.2 Hz), 4.87 (d, 1H), 5.95 (d, 1H, $J_{1',2'}$ = 7.5 Hz), 7.97 (s, 1H), 10.19 (bs, 1H). $^{13}$C NMR [75 MHz, $(CD_3)_2CO$] $\delta$: 12.3, 54.7, 55.2, 56.1, 72.0, 72.5, 79.4, 87.4, 90.6, 97.5, 112.1, 137.1, 151.1 163.3. MS (ES+) *m/z*: 501.1 $(M + H)^+$. Anal. Calcd for $C_{20}H_{32}N_4O_7SSi$: C, 47.98; H, 6.44; N, 11.19. Found: C, 47.75; H, 6.65; N, 11.60.

**5′,*N*$^{4''}$-Cyclo{1-[2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-β-D-ribofuranosyl]thymine}-3′-spiro-5″-[4″-(methoxycarbonylmethylcarbonyl)amino-1″,2″-oxathiole-2″,2″-dioxide] (23).** A suspension of dimethyl malonate (0.035 mL, 0.31 mmol) and potassium carbonate (0.043 g, 0.31 mmol) in THF was stirred at room temperature for 30 min; then **7** (0.1 g, 0.21 mmol) and tetrabutylammonium bromide (0.069 g, 0.21 mmol) were added. The reaction mixture was refluxed for 6 h and then concentrated to dryness. The residue was dissolved in ethyl acetate (20 mL), washed with brine (2 × 20 mL), dried ($Na_2SO_4$), filtered, and evaporated to dryness. The residue thus obtained was purified by CCTLC on the chromatotron [hexane/ethyl acetate (1:1)] to give 0.064 g (55%) of **23** as a white amorphous solid. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 1.84 (s, 3H), 2.84 (s, 2H), 3.72 (s, 3H), 4.21 (dd, 1H, $J_{5'a,5'b}$ = 11.0 Hz), 4.43 (t, 1H), 4.97 (dd, 1H, $J_{4',5'a}$ = 5.8 Hz, $J_{4',5'b}$ = 8.8 Hz), 5.03 (d, 1H), 5.94 (d, 1H, $J_{1',2'}$ = 9.0 Hz), 7.15 (s, 1H), 7.58 (s, 1H), 10.26 (bs, 1H). $^{13}$C NMR [75 MHz, $(CD_3)_2CO$] $\delta$: 12.1, 35.5, 49.7, 54.5, 74.3, 80.8, 89.1, 93.9, 94.1, 112.5, 138.6, 157.2, 163.8, 165.5, 168.8, 171.0. MS (ES+) *m/z*: 558.1 $(M + H)^+$. Anal. Calcd for $C_{22}H_{31}N_3O_{10}SSi$: C, 47.38; H, 5.60; N, 7.54. Found: C, 47.69; H, 5.55; N, 7.85.

**5′,*N*$^{4''}$-Cyclo{1-[2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-β-D-ribofuranosyl]thymine}-3′-spiro-5″-[4″-(4-*p*-methoxyphenylcarbamoyl)amino-1″,2″-oxathiole-2″,2″-dioxide] (24).** To a solution of **7** (0.1 g, 0.21 mmol) in acetonitrile was added 4-*p*-methoxyphenylisocyanate (0.062 mL, 0.63 mmol). The reaction was refluxed overnight and evaporated to dryness. The residue was dissolved in ethyl acetate (20 mL) and washed with water (2 × 20 mL). The organic layer was dried ($Na_2SO_4$), filtered, and evaporated to dryness. The residue was purified two successive times by CCTLC on the chromatotron, first using hexane/ethyl acetate (1:2) as eluent and then using dichloromethane/acetone (60:1), to give 0.073 g (58%) of **24** as a white foam. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 1.84 (s, 3H), 2.84 (s, 2H), 3.72 (s, 3H), 4.21 (dd, 1H, $J_{5'a,5'b}$ = 11.0 Hz), 3.45 (t, 1H), 4.97 (dd, 1H, $J_{4',5'a}$ = 5.8 Hz, $J_{4',5'b}$ = 8.8 Hz), 5.03 (d, 1H), 5.94 (d, 1H, $J_{1',2'}$ = 9.0 Hz), 7.15 (s, 1H), 7.58 (s, 1H), 10.26 (bs, 1H). $^{13}$ C NMR [75 MHz, DMSO-$d_6$] $\delta$: 12.6, 54.6, 56.0, 74.5, 81.0, 89.6, 93.1, 94.1, 112.5, 114.2, 121.2, 130.0, 138.6, 152.3, 157.0, 157.3, 160.8, 163.9. MS (ES+) *m/z*: 607.3 $(M + H)^+$. Anal. Calcd for $C_{26}H_{34}N_4O_9SSi$: C, 51.47; H, 5.65; N, 9.23. Found: C, 51.85; H, 5.95; N, 9.05.

**General Procedure for the Synthesis of Bicyclic Nucleosides 25−27.** To a solution of **7** (0.1 g, 0.21 mmol) in dry acetonitrile (5 mL) was added an excess of the appropriate amine (0.84 mmol), and the reaction was heated in a sealed tube at 70 °C for 20 h. After evaporation of the solvent, the residue was purified by CCTLC on the chromatotron. The chromatography eluents and yields of the isolated products are indicated below for each reaction.

**(1*R*,3*R*,4*R*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-mesyloxy-6-propylamino-3-(thymin-1′-yl)-7-aza-2-oxabicyclo[3.3.0]-oct-6-ene (25).** The general procedure was followed using propylamine (0.07 mL, 0.87 mmol). Chromatography with dichlromethane/methanol (50:1) afforded 0.07 g (65%) of **25** as a white foam. $^1$H NMR [300 MHz, $(CD_3)_2CO$] $\delta$: 0.75 (t, 3H), 1.45 (m, 2H), 1.86 (s, 3H), 3.10 (s, 2H), 3.19 (s, 6H), 3.71 (d, 1H, $J_{5'a,5'b}$ = 15.5 Hz), 4.03 (dd, 1H), 4.71 (m, 2H), 5.23 (d, 1H, $J_{4',5'}$ = 4.3 Hz), 5.77 (d, 1H, $J_{1',2'}$ = 4.4 Hz), 7.21 (s, 1H), 10.21 (s, 1H). $^{13}$C NMR [75 MHz, $(CD_3)_2CO$] $\delta$: 11.0, 12.9, 25.1, 40.6, 46.5, 61.3, 78.9, 85.9, 92.7, 96.8, 110.7, 137.3, 151.2, 160.4, 164.3. MS (ES+) *m/z*: 533.3 $(M + H)^+$. Anal. Calcd for $C_{22}H_{40}N_4O_7SSi$: C, 49.60; H, 7.57; N, 10.52. Found: C, 49.30; H, 7.68; N, 10.35.

**(1*R*,3*R*,4*R*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-isopropylamino-5-mesyloxy-3-(thymin-1′-yl)-7-aza-2-oxabicyclo-[3.3.0]oct-6-ene (26).** The general procedure was followed using isopropylamine (0.06 mL, 0.84 mmol). Chromatography with dichloromethane/methanol (30:1) gave 0.071 g (63%) of **26** as a white foam. $^1$H NMR [300 MHz, $(CD_3)_2CO$] $\delta$: 1.00 (d, 3H, $J$ = 6.4 Hz), 1.12 (d, 3H), 1.86 (s, 3H), 3.26 (s, 3H), 3.46 (m, 1H), 3.79 (d, 1H, $J_{5'a,5'b}$ = 15.8 Hz), 4.10 (dd, 1H), 4.74 (d, 1H), 5.13 (d, 1H, $J_{4',5'}$ = 4.5 Hz), 5.75 (d, 1H, $J_{1',2'}$ = 4.2 Hz), 7.29 (s, 1H), 10.23 (bs, 1H). $^{13}$C NMR [75 MHz, $(CD_3)_2CO$] $\delta$: 12.9, 22.6, 23.1, 40.6, 45.6, 61.1, 78.4, 85.6, 92.6, 96.9, 110.7, 136.3, 151.9, 160.2, 164.5. MS (ES+) *m/z*: 533.2 $(M + H)^+$. Anal. Calcd for $C_{22}H_{40}N_4O_7SSi$: C, 49.60; H, 7.57; N, 10.52. Found: C, 49.06; H, 7.55; N, 10.85.

**(1*R*,3*R*,4*R*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-(*N*,*N*-dimethylamino)-5-mesyloxy-3-(thymin-1′-yl)-7-aza-2-oxabicyclo[3.3.0]oct-6-ene (27).** The general procedure was

followed using *N*,*N*-dimethylamine (0.06 mL, 0.84 mmol). Chromatography with dichloromethane/methanol (30:1) gave 0.08 g (69%) of **27** as a white foam. $^1$H NMR [300 MHz, $(CD_3)_2CO$] $\delta$: 1.83 (s, 3H), 2.93 (s, 6H), 3.23 (s, 3H), 3.72 (d, 1H, $J_{5'a,5'b}$ = 15.7 Hz), 4.04 (dd, 1H), 4.81 (d, 1H), 5.23 (d, 1H, $J_{4',5'}$ = 4.5 Hz), 5.89 (d, 1H, $J_{1',2'}$ = 4.3 Hz), 7.26 (s, 1H), 10.20 (bs, 1H). $^{13}$C NMR [75 MHz, $(CD_3)_2CO$] $\delta$: 12.7, 40.9, 45.7, 61.2, 78.5, 85.4, 92.1, 96.3, 110.4, 136.1, 151.2, 160.5, 164.5. MS (ES+) *m/z*: 519.2 $(M + H)^+$. Anal. Calcd for $C_{21}H_{38}N_4O_7SSi$: C, 48.63; H, 7.38; N, 10.80. Found: C, 48.41; H, 7.55; N, 10.45.

**General Procedure for the Synthesis of Nucleosides 28−31.** To a solution of **7** (0.1 g, 0.21 mmol) in dry acetonitrile (4 mL) was added the corresponding C-protected amino acid (0.31 mmol) and triethylamine (0.047 mL, 0.31 mmol). The reaction was refluxed overnight and evaporated to dryness. The residue was dissolved in ethyl acetate (20 mL) and washed with water (2 × 20 mL). The organic layer was dried ($Na_2SO_4$), filtered, and evaporated to dryness. The residue was purified by CCTLC on the chromatotron with hexane/ethyl acetate (1:2). The yields of the isolated products together with the analytical and spectroscopic data are indicated below for each reaction.

**(1*R*,3*R*,4*R*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-6-{1-(*E*)-{*N*-[1S-(benzyloxycarbonyl)isobutyl]-aminosulfonyl}methylene}-3-(thymin-1′-yl)-7-aza-2-oxabicyclo[3.3.0]octane (28).** Following the general procedure, a solution of **7** and H-(L)-Val-OBn·HCl (0.06 g, 0.31 mmol) was reacted to give 0.07 g (63%) of **28** as a white foam. $^1$H NMR [300 MHz, $(CD_3)_2CO$] $\delta$: 1.02 (d, 3H, $J$ = 6.8 Hz), 1.05 (d, 3H), 1.89 (s, 3H), 3.60 (t, 2H, $J_{4',5'a}$ = 6.1 Hz, $J_{5'a,5'b}$ = 12.2 Hz), 3.92 (t, 1H, $J$ = 6.1 Hz), 4.20 (t, 1H), 5.15 (d, 1H), 5.31 (s, 1H), 5.63 (d, 1H, $J_{1',2'}$ = 6.8 Hz), 5.70 (s, 2H), 7.18 (t, 1H), 7.44 (m, 5H), 7.68 (s, 1H), 7.80 (d, 1H), 10.55 (bs, 1H). $^{13}$C NMR [75 MHz, $(CD_3)_2CO$] $\delta$: 12.1, 16.9, 26.6, 48.5, 60.2, 72.1, 76.2, 84.0, 84.3, 91.2, 92.1, 111.4, 127.3, 128.7, 136.9, 140.3, 152.9, 163.5, 164.5, 172.4. MS (ES+) *m/z*: 665.8 $(M + H)^+$. Anal. Calcd for $C_{30}H_{44}N_4O_9SSi$: C, 54.20; H, 6.67; N, 8.43. Found: C, 54.60; H, 6.12; N, 8.12.

**(1*R*,3*R*,4*R*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-6-{1-(*E*)-{*N*-[1S-(benzyloxycarbonyl)ethyl]aminosulfonyl}-methylene}-3-(thymin-1′-yl)-7-aza-2-oxabicyclo[3.3.0]-octane (29).** Following the general procedure, a solution of **7** and H-(L)-Ala-OBn·HCl (0.06 g, 0.31 mmol) was reacted to give 0.08 g (63%) of **29** as a white foam. $^1$H NMR [300 MHz, $(CD_3)_2$-CO] $\delta$: 1.50 (t, 3H, $J$ = 7.2 Hz), 1.84 (s, 3H), 3.52 (d, 1H, $J_{4',5'a}$ = 3.0 Hz, $J_{5'a,5'b}$ = 14.0 Hz), 3.63 (dd, 1H, $J_{4',5'b}$ = 6.1 Hz), 4.09 (m, 1H), 4.60 (s, 1H), 4.82 (d, 1H), 4.85 (dd, 2H, $J$ = 7.1 Hz, $J$ = 19.4 Hz), 5.81 (s, 1H), 6.12 (d, 1H, $J_{1',2'}$ = 8.3 Hz), 7.03 (bs, 1H), 7.35 (m, 5H), 7.40 (s, 1H), 7.81 (d, 1H), 10.20 (bs, 1H). $^{13}$C NMR [75 MHz, $(CD_3)_2CO$] $\delta$: 12.1, 19.6, 50.9, 52.6, 68.3, 78.5, 84.0, 84.5, 91.1, 91.6, 111.4, 129.5, 135.4, 153.4, 158.2, 162.3. MS (ES+) *m/z*: 637.2 $(M + H)^+$. Anal. Calcd for $C_{28}H_{40}N_4O_9SSi$: C, 52.81; H, 6.33; N, 8.80. Found: C, 52.20; H, 6.15; N, 8.25.

**(1*R*,3*R*,4*R*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-6-{1-(*E*)-{*N*-[1S-(methoxycarbonyl)methyl]aminosulfonyl}-methylene}-3-(thymin-1′-yl)-7-aza-2-oxabicyclo[3.3.0]-octane (30).** Following the general procedure, a solution of **7** and H-(L)-Gly-OMe·HCl (0.04 g, 0.31 mmol) was reacted to give 0.07 g (60%) of **30** as a white foam. $^1$H NMR [300 MHz, $(CD_3)_2CO$] $\delta$: 1.89 (s, 3H), 3.56 (d, 1H, $J_{4',5'a}$ = 3.1 Hz, $J_{5'a,5'b}$ = 14.3 Hz), 3.65 (dd, 1H, $J_{4',5'b}$ = 6.3 Hz), 3.75 (s, 3H), 4.12 (m, 1H), 4.64 (s, 1H), 4.83 (d, 1H), 5.83 (s, 1H), 6.10 (d, 1H, $J_{1',2'}$ = 8.1 Hz), 7.06 (bs, 1H), 7.45 (s, 1H), 7.80 (d, 1H), 10.15 (bs, 1H). MS (ES+) *m/z*: 547.2 $(M + H)^+$. Anal. Calcd for $C_{21}H_{34}N_4O_9$-SSi: C, 46.14; H, 6.27; N, 10.25. Found: C, 46.36; H, 6.85; N, 10.45.

**(1*R*,3*R*,4*R*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-mesyloxy-6-(2-methoxycarbonylethylamino)-3-(thymin-1′-yl)-7-aza-2-oxabicyclo[3.3.0]oct-6-ene (31).** Following the general procedure, a solution of **7** and H-$\beta$-Ala-OMe·HCl (0.043 g, 0.31 mmol) was reacted to give 0.06 g (60%) of **31**. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 1.86 (s, 3H), 2.45 (t, 2H), 3.25 (s, 3H), 3.58 (s, 3H), 3.61 (m, 2H), 3.81 (dd, 1H), 3.99 (d, 1H, $J_{5'a,5'b}$ = 15.5 Hz), 4.55 (d, 1H), 5.25 (d, 1H), 5.63 (d, 1H, $J_{1',2'}$ = 7.6 Hz), 7.19 (s, 1H), 10.1 (bs, 1H). $^{13}$C NMR [75 MHz, $(CD_3)_2CO$] $\delta$: 12.8, 35.3, 40.9, 45.9, 47.2, 61.5, 78.8, 85.4, 92.4, 96.5, 110.7, 136.5, 151.7, 163.2, 164.5, 172.0. MS (ES+) *m/z*: 577.2 $(M + H)^+$. Anal. Calcd for $C_{23}H_{40}N_4O_9SSi$: C, 47.90; H, 6.99; N, 9.71. Found: C, 47.75; H, 6.55; N, 9.79.

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**Supporting Information Available:** General experimental methods, NMR procedures, and semiempirical calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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