

# Synthesis and Structural Characterization of Pyrimidine Bi- and Tricyclic Nucleosides with Sugar Puckers Conformationally Locked into the Eastern Region of the Pseudorotational Cycle<sup>†</sup>

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Received January 24, 2003

Reaction of 5'-O-tosyl TSAO-m<sup>3</sup>T (**1**) with amines has led to the synthesis of new classes of bi- and tricyclic nucleosides. Full details about the synthesis of these compounds and a plausible mechanism to explain their obtention are reported. In addition, we describe the development of a second, more efficient, and higher yielding synthetic route as a general approach for the synthesis of some of these bicyclic nucleosides. To study the conformational behavior of the bi- and tricyclic nucleosides described in this paper, intensive NMR investigations and molecular modeling studies were performed. Conformational analysis indicates that the furanose ring of the compounds described here prefers the eastern side of the pseudorotation cycle with the base substituents preferentially in the anti range. The torsion angle  $\gamma$  describing the C-4'-C-5' bond is found to prefer the +sc range. These compounds represent a novel class of E-type conformationally restricted bicyclic ribonucleosides containing a [3.3.0]-fused carbohydrate moiety. The bicyclic nucleosides described herein present an interesting potential for diverse and selective chemical treatments on the 2'-hydroxyl and/or the functionalities incorporated at the bridge between C-3' and C-5'.

## Introduction

Bicyclic nucleosides are a type of nucleosides in which the natural furanose sugar moiety has been replaced by a bicyclo ring structure. Such substitution results in a reduction of the conformational freedom of the nucleosides.<sup>1</sup>

Some naturally occurring bicyclic nucleosides show important biological activities. Among them, the most notable are the griseolic acids,<sup>2</sup> which are known to inhibit 3',5'-cyclic nucleotide phosphodiesterase.<sup>2,3</sup> Additionally, some derivatives of griseolic acids have been reported to be potent antihypertensive agents.<sup>4</sup> Other natural carbohydrate-modified polycyclic nucleosides with interesting properties are the antibiotics, herbicides,<sup>5</sup>

and aureonucleomycins.<sup>6,7</sup> These compounds are unusual nucleosides having furano-pyranopyran skeletons.<sup>7</sup>

On the other hand, nucleoside analogues with bicyclic carbohydrate moieties have been designed as the monomers in conformationally restricted oligonucleotide sequences.<sup>1,8-13</sup> Due to the decrease in conformational freedom introduced by the bicyclic nucleosides, these oligonucleotides have displayed very promising results as compounds with improved recognition of complemen-

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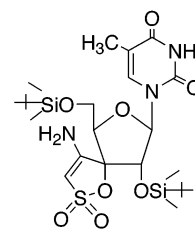
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tary RNA and DNA sequences.<sup>1,8</sup> Improved binding affinities have also been introduced with some tricyclic nucleosides.<sup>14</sup> Furthermore, some bicyclic nucleosides have received much attention in studies on the interactions of nucleoside/nucleotide substrates with corresponding receptors and enzymes.<sup>15,16</sup>

Finally, a plethora of conformationally restricted nucleosides has been synthesized for potential antiviral activity.<sup>15,17,18</sup> Among them, nucleoside analogues incorporating a fused methylene group,<sup>19</sup> oxirane,<sup>20</sup> oxetane,<sup>21</sup> or perhydro-1,3-oxazine<sup>22</sup> inhibit HIV replication.

All of these findings triggered numerous studies on bi- and tricyclic nucleosides in the past decade. The synthesis of these complex systems is rather difficult and challenging and has spurred great interest among synthetic chemists. Most of the approaches developed required multistep processes and careful control of regio- and stereochemistry to get the desired bicyclic or polycyclic nucleosides. Therefore, as suggested by Wengel and co-workers,<sup>8c</sup> there is a need not only for development of improved syntheses of known interesting analogues but also for the introduction of novel structures within this field.

Our research goal has been the synthesis of hypermodified nucleosides as potential anti-HIV agents.<sup>23–27</sup> In this context, we have developed a family of potent and highly specific inhibitors of HIV-1 reverse transcriptase.<sup>26,27</sup>



TSAO-T (1)

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

The prototype of this family of compounds is the thymine derivative TSAO-T (1, Figure 1).

As a part of our program to develop novel analogues of TSAO-T with improved activity/toxicity profile, we tried to transform **2** into **3** by nucleophilic displacement of the tosyl group with methylamine (Scheme 1).

Unexpectedly, treatment of **2** with methylamine afforded the hitherto unknown bicyclic nucleosides **4** and **5**. The novelty of these structures prompted us to extend this reaction to other amines. Here, we report the synthesis of novel bicyclic and tricyclic nucleosides<sup>28</sup> and propose a mechanism for their formation through a versatile and very accessible cyclic intermediate. This intermediate can be considered as a useful synthon for the synthesis of new highly functionalized bicyclic nucleosides.

Due to the bicyclic or tricyclic structure of the nucleosides obtained, their conformational freedom might be restricted. Therefore, we considered of interest to perform a conformational analysis of such polycyclic nucleosides.

## Results

**Chemistry.** When 5'-O-tosyl derivative **2**<sup>29</sup> was reacted, in a sealed tube, with an excess (5 equiv) of 2 M solution of methylamine in methanol, the bicyclic nucleosides **4** (18%) and **5** (18%) were obtained (Scheme 1), together with the 4',5'-didehydro nucleoside **6**<sup>30</sup> (25%). Under these reaction conditions, the expected 5'-methylamino-5'-deoxy TSAO derivative **3** was not detected. Formation of 4',5'-unsaturated pyrimidine nucleosides has been described in the literature in reactions of 5'-O-

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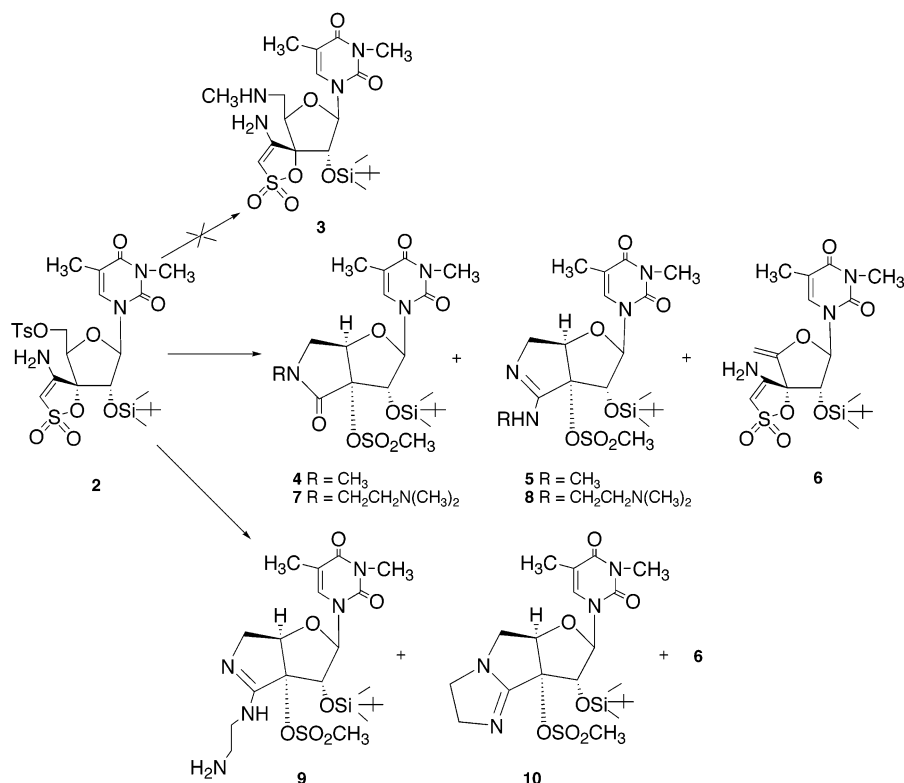
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## SCHEME 1



tosyl nucleosides with nucleophiles.<sup>30,31</sup> When the reaction was performed with other primary amines the results were similar. Thus, reaction of **2** with *N,N*-dimethylethylenediamine (Scheme 1) afforded the bicyclic nucleosides **7** (27%) and **8** (10%) together with the 4',5'-didehydro nucleoside **6**<sup>30</sup> (26%).

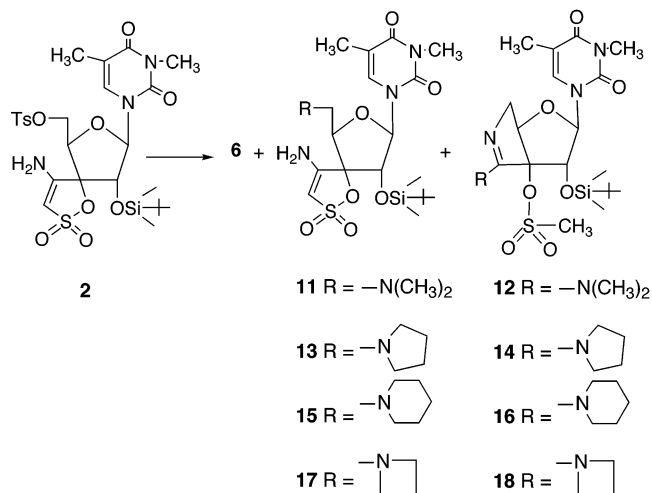
Similarly, reaction of **2** with an excess of ethylenediamine, in refluxing acetonitrile, gave the bicyclic nucleoside **9** (20%) and tricyclic nucleoside **10** (28%) together with the 4',5'-didehydro nucleoside **6**<sup>30</sup> (35%) as the major compound.

It should be pointed out that in all the reactions so far described the expected compounds resulting from the nucleophilic substitution of the 5'-tosyl group by the amines, were not detected.

Next, the reaction was studied with secondary amines. Thus, when **2** was reacted (Scheme 2) with an excess (5 equiv) of *N,N*-dimethylamine (2 M in THF) or with cyclic amines such as pyrrolidine, piperidine, or azetidine, in refluxing acetonitrile, besides the compounds resulting from the nucleophilic substitution of the 5'-tosyl group by the corresponding amines [**11** (23%), **13** (34%), **15** (26%), and **17** (12%)] and the elimination 4',5'-didehydro derivative **6**<sup>30</sup> (18–28%), a third compound was isolated and identified as the bicyclic nucleoside [**12** (8%), **14** (34%), **16** (40%), and **18** (12%)].

Structures of the novel compounds were assigned on the basis of their analytical and spectroscopic data. Assignment of the structures of bicyclic nucleosides **4**, **5**, **7**–**9**, **12**, **14**, **16**, and **18** was not obvious, this was achieved by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy using mono-

## SCHEME 2



and bidimensional techniques (gHMBC<sup>32</sup> and gHSQC<sup>33</sup>). Figure 2 shows the most important long-range correlations observed in the gHMBC experiments.

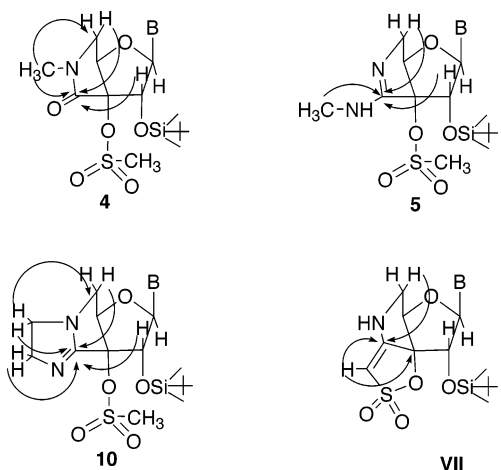
Bicyclic nucleosides **4** and **5** were chosen as model compounds. Structures of the other bicyclic nucleosides were determined, then, through comparison of their <sup>1</sup>H NMR spectra to those of the model compounds, since they only differ from one another in the signals corresponding to the N-substituent.

In compound **4** (Figure 2), the NMe protons ( $\delta$  2.86 ppm) showed long-range correlations with the carbonyl carbon ( $\delta$  163.8 ppm) and with the C-5' carbon ( $\delta$  54.9

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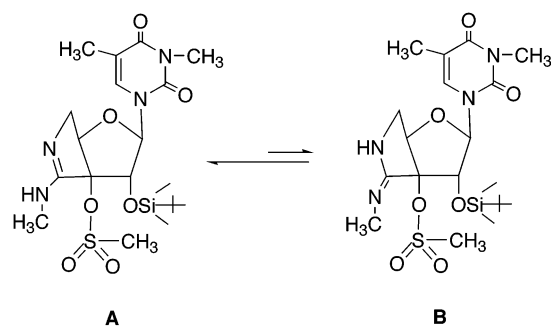
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**FIGURE 2.** gHMBC NMR correlations, indicated by arrows, for compounds **4**, **5**, **10**, and **VII**.

**SCHEME 3. Tautomeric Forms of Compound 5**



ppm), indicating that the methyl group is attached to the endocyclic nitrogen. The H-2' proton ( $\delta$  4.42 ppm) and the H-5' protons ( $\delta$  3.44 and 3.85 ppm) also showed long-range correlations with the carbonyl carbon, only possible in the cyclized proposed structure.

In compound **5** (Figure 2), the NMe protons ( $\delta$  2.85 ppm) only showed long-range correlations with the non-protonated imine carbon ( $\delta$  160.8 ppm), indicating that the methyl group is attached to the exocyclic nitrogen. Furthermore, the correlations observed between H-5' protons ( $\delta$  3.87, 4.06 ppm) or H-2' protons ( $\delta$  4.41 ppm) and the imino carbon allowed the unambiguous assignment of a cyclized structure.

Compound **5** could exist in two different tautomeric forms (**A** and **B**) (Scheme 3). The  $^{13}\text{C}$  NMR spectrum of **5** (in  $\text{CDCl}_3$ ) showed broadened signals for C-5', C-3',  $\text{CH}_3\text{-NH}$ , and  $\text{C=N}$  carbon atoms, which suggests the existence of an equilibrium between both tautomers. According to literature data,<sup>34</sup> the methyl carbon atom appearing at  $\delta$  29.6 ppm is compatible with a  $\text{CH}_3\text{NH}$  grouping and therefore with tautomer **A**, whereas a methyl of a  $\text{CH}_3\text{N=}$  grouping (as in tautomer **B**) should appear around 42.0 ppm.<sup>34</sup> Therefore, in  $\text{CDCl}_3$  solution, compound **5** should probably exist as an equilibrium between both tautomers, with the equilibrium shifted to tautomer **A**.

Finally, the structure of tricyclic nucleoside **10** was unequivocally assigned from mono- and bidimensional  $^1\text{H}$  and  $^{13}\text{C}$  NMR (1D and 2D) techniques. Figure 2 shows

the most relevant long-range correlations observed in the gHMBC experiment.

**Proposed Mechanism.** In view of the experimental results shown above, the following mechanism is proposed for the reaction between the 5'-O-tosyl compound **2** and primary or secondary alkylamines (Scheme 4). We postulate that the reaction between **2** and alkylamines may follow two alternative pathways:

**Path A.** The reaction is initiated by a nucleophilic attack of the alkylamine to the 5'-O-tosyl group to give the nucleophilic substitution product **I**. With secondary alkylamines the reaction stops at this step, thus leading to compounds **11**, **13**, **15**, and **17**. However, with primary alkylamines a subsequent intramolecular nucleophilic attack of the 5'-alkylamine at the C-4''-carbon atom of the spiro aminooxathiole dioxide ring may occur to give intermediate **II**. A proton transfer at the next step would give **III**. The resulting electronic shifts followed by ring opening give **IV**. Hydrolysis of the imino group of **IV** would give the N-substituted bicyclic nucleosides **4** and **7**.

In the reaction between **2** and ethylenediamine, hydrolysis of **IV** would give **V**, and elimination of water through **VI** would give the Schiff base and, therefore, the tricyclic nucleoside **10**.

**Path B.** Alternatively, the corresponding alkylamine present in the media could act as a base promoting the intramolecular attack of the 4''-amino group of the spiro aminooxathiole dioxide ring to the 5'-tosyl to give the cyclic enamine intermediate **VII**. Subsequent attack of the alkylamine at C-4'' carbon atom of the spiroaminooxathiole dioxide would give intermediate **VIII**. A proton transfer at the next step would give **IX**. The resulting electronic shifts followed by ring opening would give the bicyclic nucleosides **5**, **8**, **9**, **12**, **14**, **16**, and **18**. According to path B, these bicyclic nucleosides seem to come from a common intermediate system, the cyclic enamine **VII**.

Participation of intermediate **VII** and thus support for the mechanism proposed was demonstrated as follows:

Treatment of **2** under basic nonnucleophilic conditions (potassium carbonate), to avoid further reactions with the nucleophile, afforded the cyclic compound **VII** in 68% yield (Scheme 5). The structure of **VII** was unequivocally determined by NMR spectroscopy (see the Experimental Section and Figure 2).

When **VII** was reacted with excess of dimethylamine (2 M in THF), the bicyclic nucleoside **12** was obtained in 50% yield (Scheme 5). A similar treatment of **VII** with *N,N*-dimethylethylenediamine (Scheme 5) afforded exclusively the bicyclic nucleoside **8** (68%).

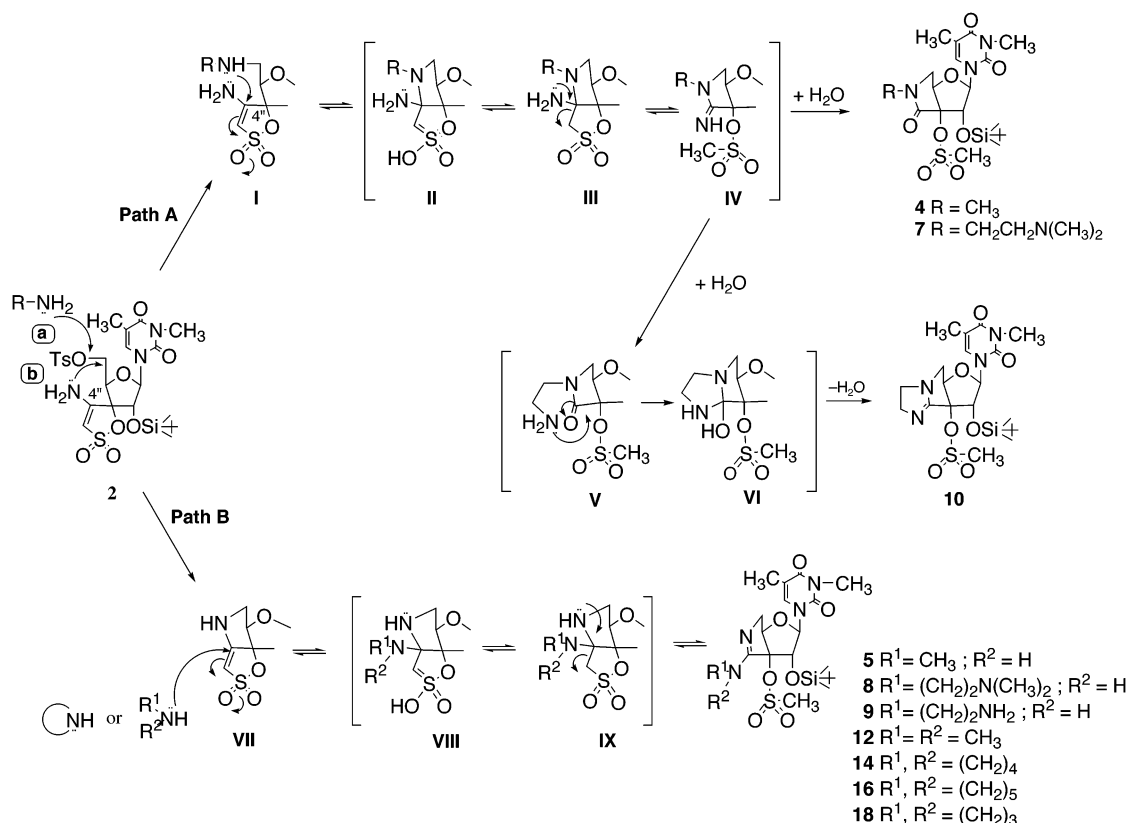
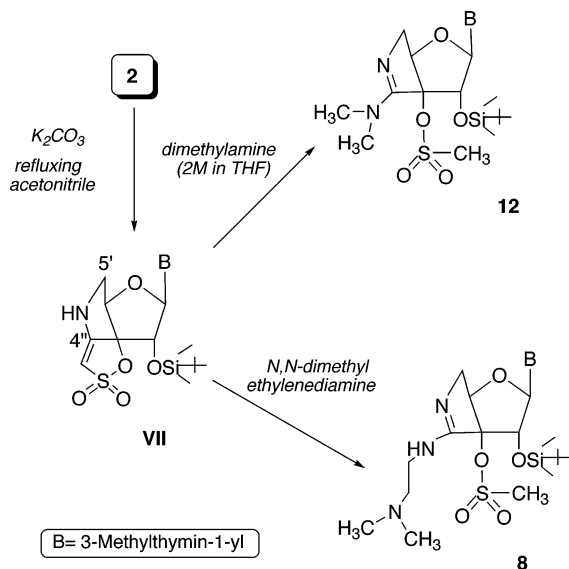
The experimental results shown above not only supported the mechanism proposed, for the reaction of **2** with alkylamines, but also indicate that compound **VII** can be considered as a useful synthon for the synthesis of highly functionalized polycyclic nucleosides, in good yields.

**Conformational Behavior in Solution.** To study the conformational behavior of the bicyclic nucleosides described in this paper, intensive NMR investigations and molecular modeling studies were performed with **4**, **5**, **10**, and **12** that we have chosen as model compounds.

The conformation of the furanose ring in solution can be determined experimentally by  $^1\text{H}$  NMR from vicinal proton–proton coupling constants using the concept of

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SCHEME 4. Proposed Mechanism for the Reaction between 2 and Amines

SCHEME 5. Reaction of VII with Dimethylamine and *N,N*-Dimethylethylenediamine

pseudorotation<sup>35</sup> in which the conformation of the sugar ring is fully described by two parameters: a phase angle of pseudorotation ( $P$ ) and a puckering amplitude ( $\nu_m$ ). Our compounds have an additional structural feature which is the presence of a fused five-membered ring. Since the C(4')–C(5') bond (torsion angle  $\gamma$ ) is part of both fused

rings, an interdependence of the geometry of both rings may exist. For this reason, an additional geometrical parameter (the torsion angle  $\gamma$  describing the C-4'–C-5' bond) should be calculated in order to define the global conformation of the bicyclic nucleoside. Finally, to complete our study, the conformation around the glycosidic bond was studied.

Using the computer program PSEUROT,<sup>36</sup> it is possible to calculate the pseudorotational parameters of the furanose ring from three interprotonic coupling constants ( $^3J_{H1',H2'}$ ,  $^3J_{H2',H3'}$ ,  $^3J_{H3',H4'}$ ). In the case of our bicyclic nucleosides, it is not possible to completely describe the sugar pucker of the furanose in an analogous way due to the H-coupling barrier at C(3'). Thus, the pseudorotational parameters ( $P$  and  $\nu_m$ ) should be calculated using only one proton–proton vicinal coupling constant ( $^3J_{H1',H2'}$ ). Qualitatively, the  $^3J_{H1',H2'}$  coupling constants of **4**, **5**, **10**, and **12** comply with both an *E*-type conformation with  $P$  in the 54–108° range and a high *S*-type with  $P$  in the 180–234° range (Table 1).

<sup>1</sup>H NMR NOE experiments were used to corroborate the information obtained with the PSEUROT program about the conformation of the furanose ring. NOE methods were already successfully used for this purpose in other nucleosides.<sup>37</sup> Experimentally, the strong and positive NOE observed between H-1' and H-4' were consistent with a O4'-endo conformation.<sup>38</sup> Thus, only conformations in the Eastern part of the pseudorotational circuit<sup>39</sup> (Figure 3) were considered.

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**TABLE 1. Comparison of Experimental and Theoretical Data**

| <sup>1</sup> H NMR Experimental Data <sup>a</sup> |                                                  |                                      |                                      |                                       |
|---------------------------------------------------|--------------------------------------------------|--------------------------------------|--------------------------------------|---------------------------------------|
| compd                                             | $J_{H1'H2'}$<br>(Hz)                             | $J_{H4'H5'a}$<br>(Hz)                | $J_{H4'H5'b}$<br>(Hz)                | P furanose ring <sup>b</sup><br>(deg) |
| <b>4</b>                                          | 5.5                                              | 0                                    | 4.9                                  | 72–108, 198–234                       |
| <b>5</b>                                          | 4.2                                              | 0                                    | 4.4                                  | 54–90, 198–234                        |
| <b>10</b>                                         | 7.2                                              | 0                                    | 4.8                                  | 90–108, 180–216                       |
| <b>12</b>                                         | 3.6                                              | 0                                    | 4.3                                  | 54–90, 216–234                        |
| Theoretical Data                                  |                                                  |                                      |                                      |                                       |
| compd                                             | $\theta_{H1'-C1'-C2'-H2'}$ <sup>c</sup><br>(deg) | $\theta_{H4'-C4'-C5'-H5'R}$<br>(deg) | $\theta_{H4'-C4'-C5'-H5'S}$<br>(deg) | P furanose ring (deg) $\nu_m^d$       |
| <b>4</b>                                          | 135.4 (4.4)                                      | −93.7                                | +28.5                                | 78 34                                 |
| <b>10</b>                                         | 157.2 (6.6)                                      | −100.3                               | +20.8                                | 120 37                                |
| <b>12</b>                                         | 121.3 (2.9)                                      | −93.2                                | +28.8                                | 58 28                                 |

<sup>a</sup> Measured in CDCl<sub>3</sub> at 300 MHz. <sup>b</sup> Pseudorotation angle (*P*) deduced from the observed coupling constant  $J_{H1',H2'}$ . It is evident that the observed coupling constant  $J_{H1',H2'}$  yields two possible conformational ranges. <sup>c</sup> Dihedral angle, with back-calculated  $^3J_{HH}$  in parentheses. <sup>d</sup> Maximum out-of-plane pucker.

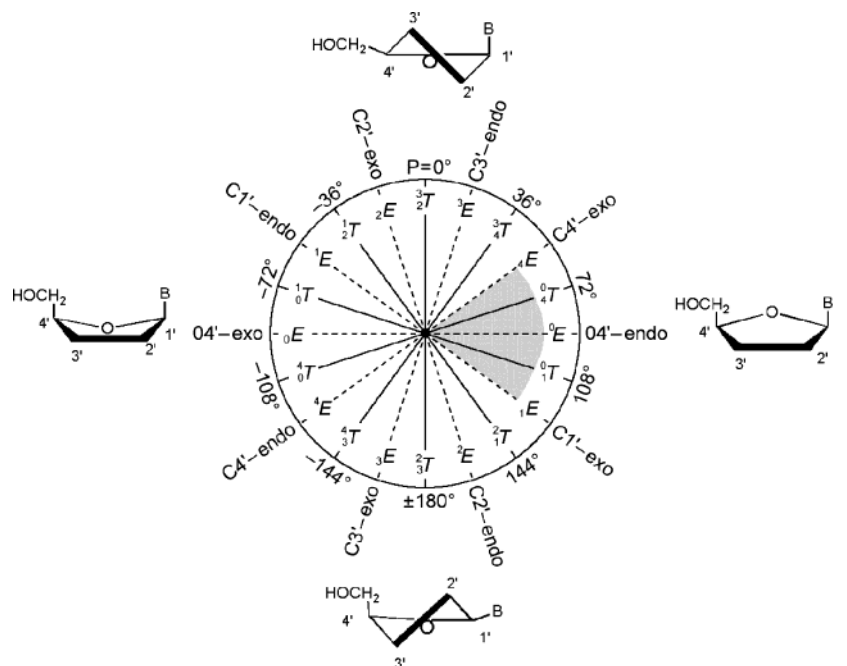
Since it is difficult to establish the presence of a single conformation in solution using a unique  $^3J_{H,H}$  (due to the fact that the expected value of  $^3J_{H1',H2'}$  is very similar for a pure *E*-type conformation and for a model invoking an N/S exchange), the added information provided by  $J_{C,H}$  values can be helpful. In fact,  $^3J_{C,H}$  coupling constants have been previously used in our group<sup>40</sup> to determine the conformation of nucleosides with an H-coupling barrier at C (3') and also as conformational probes in different sugars.<sup>41</sup> The procedure, similar to PSEUROT, relates the vicinal carbon–proton coupling constant values to the pseudorotational parameters *P* and  $\nu_m$ . Thus, information about the geometry of the furanose ring was obtained from the five vicinal coupling constants ( $J_{H1',H2'}$ ,  $J_{C4',H2'}$ ,  $J_{C4',H1'}$ ,  $J_{C2',H4'}$ , and  $J_{C1',H4'}$ ).<sup>40,42</sup> The pseu-

dorotational parameters obtained suggested that the furanose moiety of our bicyclic nucleosides nucleosides exists in an East conformation (Figure 3). Thus, the calculated sugar ring pucker (*P*) using this method is in the range predicted by the PSEUROT method and NOE experiments.

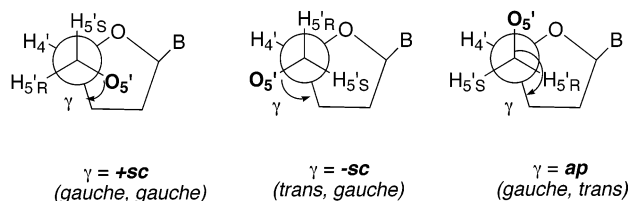
Bicyclic nucleosides are usually found in a low energy conformation, but there may be a lower proportion of other conformers. Variable-temperature <sup>1</sup>H NMR experiments have proved useful to detect mixtures of conformers in solution.<sup>9a,18c,37</sup> For this reason, with the purpose of detecting a possible equilibrium between different conformational states we recorded <sup>1</sup>H NMR spectra of **4**, **5**, **10**, and **12** in chloroform, acetone and methanol at different temperatures. We found small changes in chemical shift, and coupling constants between the different solvents and/or the high- and low-temperature spectra. Consequently, the situation could be explained as a dynamic equilibrium between two or more conformations in the East part of the pseudorotation cycle that it is shifted toward a major conformer.

In addition, the orientation about the C4'–C5' bond in the bicyclic nucleosides **4**, **5**, **10**, and **12** has been studied using  $^3J_{H,H}$  coupling constants as well as NOE experiments. In natural nucleosides, rotation about the exocyclic C4'–C5' bond allows three main conformations (Figure 4). In our case, the C(4')–C(5') bond (torsion angle  $\gamma$ ) is part of both fused rings and the rotation about this bond should be restricted.

For all of these compounds, the  $J_{H4',H5'}$  coupling constants are very similar and were found to be <1 Hz for one H-5' and 4.3–4.9 Hz for the other H-5' (Table 1). In addition, positive NOE between H-4' and both H-5' were observed. However, the NOE intensity between H-4' and one of the H-5' is smaller (~1.1) than with the other (~4.0).



**FIGURE 3.** Pseudorotation cycle of the furanose ring in nucleosides. Envelope (E) and twist (T) forms alternate every 18°. Representative conformers for the four cardinal points are indicated. The shaded area indicates the preferred pseudorotational region for bicyclic nucleosides **4**, **5**, **10**, and **12**.



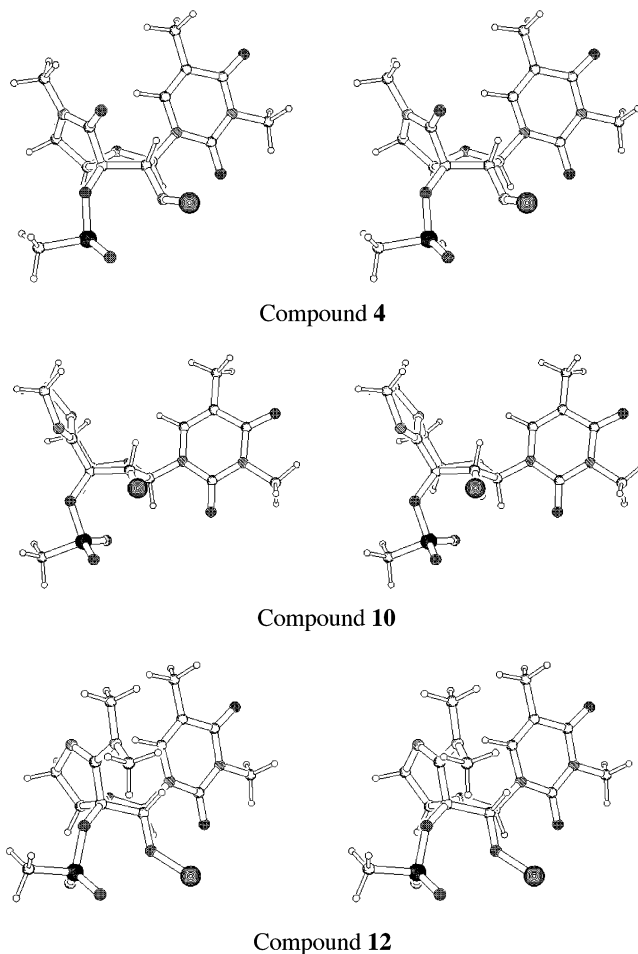
**FIGURE 4.** Rotation about the exocyclic C4'–C5' bond allows three main conformations in natural nucleosides.

All the experimental data are indicative of a gauche–gauche disposition of H-4', and the two H-5' are only compatible with a torsional angle  $\gamma$  in the synclinal (+sc) range<sup>39</sup> (Figure 4).

Finally, the conformation around the glycosidic bond of **4**, **5**, **10**, and **12** was studied from NOE experiments. Positive NOEs between the base proton H-6 and the sugar protons H-1' and H-2' were observed. This fact is indicative of the tendency of the base to occur in both the syn and anti conformations in solution. However, from the comparison of the NOE intensity ratios H-6/H-2' and H-6/H-1' we can conclude that these compounds show a higher propensity to be found in the anti conformation.

**Molecular Modeling Studies.** To determine the conformation of compounds **4**, **5**, **10**, and **12**, molecular modeling studies were carried out in addition to the NMR solution studies. Semiempirical quantum chemical methods proved unsuitable for studying the conformational behavior of the bicyclic and tricyclic nucleosides as they showed a strong tendency to make the furanose ring planar. Similarly, the unrestrained molecular dynamics simulations for these compounds did not result in major conformational changes from the initial structure, be it the syn or the anti conformer, and the average values obtained for the pseudorotation phase angle (154° and 152°, respectively) were also incompatible with the experimental information (Table 1).

To obtain better agreement between the structural parameters and the experimental data, a mixed molecular mechanics–quantum chemical approach was then followed. First, a molecular dynamics simulation for compound **12** that incorporated torsional restraints compatible with the experimental values for  $^3J_{H1',H2'}$  and  $\gamma$  showed a syn  $\rightarrow$  anti transition after 750 ps when the initial structure was syn, and a stable anti conformation when this was the starting structure. This result strongly suggests a preference for the anti conformation over the syn, in agreement with the experimental evidence. In addition, the sugar pucker in the anti conformer adopted a value comprised within the experimentally allowed range (Table 1) after about 75 ps and was maintained thereafter. When an energy-minimized average structure from the dynamics trajectory was optimized using density functional theory and a 3-21G\* basis set, a C4'-exo ( $_4E$ )



**FIGURE 5.** Stereo representations of the structures calculated for compounds **4**, **10**, and **12**, as optimized at the B3LYP/3-21G\* level. The concentric sphere corresponds to the silicon atom from the *tert*-butyldimethylsilyl group (not plotted for clarity).

puckering for **12** and torsional angles that were fully consistent with the experimental J coupling constants were obtained (Table 1). Therefore, in compound **12**, and by extension in compound **5** as well, atoms C3', C4', N, and C5' are almost coplanar and the C4' in the sugar ring is displaced from the plane formed by C3', C2', C1', and O4' (Figure 5).

In a similar way, the calculated structures for **4** and **10** show, respectively, ( $^0T_1$ ) and ( $_1E$ ) puckerings which also are in good agreement with the experimental data (Table 1). In the bicyclic compound **4**, C4' is the only out-of-plane atom in the pyrrolidinone ring and the furanose ring adopts a twisted conformation that is very close to O4'-endo (Figure 5). In tricyclic compound **10**, the central ring is puckered in an envelope form with atoms C4'', C3', C4', and C5' in a plane (Figure 5). This forces the C1' furanose ring atom out of the plane formed by C2', C3', C4', and O4' for which reason its conformation is best described as C1'-exo.

The calculated structures also shed additional light on another issue that was addressed by the NMR experi-

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ments, namely, the disposition of torsional angles  $H4'-C4'-C5'-H5'_R$  and  $H4'-C4'-C5'-H5'_S$ . The values of  $-93.7^\circ$  and  $+28.5^\circ$  measured for the former and the latter, respectively, in compound **12** can account for the differing  $^3J_{H4',H5'} < 1$  Hz and  $^3J_{H4',H5'} = 4.3$  Hz coupling constant values observed between  $H4'$  and each of the  $H5'$  hydrogens (Table 1). Similarly, the calculated structures for **4** and **10** also show torsional angles  $H4'-C4'-C5'-H5'_R$  and  $H4'-C4'-C5'-H5'_S$  that are compatible with the experimental data (Table 1).

**Conclusions.** Starting from TSAO-derivatives, new bi- and tricyclic ribo nucleosides were obtained. The functionalized bridge between the centers  $C(3')$  and  $C(5')$  present in these compounds offers a convenient scaffold for introducing functional groups at a unique position. Compound **VII** is a versatile intermediate that has proved very useful for obtaining this type of structures in high yield.

The furanose ring in solution for these compounds does not appear to be involved in a conformational  $N \rightleftharpoons S$  equilibrium as in the case of conventional nucleosides. Rather, the whole series of nucleosides herein described covers the eastern side of the pseudorotation cycle, with the precise conformation of the ribofuranose being finely tuned by the nature of the substituents on the fused ring directly attached to it (Figure 5). Thus, these compounds can be considered as a novel class of *E*-type conformationally restricted bi- and tricyclic ribonucleosides containing [3.3.0]-fused carbohydrate moieties. The *E*-type is an unusual high-energy conformation in unmodified nucleosides<sup>39</sup> but has been found to be the preferred furanose conformation in other bicyclic and tricyclic nucleoside analogues.<sup>13c,43,44</sup> Therefore, we find evidence that the presence in these nucleosides of the fused ring systems impose limitations in their flexibility that restrict the puckering of the furanose ring to a very well-defined region of the pseudorotation cycle that is nevertheless distinct for each of the bicyclic nucleosides obtained, as assessed by both NMR and theoretical methods. In addition, conformational studies showed a preferred disposition for the base substituents in the anti range and a torsion angle  $\gamma$  describing the  $C-4'-C-5'$  bond in the +sc range.

## Experimental Section

The names of the bi- and tricyclic 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.

**General Procedure for the Synthesis of Nucleosides 4–18.** To a solution of **2**<sup>29</sup> (0.15 g, 0.23 mmol) in dry acetonitrile (5 mL) was added an excess of the appropriate amine (1.15 mmol), and the reaction mixture was refluxed for 20 h. For low boiling point amines (2 M methanolic solution of methylamine, *N,N*-dimethylamine (2 M in THF), or azetidine), the reaction was heated in a sealed tube at 70 °C for 20 h. After evaporation of the solvents, the residue was purified by CCTLC

on the chromatotron. The chromatography eluent and yield of the isolated products (**4–18**) are indicated below for each reaction.

**(1R,3R,4R,5R)-4-tert-Butyldimethylsilyloxy-5-mesyloxy-7-methyl-6-oxo-3-[(3'-N-methyl)thymine-1'-yl]-7-aza-2-oxabicyclo[3.3.0]octane, (1R,3R,4R,5R)-4-tert-Butyldimethylsilyloxy-5-mesyloxy-6-methylamino-3-[(3'-N-methyl)thymine-1'-yl]-7-aza-2-oxabicyclo[3.3.0]oct-6-ene, and [1-[2'-O-tert-Butyldimethylsilyl-5'-deoxy- $\beta$ -D-erythro-pent-4'-ene-furanosyl]-3-N-methylthymine]-3'-spiro-5''-(4'-amino-1'',2''-oxathiole 2'',2''-dioxide) (**4**, **5**, and **6**).** The general procedure was followed using a 2 M methanolic solution of methylamine (0.58 mL, 1.15 mmol). Chromatography with dichloromethane/methanol (30:1) gave, from the fastest moving band, 0.03 g (25%) of **6**<sup>30</sup> as a syrup.

From the intermediate moving band, 0.02 g (18%) of **4** was isolated as an amorphous solid:  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.93 (s, 3H), 2.86 (s, 3H,  $CH_3N$ ), 3.20 (s, 3H), 3.33 (s, 3H), 3.44 (d, 1H,  $H-5'_a$ ,  $J_{5'a,5'b} = 11.2$  Hz), 3.85 (dd, 1H,  $H-5'_b$ ), 4.42 (d, 1H,  $H-2'$ ), 4.94 (d, 1H,  $J_{4',5'} = 4.9$  Hz), 5.89 (d, 1H,  $J_{1',2'} = 5.5$  Hz), 6.91 (s, 1H);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  13.4, 28.0, 31.1, 41.1, 54.9 ( $C-5'$ ), 78.2, 79.3, 89.6, 90.4, 110.4, 132.5, 150.9, 163.2, 163.8 (CO); MS *m/e* FAB 504.2 ( $MH^+$ ). Anal. Calcd for  $C_{20}H_{33}N_3O_8SSi$ : C, 47.70; H, 6.60; N, 8.34; S, 6.37. Found: C, 47.50; H, 6.58; N, 8.31; S, 6.10.

From the slowest moving band, 0.02 g (18%) of **5** was isolated as an amorphous solid:  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.94 (s, 3H), 2.85 (s, 1H,  $N-CH_3$ ), 3.09 (s, 3H), 3.33 (s, 3H), 3.87 (d, 1H,  $H-5'_a$ ,  $J_{5'a,5'b} = 15.6$  Hz), 4.06 (dd, 1H,  $H-5'_b$ ), 4.41 (d, 1H,  $H-2'$ ), 5.04 (d, 1H,  $J_{4',5'} = 4.4$  Hz), 5.93 (d, 1H,  $J_{1',2'} = 4.2$  Hz), 6.95 (s, 1H,  $H-6$ );  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  13.4, 27.9, 29.6 ( $CH_3-NH$ ), 40.1, 59.1, 76.9, 85.1, 94.4, 91.6, 109.9, 132.5, 150.9 ( $C-2$ ), 160.8 ( $C=N$ ), 163.3; HRMS *m/e* FAB 503.1993 ( $MH^+$ ,  $C_{20}H_{34}N_4O_7SSi$  requires 503.1995). Anal. Calcd for  $C_{20}H_{34}N_4O_7SSi$ : C, 47.79; H, 6.82; N, 11.15; S, 6.38. Found: C, 47.50; H, 6.58; N, 11.10; S, 6.20.

**(1R,3R,4R,5R)-4-tert-Butyldimethylsilyloxy-5-mesyloxy-7-[N,N-dimethylethyl-6-oxo-3-[(3'-N-methyl)thymine-1'-yl]-7-aza-2-oxabicyclo[3.3.0]octane, (1R,3R,4R,5R)-4-tert-Butyldimethylsilyloxy-5-mesyloxy-6-N,N-dimethylethylenediamino-3-[(3'-N-methyl)thymine-1'-yl]-7-aza-2-oxabicyclo[3.3.0]oct-6-ene, and [1-[2'-O-tert-Butyldimethylsilyl-5'-deoxy- $\beta$ -D-erythro-pent-4'-ene-furanosyl]-3-N-methylthymine]-3'-spiro-5''-(4'-amino-1'',2''-oxathiole 2'',2''-dioxide) (**7**, **8**, and **6**).** The general procedure was followed using *N,N*-dimethylethylenediamine (0.1 mL, 1.15 mmol). Chromatography with dichloromethane/methanol (20:1) afforded, from the fastest moving band, 0.03 g (26%) of **6**.<sup>30</sup>

From the intermediate band, 0.04 g (27%) of **7** was isolated as a white amorphous solid:  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.95 (s, 3H), 2.28 (s, 6H), 2.39, 2.60 (2m, 2H), 3.23, 3.67 (2m, 2H), 3.25 (s, 3H), 3.33 (s, 3H), 3.50 (d, 1H,  $J_{5'a,5'b} = 10.9$  Hz), 3.85 (dd, 1H), 4.35 (d, 1H), 4.94 (d, 1H,  $J_{4',5'} = 5.3$  Hz), 5.95 (d, 1H,  $J_{1',2'} = 7.5$  Hz), 6.95 (s, 1H);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  13.25, 28.1, 40.7, 45.4, 40.8, 50.7, 55.7, 76.4, 78.2, 87.5, 89.6, 111.0, 133.0, 150.9, 163.2, 167.7; HRMS *m/e* FAB 561.2422 ( $MH^+$ ,  $C_{23}H_{40}N_4O_8SSi$  requires 561.2424). Anal. Calcd for  $C_{23}H_{40}N_4O_8SSi$ : C, 49.27; H, 7.19; N, 9.99; S, 5.72. Found: C, 49.39; H, 7.17; N, 10.13; S, 5.50.

From the slowest moving band, 0.01 g (10%) of **8** was isolated as an amorphous solid:  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.93 (s, 3H), 2.27 (s, 6H), 2.52 (m, 2H), 3.23, 3.34 (2m, 2H), 3.19 (s, 3H), 3.31 (s, 3H), 3.45 (d, 1H,  $J_{5'a,5'b} = 10.8$  Hz), 3.90 (dd, 1H), 4.38 (d, 1H), 4.94 (d, 1H,  $J_{4',5'} = 4.5$  Hz), 5.95 (d, 1H,  $J_{1',2'} = 5.9$  Hz), 6.97 (s, 1H). Anal. Calcd for  $C_{23}H_{41}N_5O_7SSi$ : C, 49.35; H, 7.38; N, 12.51; S, 5.73. Found: C, 49.40; H, 7.27; N, 12.43; S, 5.65.

**(1R,3R,4R,5R)-4-tert-Butyldimethylsilyloxy-5-mesyloxy-6-ethylenediamino-3-[(3'-N-methyl)thymine-1'-yl]-7-aza-2-oxabicyclo[3.3.0]oct-6-ene, (1R,8R,10R,11R)-11-tert-Butyldimethylsilyloxy-1-mesyloxy-10-[(3'-N-methyl)thymine-1'-yl]-3,6-diaza-9-oxatricyclo[6.3.0.0<sup>2,6</sup>]undec-2-ene, and**

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[1-[2'-*O*-*tert*-Butyldimethylsilyl-5'-deoxy- $\beta$ -D-erythro-pent-4'-ene-furanosyl]-3-*N*-methylthymine]-3'-spiro-5''-(4''-amino-1'',2''-oxathiole 2'',2''-dioxide) (**9**, **10**, and **6**). The general procedure was followed using ethylenediamine (0.08 mL, 1.15 mmol). Two successive purifications, first with dichloromethane/methanol (10:1) and then with hexane/ethyl acetate (1:2) gave, from the fastest moving band, 0.04 g (35%) of **6**.<sup>30</sup>

From the intermediate band, 0.03 g (28%) of **10** was isolated as a white amorphous solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.95 (s, 3H), 3.06, 3.47 (2m, 2H), 3.26 (m, 2H), 3.31 (s, 6H), 4.03, 4.25 (2m, 2H), 4.16 (d, 1H), 5.13 (d, 1H,  $J_{4',5'} = 4.8$  Hz), 6.00 (d, 1H,  $J_{1',2'} = 7.2$  Hz), 7.00 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  13.3, 28.1, 50.4, 50.4, 41.7, 51.2, 76.4, 83.0, 87.8, 88.7, 110.9, 132.6, 151.0, 163.2, 170.4; MS *m/e* FAB 515.2 (MH<sup>+</sup>). Anal. Calcd for C<sub>21</sub>H<sub>34</sub>N<sub>4</sub>O<sub>7</sub>SSi: C, 49.01; H, 6.66; N, 10.89; S, 6.23. Found: C, 49.29; H, 6.26; N, 10.73; S, 6.20.

From the slowest band, 0.02 g (20%) of **9** was isolated as a white amorphous solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  2.10 (s, 3H), 3.20 (m, 2H), 3.42 (s, 3H), 3.47 (s, 3H), 3.48 (m, 2H), 4.08 (d, 1H,  $J_{5'a,5'b} = 14.6$  Hz), 4.29 (dd, 1H), 5.00 (d, 1H), 5.35 (d, 1H,  $J_{4',5'} = 4.0$  Hz), 5.90 (d, 1H,  $J_{1',2'} = 2.6$  Hz), 7.43 (s, 1H). Anal. Calcd for C<sub>21</sub>H<sub>37</sub>N<sub>5</sub>O<sub>7</sub>SSi: C, 47.44; H, 7.01; N, 13.17; S, 6.03. Found: C, 47.49; H, 7.20; N, 13.03; S, 6.02.

[1-[2'-*O*-*tert*-Butyldimethylsilyl-5'-deoxy-5''-(*N,N*-dimethylamino)- $\beta$ -D-ribofuranosyl]-3-*N*-methylthymine]-3'-spiro-5''-(4''-amino-1'',2''-oxathiole-2'',2''-dioxide), (1*R*,3*R*,4*R*,5*R*)-4-*tert*-Butyldimethylsilyloxy-5-mesyloxy-6-*N,N*-(dimethylamino)-3-[(3'-*N*-methyl)thymine-1'-yl]-7-aza-2-oxabicyclo[3.3.0]oct-6-ene, and [1-[2'-*O*-*tert*-Butyldimethylsilyl-5'-deoxy- $\beta$ -D-erythro-pent-4'-ene-furanosyl]-3-*N*-methylthymine]-3'-spiro-5''-(4''-amino-1'',2''-oxathiole 2'',2''-dioxide) (**11**, **12**, and **6**). The general procedure was followed using *N,N*-dimethylamine (2 M in THF) (0.58 mL, 1.15 mmol). Two successive purifications, with dichloromethane/methanol (50:1) and then with dichloromethane/methanol/ammonium hydroxide (20:1:0.5%), gave, from the fastest moving band, 0.03 g (28%) of **6**.<sup>30</sup>

From the intermediate band, 0.01 g (8%) of **12** was isolated as a syrup: <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>CO]  $\delta$  1.83 (s, 3H), 2.93 (s, 3H), 3.23 (2s, 6H), 3.72 (d, 1H,  $J_{5'a,5'b} = 15.7$  Hz), 4.04 (dd, 1H), 4.81 (d, 1H), 5.23 (d, 1H,  $J_{4',5'} = 4.3$  Hz), 5.89 (d, 1H,  $J_{1',2'} = 4.3$  Hz), 7.26 (s, 1H). Anal. Calcd for C<sub>21</sub>H<sub>36</sub>N<sub>4</sub>O<sub>7</sub>SSi: C, 48.82; H, 7.02; N, 10.84; S, 6.20. Found: C, 48.73; H, 7.07; N, 10.95; S, 6.10.

From the slowest moving band, 0.03 g (23%) of **11** was isolated as a syrup: <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>CO]  $\delta$  1.90 (s, 3H), 2.25 (s, 6H), 2.77 (d, 2H), 3.26 (s, 3H), 4.29 (t, 1H,  $J_{4',5'} = 5.3$  Hz), 4.96 (d, 1H), 5.63 (s, 1H), 5.67 (d, 1H,  $J_{1',2'} = 7.2$  Hz), 6.70 (bs, 2H), 7.65 (s, 1H). Anal. Calcd for C<sub>21</sub>H<sub>36</sub>N<sub>4</sub>O<sub>7</sub>SSi: C, 48.82; H, 7.02; N, 10.84; S, 6.20. Found: C, 48.80; H, 6.97; N, 10.65; S, 6.00.

[1-[2'-*O*-*tert*-Butyldimethylsilyl-5'-deoxy-5''-pyrrolidinyl- $\beta$ -D-ribofuranosyl]-3-*N*-methylthymine]-3'-spiro-5''-(4''-amino-1'',2''-oxathiole-2'',2''-dioxide), (1*R*,3*R*,4*R*,5*R*)-4-*tert*-Butyldimethylsilyloxy-5-mesyloxy-6-pyrrolidinyl-3-[(3'-*N*-methyl)thymine-1'-yl]-7-aza-2-oxabicyclo[3.3.0]oct-6-ene, and [1-[2'-*O*-*tert*-Butyldimethylsilyl-5'-deoxy- $\beta$ -D-erythro-pent-4'-ene-furanosyl]-3-*N*-methylthymine]-3'-spiro-5''-(4''-amino-1'',2''-oxathiole 2'',2''-dioxide) (**13**, **14**, and **6**). The general procedure was followed using pyrrolidine (0.1 mL, 1.15 mmol). The reaction was heated at 80 °C for 5 h. Chromatography with dichloromethane/methanol/ammonium hydroxide (10:1:0.5%) gave, from the fastest moving band, 0.019 g (18%) of **6**<sup>30</sup> as a syrup.

From the intermediate band, 0.04 g (34%) of **14** was isolated as an amorphous solid: <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>CO]  $\delta$  1.82 (s, 3H), 1.83 (m, 4H), 3.18 (s, 3H), 3.22 (s, 3H), 3.38 (m, 4H), 3.81 (d, 1H,  $J_{5'a,5'b} = 15.7$  Hz), 4.07 (dd, 1H), 4.95 (d, 1H), 5.23 (d, 1H,  $J_{4',5'} = 3.9$  Hz), 5.77 (d, 1H,  $J_{1',2'} = 2.8$  Hz), 7.23 (s, 1H). Anal. Calcd for C<sub>23</sub>H<sub>38</sub>N<sub>4</sub>O<sub>7</sub>SSi: C, 50.90; H, 7.06; N, 10.32; S, 5.91. Found: C, 50.80; H, 6.98; N, 10.20; S, 5.63.

From the slowest moving band, 0.04 g (34%) of **13** was isolated as an amorphous solid: <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>CO]  $\delta$  1.68 (m, 4H), 1.90 (s, 3H), 2.54 (m, 4H), 2.91 (m, 2H), 3.26 (s, 3H), 4.30 (dd, 1H,  $J_{4',5'a} = 4.0$ ,  $J_{4',5'b} = 4.1$  Hz), 4.94 (d, 1H), 5.64 (s, 1H), 5.72 (d, 1H,  $J_{1',2'} = 7.4$  Hz), 6.55 (bs, 2H), 7.63 (s, 1H). Anal. Calcd for C<sub>23</sub>H<sub>38</sub>N<sub>4</sub>O<sub>7</sub>SSi: C, 50.90; H, 7.06; N, 10.32; S, 5.91. Found: C, 50.77; H, 7.00; N, 10.11; S, 5.60.

[1-[2'-*O*-*tert*-Butyldimethylsilyl-5'-deoxy-5''-piperidyl- $\beta$ -D-ribofuranosyl]-3-*N*-methylthymine]-3'-spiro-5''-(4''-amino-1'',2''-oxathiole 2'',2''-dioxide), (1*R*,3*R*,4*R*,5*R*)-4-*tert*-Butyldimethylsilyloxy-5-mesyloxy-6-piperidyl-3-[(3'-*N*-methyl)thymine-1'-yl]-7-aza-2-oxabicyclo[3.3.0]oct-6-ene, and [1-[2'-*O*-*tert*-Butyldimethylsilyl-5'-deoxy- $\beta$ -D-erythro-pent-4'-ene-furanosyl]-3-*N*-methylthymine]-3'-spiro-5''-(4''-amino-1'',2''-oxathiole 2'',2''-dioxide) (**15**, **16**, and **6**). The general procedure was followed using piperidine (0.15 mL, 1.15 mmol). Chromatography with dichloromethane/methanol (50:1) afforded, from the fastest moving band, 0.02 g (24%) of **6**.<sup>30</sup>

From the intermediate moving band, 0.05 g (40%) of **16** was isolated as an amorphous solid: <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>CO]  $\delta$  1.54 (m, 6H), 1.82 (s, 3H), 3.22 (s, 3H), 3.24 (s, 3H), 3.32 (m, 4H), 3.86 (d, 1H,  $J_{5'a,5'b} = 16.1$  Hz), 4.12 (dd, 1H), 4.82 (d, 1H), 5.23 (d, 1H,  $J_{4',5'} = 3.6$  Hz), 5.70 (d, 1H,  $J_{1',2'} = 1.9$  Hz), 7.11 (s, 1H). Anal. Calcd for C<sub>24</sub>H<sub>40</sub>N<sub>4</sub>O<sub>7</sub>SSi: C, 51.78; H, 7.24; N, 10.06; S, 5.76. Found: C, 51.45; H, 7.18; N, 10.00; S, 5.50.

From the slowest moving band, 0.03 g (26%) of **15** was isolated as an amorphous solid: <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>CO]  $\delta$  1.54 (m, 6H), 1.91 (s, 3H), 2.48 (m, 4H), 2.79 (m, 2H), 3.27 (s, 3H), 4.34 (m, 1H), 4.91 (d, 1H), 5.63 (s, 1H), 5.73 (d, 1H,  $J_{1',2'} = 7.30$  Hz), 6.49 (bs, 2H), 7.61 (s, 1H). Anal. Calcd for C<sub>24</sub>H<sub>40</sub>N<sub>4</sub>O<sub>7</sub>SSi: C, 51.78; H, 7.24; N, 10.06; S, 5.76. Found: C, 51.50; H, 7.21; N, 9.89; S, 5.60.

[1-[2'-*O*-*tert*-Butyldimethylsilyl-5'-deoxy-5''-azetidyl- $\beta$ -D-ribofuranosyl]-3-*N*-methylthymine]-3'-spiro-5''-(4''-amino-1'',2''-oxathiole-2'',2''-dioxide), (1*R*,3*R*,4*R*,5*R*)-4-*tert*-Butyldimethylsilyloxy-5-mesyloxy-6-azetidyl-3-[(3'-*N*-methyl)thymine-1'-yl]-7-aza-2-oxabicyclo[3.3.0]oct-6-ene, and [1-[2'-*O*-*tert*-Butyldimethylsilyl-5'-deoxy- $\beta$ -D-erythro-pent-4'-ene-furanosyl]-3-*N*-methylthymine]-3'-spiro-5''-(4''-amino-1'',2''-oxathiole 2'',2''-dioxide) (**17**, **18**, and **6**). The general procedure was followed using azetidine (0.15 mL, 1.15 mmol). Chromatography with dichloromethane/methanol (50:1) afforded from the fastest moving band 0.03 g (26%) of **6**.<sup>30</sup>

From the intermediate band, 0.01 g (12%) of **18** was isolated as an amorphous solid: <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>CO]  $\delta$  1.82 (s, 3H), 2.25 (m, 2H), 3.24 (s, 3H), 3.28 (s, 3H), 3.79 (d, 1H,  $J_{5'a,5'b} = 15.6$  Hz), 4.02 (t, 4H), 4.05 (dd, 1H), 4.73 (d, 1H), 5.21 (d, 1H,  $J_{4',5'} = 3.9$  Hz), 5.81 (d, 1H,  $J_{1',2'} = 2.8$  Hz), 7.09 (s, 1H). Anal. Calcd for C<sub>22</sub>H<sub>36</sub>N<sub>4</sub>O<sub>7</sub>SSi: C, 50.00; H, 6.81; N, 10.60; S, 6.06. Found: C, 49.80; H, 6.77; N, 10.50; S, 5.97.

From the slowest band, 0.01 g (12%) of **17** was isolated as an amorphous solid: <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>CO]  $\delta$  1.91 (s, 3H), 2.87 (m, 2H), 3.21 (m, 2H), 3.25 (s, 3H), 3.33 (m, 2H), 4.20 (t, 1H,  $J_{4',5'} = 4.1$  Hz), 4.87 (d, 1H), 5.64 (s, 1H), 5.82 (d, 1H,  $J_{1',2'} = 8.1$  Hz), 6.53 (bs, 2H), 7.64 (s, 1H). Anal. Calcd for C<sub>22</sub>H<sub>36</sub>N<sub>4</sub>O<sub>7</sub>SSi: C, 50.00; H, 6.81; N, 10.60; S, 6.06. Found: C, 49.83; H, 6.50; N, 10.45; S, 5.63.

5',*N*<sup>4'</sup>-Cyclo[1-[2'-*O*-*tert*-butyldimethylsilyl-5'-amino-5'-deoxy- $\beta$ -D-ribofuranosyl]-3-*N*-methylthymine]-3'-spiro-5''-(4''-amino-1'',2''-oxathiole 2'',2''-dioxide) (**VII**). To a solution of **2**<sup>25</sup> (0.34 g, 0.53 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  $\times$  20 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and evaporated to dryness. The residue was purified by CCTLC on the chromatotron (dichloromethane/methanol, 10:1) to give 0.17 g (68%) of **VII** as a white foam: <sup>1</sup>H NMR [(CD<sub>3</sub>)<sub>2</sub>CO]  $\delta$  1.92 (s, 3H), 3.26 (s, 3H), 4.01 (m, 2H), 4.95 (m, 1H), 5.20 (d, 1H), 5.64 (s, 1H), 6.00 (d, 1H,  $J_{1',2'} = 8.9$

Hz), 6.56 (bs, 1H), 7.65 (s, 1H);  $^{13}\text{C}$  NMR  $[(\text{CD}_3)_2\text{CO}]$   $\delta$  12.7, 27.9, 54.2, 74.1, 80.9, 88.0, 93.7, 94.0, 111.0, 136.8, 151.8, 157.4, 163.7. Anal. Calcd for  $\text{C}_{19}\text{H}_{29}\text{N}_3\text{O}_7\text{SSi}$ : C, 48.39; H, 6.20; N, 8.91; S, 6.80. Found: C, 48.29; H, 5.17; N, 6.13; S, 6.50.

**Reaction of VII with Dimethylamine (2 M in THF).** To a solution of VII (0.15 g, 0.32 mmol) in dry acetonitrile (4 mL) was added *N,N*-dimethylamine (2 M in THF) (0.60 mL, 1.60 mmol). 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 with dichloromethane/methanol (25:1) to give 0.08 g (50%) of 12.

**Reaction of VII with *N,N*-Dimethylethylenediamine.** To a solution of VII (0.15 g, 0.32 mmol) in dry acetonitrile (4 mL) was added *N,N*-dimethylethylenediamine (0.14 mL, 1.60 mmol). 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 with dichloromethane/methanol (50:1) to give 0.12 g (68%) of 8.

**Acknowledgment.** We thank the Ministry of Education of Spain for grants to Cristina Chamorro and María-Cruz Bonache. The Spanish CICYT (Project No. SAF2000-0153-C02-01), the Comunidad de Madrid (Project No. 08.2/0044/2000 1), and the European Commission (ref QLK2-CT-2000-00291) are acknowledged for financial support. The European Commission is also acknowledged for the René Descartes-2001 Prize.

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

JO034088L