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One-Pot Synthesis of Polycyclic Nucleosides with Unusual Molecular Skeletons

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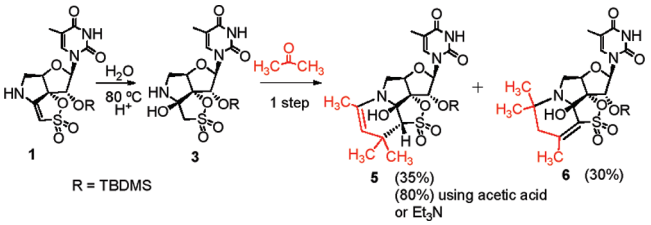

An α hydroxy pyrrolidine tricyclic nucleoside **3** and its spontaneous reaction with acetone is described. In this transformation highly functionalized polycyclic nucleosides with rather unusual molecular skeletons are formed in a complete regio- and stereoselective way. The reaction involves the formation of three new bonds, two of them novel carbon−carbon bonds, in a one-pot way. An enamine−iminium mechanism with participation of carbinolamine, iminium ion, and enamine intermediates is proposed as a plausible explanation for this transformation. The scope of the reaction is briefly studied concluding that the nature of the ketone (R^1COR^2) is critical for the initial attack of the NH to the carbonyl group.

Introduction

One of the main challenges of the synthetic organic chemists is to discover novel and efficient reactions which would allow the generation of structural, functional, and stereochemical complex molecules. The formation of multiple carbon−carbon bonds in a single chemical step represents a particularly useful approach to achieve this goal.[1,2]

In previous papers from our group the spirocyclic enamino sultone **1** (Scheme 1) as a versatile intermediate for the synthesis of a variety of highly functionalized polycyclic nucleosides having skeletal and stereochemical diversity was reported.[3,4] These compounds were efficiently obtained by a one-step reaction of **1** with *O*-, *N*-, *S*-, and *C*-nucleophiles and amino acids.[4]

Among the different reactions carried out, the hydrolysis (H_2O/CH_3CN) of **1** under basic non-nucleophilic conditions (potassium carbonate) attracted our attention (Scheme 1).[4] In this reaction the bicyclic nucleoside **4**, in which a γ-lactam ring was fused to the ribose moiety, was obtained in 68% yield. Formation of **4** was explained by a Michael-type addition of the nucleophile (H_2O) to the conjugated double bond of the α,β-unsaturated cyclic sulfonate ester in **1** (position 4″) to give intermediate **2**, which spontaneously tautomerizes to **3**. A subsequent ring-opening would give **4** (Scheme 1).[4]

In this paper we describe work carried out with the purpose of unequivocally characterizing intermediates **2** and/or **3** to provide evidence for their participation in the formation of **4**, and thus in the proposed mechanism. In addition, we report a serendipitous reaction that allows the formation of a unique class of polycyclic nucleosides. In this reaction two novel carbon−carbon bonds were formed in a single chemical step and iminium ions were postulated as active intermediates.

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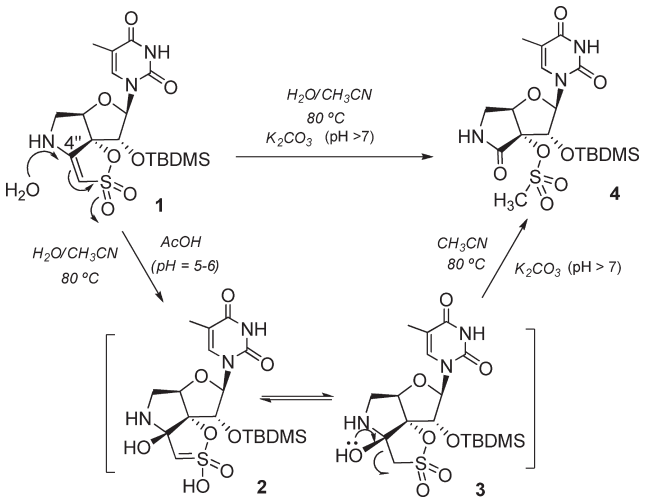
SCHEME 1. Synthesis of 3 and 4 As a Function of pH



Results and Discussion

Chemistry. To identify the optimal conditions that might afford the proposed intermediates **2** and/or **3**, the hydrolysis of enamine sultone **1** (in a 1:1 mixture of water:acetonitrile) was studied as a function of reaction time, temperature, and pH. Among the set of reactions assayed, the best results were obtained under weak acid media (pH adjusted at 5−6 with acetic acid), 80 °C, and 8 h reaction time. Under these conditions, compound **3** was obtained in 93% yield (Scheme 1).

Reaction of **3** with potassium carbonate (0.1 equiv) in acetonitrile at 80 °C afforded the bicyclic nucleoside **4** in 80% yield (Scheme 1). This experimental result unambiguously showed that compound **3** is an intermediate in the formation of **4** and supported our previously proposed mechanism.[4]

In addition, during the ^{1}H NMR studies aimed to elucidate the structure of **3**, an intriguing and unexpected result was observed when acetone-d_6 was used as the solvent. Thus, after 24 h, nucleoside **3** was transformed into a mixture of compounds that initially could not be identified. When **3** was dissolved in dry acetone and the solution was stirred at room temperature for 24 h two novel compounds, **5** and **6**, were isolated in 35% and 30% yield, respectively, after purification (Scheme 2). Conversely, when compound **3** was treated with an equimolar amount of acetone no transformation took place and **3** remained unaltered, thus indicating that a large excess of acetone is needed to drive the reaction forward (> 20 equiv of acetone per 1 equiv of **3**).

Structural assignment of **5** and **6** was not easy and this was achieved by ^{1}H and ^{13}C NMR spectroscopy, using mono- and bidimensional techniques (gHMBC,[5] gHSQC,[6] and ROESY experiments).

The ^{1}H NMR spectrum of **5** (Figure 1a) showed the disappearance of the characteristic AB system at ca. δ 3.60 ppm present in the starting compound (**3**) and the presence of five new singlets: δ 1.35, 1.36, and 1.78 ppm (3H each) and δ 3.45 and 4.41 ppm (1H each). The ^{1}H decoupled ^{13}C NMR spectrum of **5** showed 22 distinct resonances in agreement with the proposed structure.

On the other hand, the gHSQC spectrum showed the presence of four quaternary carbons (δ 32.3, 93.0, 94.4, and 134.7 ppm). Figures 1a and 2 show the correlations observed from the gHSQC and gHMBC spectra of **5**, respectively.

The stereochemistry of the new stereogenic center created on C-3″ was established as *R* on the basis of a ROESY experiment (Figure 1b). Thus, the signal at δ 3.45 ppm has a correlation with the signal of the H-2′ proton of the sugar indicating that these protons were at the same upper side of the furanose ring.

Similarly, the structure of **6** was also assigned on the basis of NMR experiments. Figure 3 shows the correlations observed in the gHMBC spectrum.

Mechanistic Considerations. Formation of nucleosides **5** and **6** indicated that **3** underwent an unusual reaction with acetone in which three new bonds, two of them novel carbon−carbon bonds, were formed to give in a one-pot way a novel six-membered ring in which the nitrogen and the carbon adjacent to the OSO_2 of the starting nucleoside **3** are now ring atoms (Scheme 2). The defined absolute stereochemistry of the new stereogenic center formed on C-3″ in compound **5** highlights the complete stereoselectivity of the reaction. The unique structure of the nucleosides **5** and **6** encouraged us to study in detail the transformation that **3** experiences in acetone.

A plausible mechanism for the formation of **5** and **6** is illustrated in Schemes 3 and 4, respectively. We propose that the reaction could be initiated by the nucleophilic attack of the NH of the pyrrolidine ring of **3** to the carbonyl moiety of the acetone to give the carbinolamine intermediate **8**. This easy attack is consistent with previously published results of our group that showed the high reactivity of the NH of the pyrrolidine ring present in tricyclic nucleosides toward carbonyl-containing reagents.[4] In addition, from Stork's work on the chemistry of enamines, it is known that pyrrolidines condense very efficiently with ketones and other carbonyl compounds.[7]

Next, a proton transfer mediated by the OH at the α-position of the pyrrolidine ring may afford **9**. A subsequent dehydration step can take place to afford the iminium intermediate **10** whose increase of electrophilicity might facilitate the subsequent reaction with a second molecule of acetone to afford **11**, in which a novel carbon−carbon bond is formed.

Dehydration of **11**, by elimination of the acidic proton adjacent to the SO_2, might give the iminium intermediate **12** that isomerizes to enamine **13**. Such isomerization might proceed through a proton transfer from one of the methyl groups attached to the nitrogen of the pyrrolidine ring to the oxygen (O^-) at the α-position of the pyrrolidine. Subsequently the conjugate addition of the enamine to the activated ($C{=}C{-}SO_2$) double bond of **13** might give the iminium intermediate **14**. A vast array of transformations via enamine intermediates, among them the conjugate addition to vinyl sulfones, has been reviewed by List et al. in 2007[8] giving strong support for this reaction. Finally,

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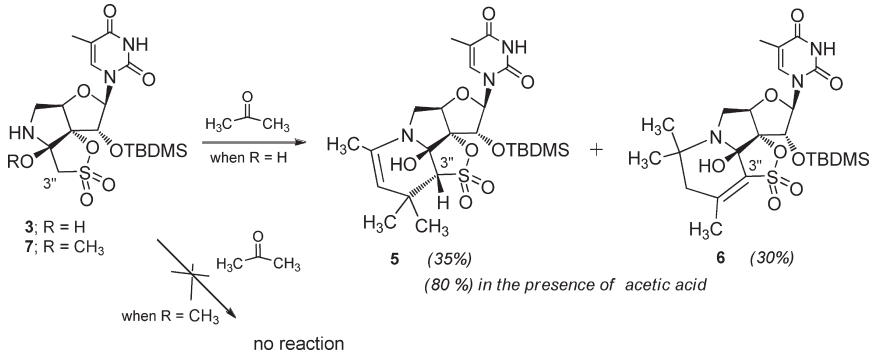
SCHEME 2. Reaction of 3 with Acetone



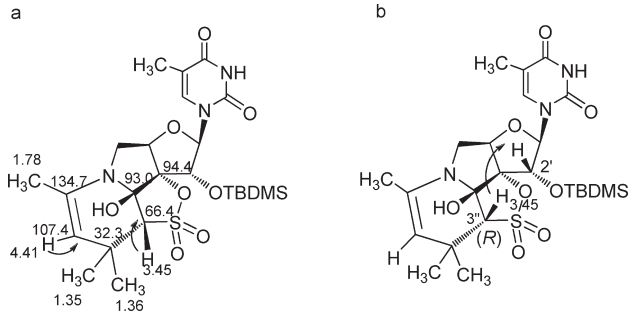


FIGURE 1. (a) gHSQC correlations in **5**. (b) ROESY correlations in **5**. Assignment of stereochemistry of H-3″.

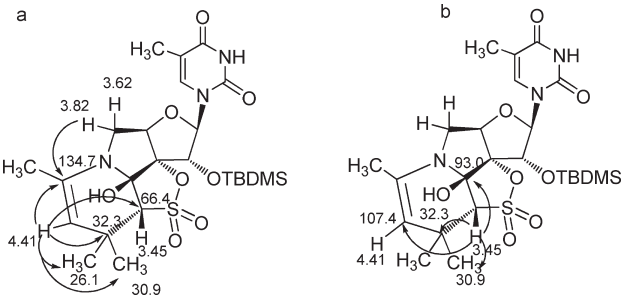


FIGURE 2. gHMBC correlations in **5**. (a) Correlations due to signal at δ 4.41 ppm. (b) Correlations observed for the signal at δ 3.45 ppm.

a proton transfer followed by isomerization of **15** would give **5**.

On the other hand, the iminium ion intermediate **12** can also follow an alternative pathway that leads to **6** (Scheme 4). The oxygen (O^-) at the α-position of the pyrrolidine ring might accept a proton from one of the neighboring methyl groups attached to the γ position with respect to the OSO_2 to afford the iminium intermediate **16**. Subsequently, a concerted intramolecular cyclization, promoted by iminium catalysis, might give **6**.

The contribution of iminium/enamine intermediates in the intramolecular cyclizations proposed to explain the

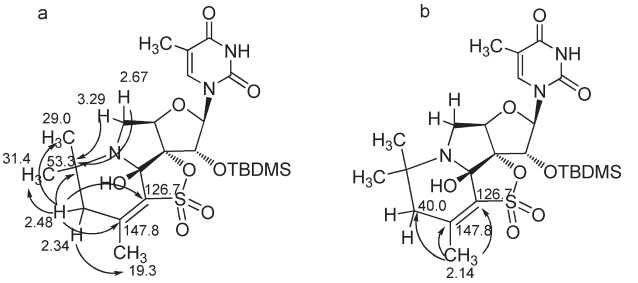


FIGURE 3. gHMBC correlations in **6**. (a) Observed correlations due to signals at δ 2.34 and 2.48 ppm. (b) Observed correlations due to signal at δ 2.14 ppm.

formation of **5** and **6** agrees with literature precedents in which a vast array of transformations have been achieved through these types of intermediates.[7−13]

A remarkable aspect of our mechanistic proposal is that the several proton transfers that take place in the formation of **5** and **6** seem to be mediated by the hydroxyl group at the α-position of the pyrrolidine ring, suggesting a critical role for this OH. To check this hypothesis, the methoxy derivative **7**, which has one OMe group at the α-position of the pyrrolidine instead of the OH (Scheme 2), was reacted with acetone and no trace of any novel compound was detected. This result proved that the OH at the α-position of the pyrrolidine ring is crucial for the progress of the reaction. A careful survey of the literature revealed that in those

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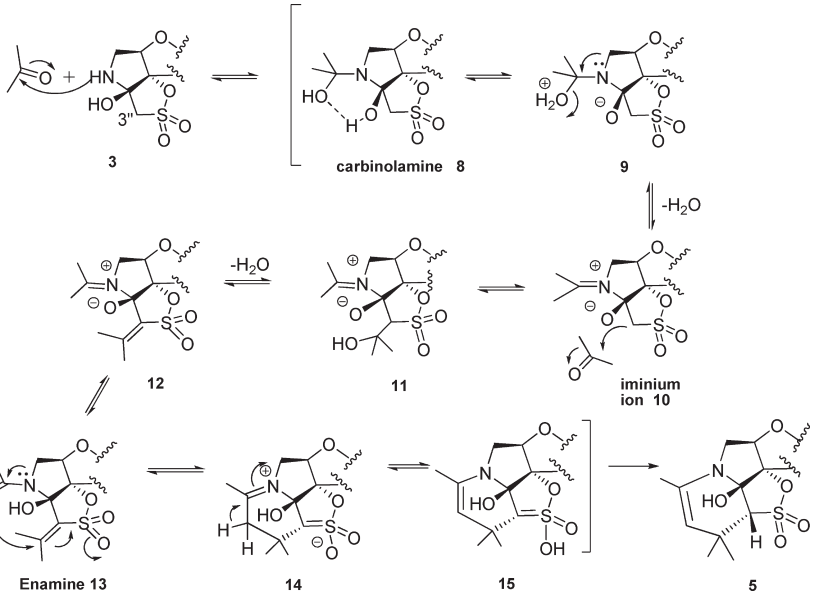
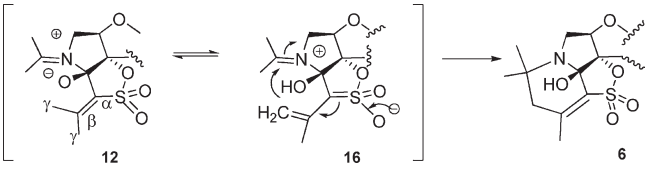
SCHEME 3. Proposed Evolution of 3 Toward 5 (enamine pathway)



SCHEME 4. Proposed Evolution of 12 Toward 6 (iminium pathway)



reactions that are catalyzed by (*S*)-proline,[8−12] or other proline-derived catalysts,[13] proton transfers have also been observed. As in our case, the crucial proton is proposed to always be transferred from the functional group at the α-position of the proline ring.

NMR and HPLC-ESI-MS Studies To Support the Proposed Mechanism. NMR studies were first performed to support the proposed mechanism. Thus, a solution of **3** (10 mg) in acetone (0.2 mL) with a small amount of acetone-d_6 (10%) was monitored by spectroscopic ^{1}H and ^{13}C NMR at room temperature during 4 days. Figure 4 outlines the portion of the ^{1}H NMR spectrum observed between δ 3.0 and 7.7 ppm.

The most significant difference between the starting and the final spectra was the disappearance of the characteristic AB system at ca. δ 3.60 ppm corresponding to the protons adjacent to the OSO_2 in **3**. Several novel intermediates were detected since the first few minutes of the reaction (10−30 min), species **X** (with a signal clearly observed at δ 7.5 ppm) is one of the most abundant. The concentration of **X** increased concomitant with decreasing **3**. After 1 h 30 min, **X** and **3** appeared in almost identical proportion and at this time a novel compound, subsequently identified as **6**, started to appear. After 7 h the starting material (**3**) was consumed and species **X** is clearly dominant. From this moment the concentration of **X** decreased concomitant with increasing **6**. After 4 days, **6** was the only compound in solution. By contrast, we were unable to detect **X**, indicating that it is an unstable intermediate (kinetic product) or a mixture of

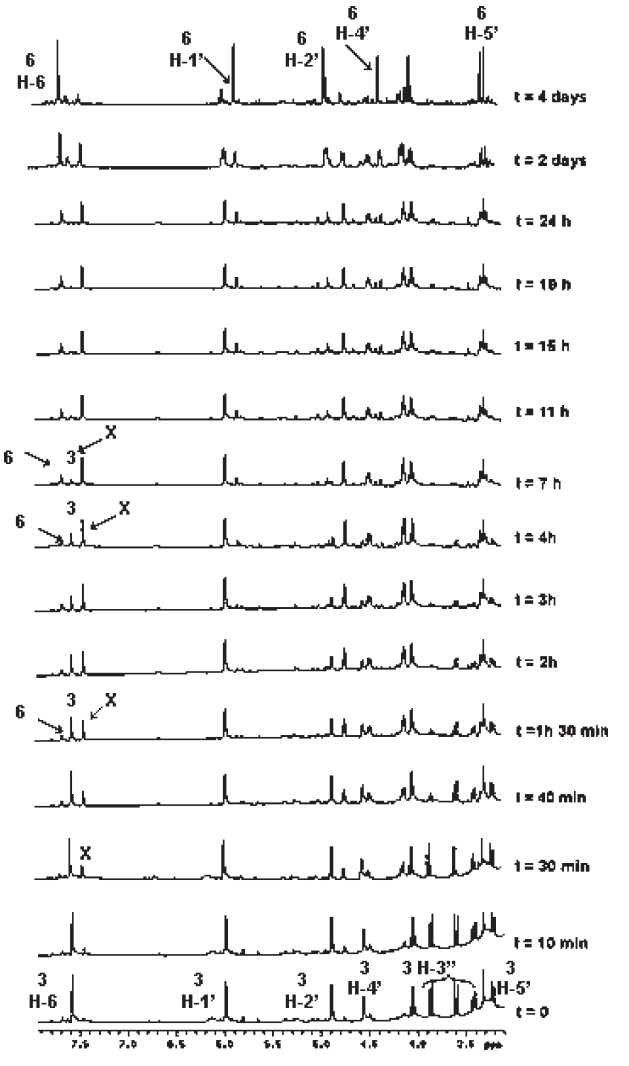


FIGURE 4. Evolution of the reaction of **3** in acetone monitored by ^{1}H NMR at different times (0−4 days).

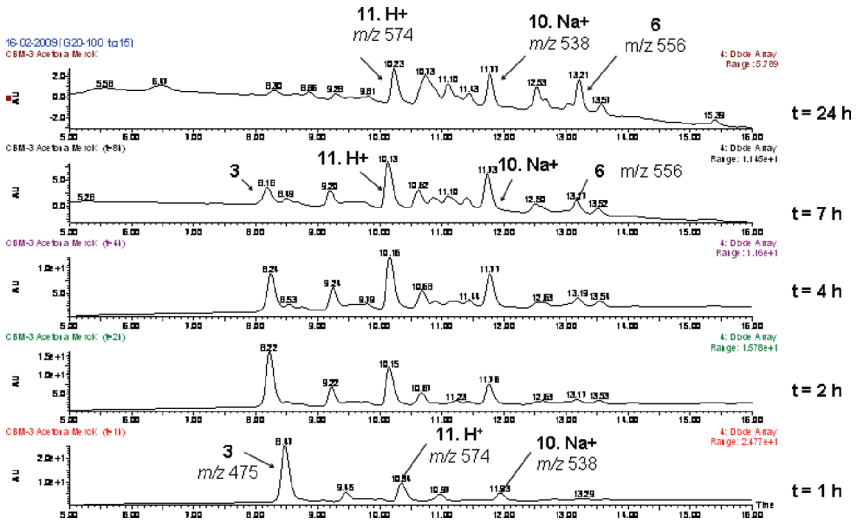


FIGURE 5. Evolution of the reaction of **3** in acetone monitored by HPLC-ESI-MS at different times (1−24 h) on a C_{18} reverse-phase column.

close related intermediates with a rapid equilibration on the NMR time scale.

The ^{13}C NMR spectrum after 7 h showed an unusual signal at δ 191.2 ppm, compatible with the presence of an iminium carbon (N=C$^+$) that according to literature data[13a] appears at δ 189.8 ppm. In the gHMBC experiment (Supporting Information), a long-range correlation between the H-5′ protons (δ 4.05 ppm) and the iminium carbon (δ 191.2 ppm) was clearly observed. This result supports the presence after 7 h of species in which a condensation takes place between the pyrrolidine portion present in **3** and acetone to give iminium intermediates.

We have also undertaken the analysis of the changes that experiment **3** in acetone by HPLC-ESI-MS (Figure 5). After 1 h the signal *m*/*z* 475, corresponding to the starting material **3**, is still clearly recognizable. There are also minor peaks *m*/*z* 538 and 574 which can be assigned to the cationized iminium intermediate **10.Na**$^+$ and the protonated intermediate **11.H**$^+$, respectively. After 7 h the signals corresponding to the iminium intermediate **10.Na**$^+$ (*m*/*z* 538) and intermediate **11.H**$^+$ (*m*/*z* 574) are the most intensive peaks. There are also minor peaks, among them those corresponding to the starting material **3** and final compound **6** (*m*/*z* 556, t_R = 13.21). After 24 h the signal of the starting material **3** appeared in the chemical noise and the intensity of the signals of **10.Na**$^+$ and **11.H**$^+$ started to decrease and those of **6** to increase.

When acetone of HPLC grade (with a higher amount of water) was employed, the evolution of the starting material **3** toward intermediate **10.Na**$^+$ (*m*/*z* 538) was clearly observed. However, neither the formation of **11.H**$^+$ nor the final compound **6** were detected even after a prolonged reaction time (13 days). This finding seems to indicate that the reaction stops in the first step in the presence of water and the reaction with a second molecule of acetone and the subsequent closing step do not take place.

It is worthy to note that only compound **6** can be detected by NMR and HPLC-ESI-MS in the reaction of **3** with acetone; however, we have been unable to detect the formation of **5**. Because **5** was only obtained after the purification process, we reasoned that the acidity of the silica gel used in the preparative Centrifugal Circular Thin-Layer Chromatography (CCTLC) (Kiesegel 60 PF_{254} gipshaltig) could play a critical role in its formation.

To check that hypothesis the reaction of **3** with acetone was monitored by HPLC-ESI-MS in the presence of acetic acid (pH adjusted to 5−6) (Figure 6). Under these conditions only a signal (*m*/*z* 556, t_R = 13.70) corresponding to the final product **5** (compound **6** appears at t_R = 13.21) was detected, while compound **6** was not formed. In addition, the presence of acetic acid led to a significant decrease in the reaction time (20 h versus 4 days).

With these experimental findings in hand we decided to repeat the reaction of **3** with acetone in the presence of acetic acid (pH adjusted to 5−6). Under these conditions, the yield of **5** increased from 35% to 80% and only traces of compound **6** were detected (Scheme 2). Taking into account that the formation of **5** and **6** seems to follow enamine and iminium pathways, respectively (Schemes 3 and 4), our results clearly indicate that the added acetic acid should facilitate the enamine pathway and therefore the formation of **5** (Scheme 3). The catalytic effect of an acid in the iminium−enamine equilibrium observed in other reported reactions supports this hypothesis.[14]

Taken together, our NMR and HPLC-ESI-MS studies provided strong support for the participation of the iminium intermediates **10** and **11** in the formation of **5** and **6**.

Finally, to reinforce the NMR and HPLC-ESI-MS studies we performed hydrogenation experiments to trap some of the enamine and/or iminium intermediates proposed for the formation of **5** and **6**. Thus, a solution of **3** in acetone was stirred under H_2 with Pd/C as catalysts (Scheme 5, path A). Under these conditions compound **18** was isolated (80% yield) and no traces of **5** or **6** (or their corresponding hydrogenated derivatives) were detected. This result confirms that a condensation takes place between the pyrrolidine NH group of **3** and acetone since the first few minutes of the reaction to form the iminium intermediate **10**.

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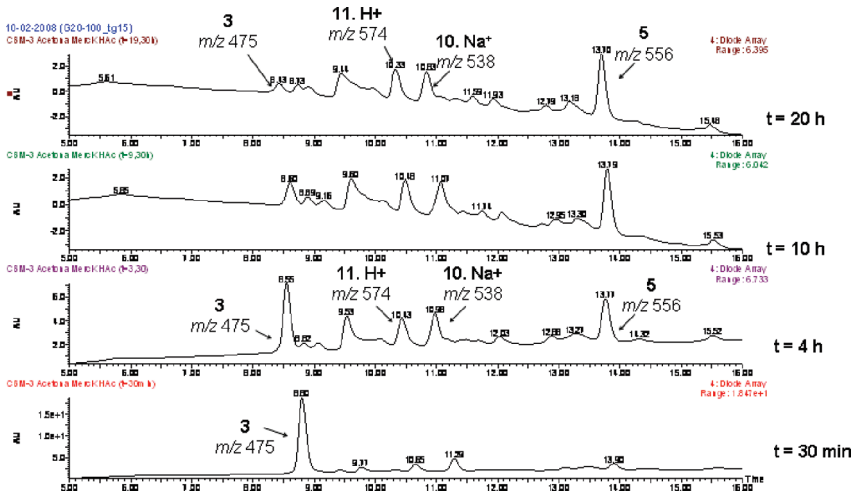
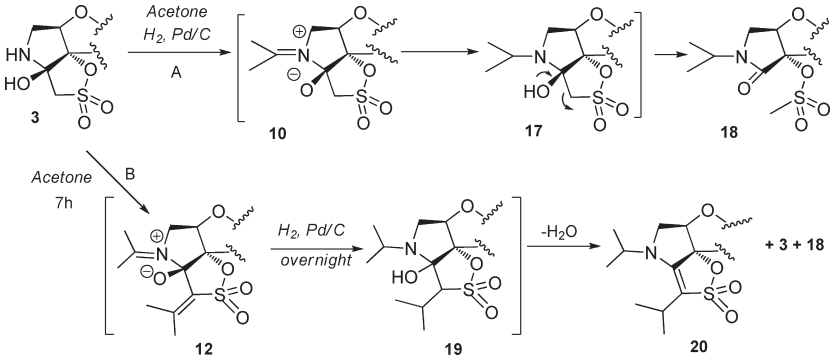


FIGURE 6. Evolution of the reaction of **3** in acetone in the presence of acetic acid (pH adjusted to 5−6) monitored by HPLC-ESI-MS on a C_{18} reverse-phase column.

SCHEME 5. Reaction of 3 with Acetone under Hydrogenation Conditions



Hydrogenation of the C=N$^+$ double bond in **10** leads to the formation of the *N*-alkylated pyrrolidine **17** that experiments the spontaneous opening of the spiro sultone ring to afford **18**. This result can be interpreted as clear evidence of the fact that the electrophilic nature of the iminium intermediate **10** should be the driving force for the attack of a second molecule of acetone at the southern hemisphere (adjacent position to the OSO_2) of the molecule. In the absence of this second molecule of acetone, intermediate **17** evolves toward **18.** On the other hand, evolution of intermediate **17** toward **18** highlights the tendency of the hydroxy group of the pyrrolidine ring to lose a proton, even under neutral conditions, and reinforces the crucial role of this OH in the hydrogen transfers of our proposed mechanism.

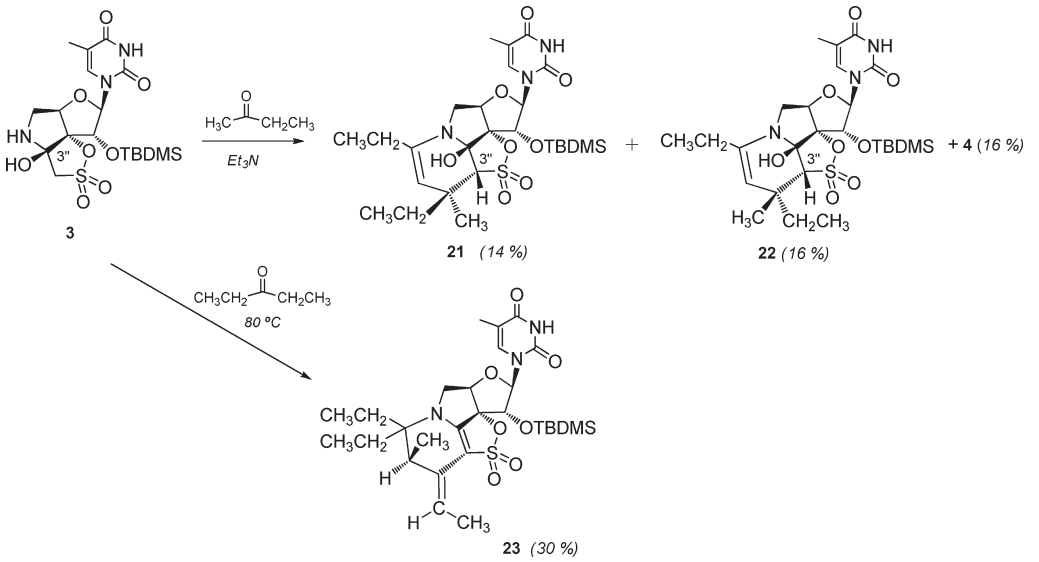
Taking into account that NMR analysis showed the maximum concentration of intermediate **X** after 7 h, we performed a similar experiment trying to trap this intermediate. Thus, a solution of **3** in acetone was allowed to react at room temperature for 7 h and then hydrogenation in the presence of Pd/C was undertaken. Under these conditions a mixture of compounds were observed from which unreacted **3** and the γ lactam **18** could be isolated. Most importantly, a novel compound (**20**) was isolated in 30% yield (Scheme 5, path B). Formation of **20** is an interesting experimental finding that strongly supports the formation, after 7 h, of intermediates in which two molecules of acetone, at the nitrogen and at the southern hemisphere (adjacent position to the OSO_2) of **3**, are present. Scheme 5, path B, illustrates a possible pathway to **20** starting from one of the most closely related intermediates (**12**). Thus, simultaneous hydrogenation of the C=N$^+$ and C=C double bonds present in **12** might lead to the formation of the *N*-alkylated pyrrolidine **19** whose dehydration might afford **20**. On the basis of these results the structure of intermediate **X** observed by ^{1}HNMR can be tentatively assigned as the high polar derivative **12** or a mixture of close related intermediates. This result supports the information obtained after 7 h with a TLC analysis of the reaction mixture in which compounds of high polarity that appear at the origin (low R_f) were detected.

It should be noted that under the conditions used (Pd/C) the endocyclic double bond present in **20** was not hydrogenated. This result is consistent with results of our group (unpublished data) showing that similar endocyclic double bonds were not hydrogenated under these soft conditions.

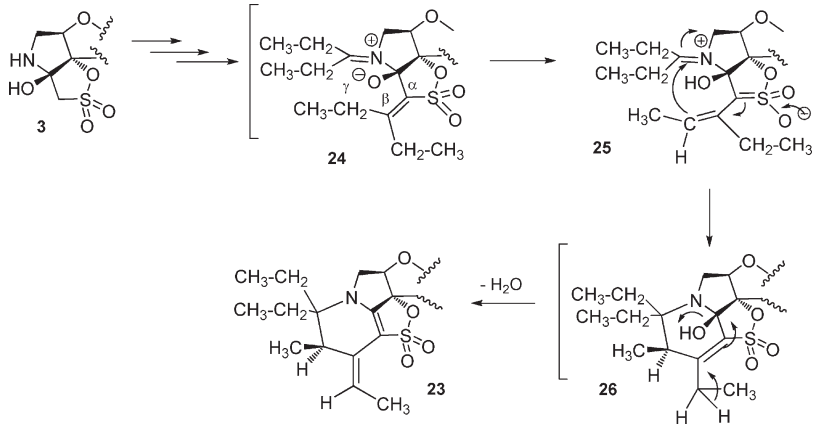
Formation of **20** can be interpreted as final evidence for the fact that the electrophilic nature of the C=N$^+$ is the driving force not only for the attack of a second molecule of acetone to the adjacent position to the OSO_2 of **3** but also for the intramolecular cyclizations that take place to afford **5** and **6**. In absence of this C=N$^+$, intermediate **19** evolves toward **20** in which two isopropyl fragments are present.

Finally, the scope of the reaction was briefly examined using a small set of ketones. Thus, aliphatic ketones (2-butanone, 3-pentanone), as well as the α,β-unsaturated

SCHEME 6. Reaction of 3 with 2-Butanone and 3-Pentanone



SCHEME 7. Proposed Evolution of 3 toward 23



ketone (methyl vinyl ketone), were reacted with **3** (Schemes 6 and 7).

Reaction of **3** with 2-butanone, either at room temperature or in the presence of acetic acid, gave complex mixtures of compounds (Scheme 6). However, addition of triethylamine gave compounds **21** (14%) and **22** (16%) together with the bicyclic nucleoside **4** (16%). Comparison of the ^{1}H NMR spectra of **21** and **22** with those of **5** and **6** revealed that their structure is similar to those of compound **5**. This experimental result clearly indicates that the addition of triethylamine should facilitate the enamine pathway and therefore the formation of compounds with structure similar to that of **5** (Scheme 3). To check that hypothesis the reaction between **3** and acetone was repeated in the presence of triethylamine. In this reaction only compound **5** was obtained in excellent (80%) yield after 4 h of reaction. Thus, the enamine pathway is favored in the presence of either an acid (acetic acid) or a base (triethylamine).

The stereochemistry of the novel stereogenic center was established as *S* for compound **21** and *R* for compound **22** on the basis of ROESY experiments (Figure 7).

On the other hand, when compound **3** was treated with 3-pentanone no reaction was observed at room temperature.

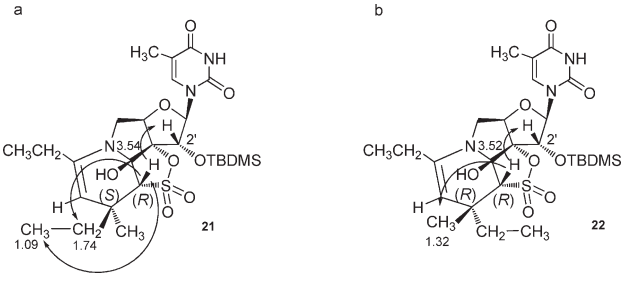


FIGURE 7. (a) ROESY correlations in **21**. (b) ROESY correlations in **22**.

However, heating at 80 °C overnight afforded compound **23** in 30% yield. Addition of acetic acid or triethylamine gave complex reaction mixtures.

Figure 8a showed the observed correlations from gHMBC of **23**. In addition, the stereochemistry of the double bond present in **23** was established on the basis of a NOE experiment, which also confirmed the stereochemistry of the newly formed stereogenic center (Figure 8b) created at C-4‴. Thus, irradiation at δ 5.5 ppm (olefinic proton) resulted in an enhancement in the signal at δ 2.29 ppm for the adjacent

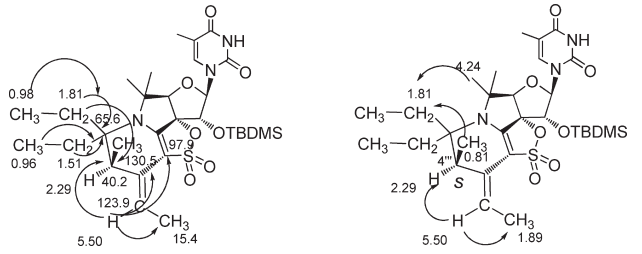
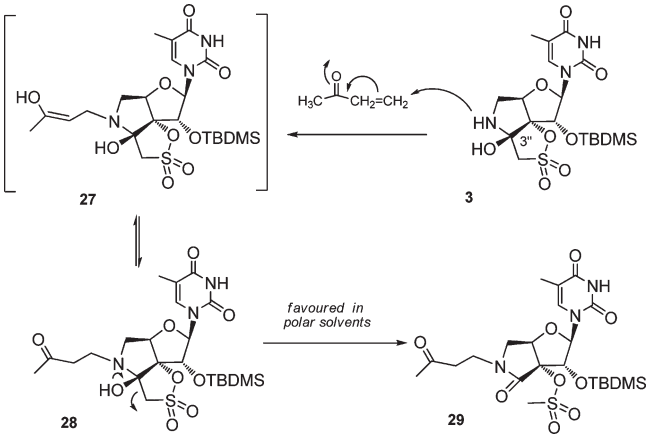


FIGURE 8. (a) gHMBC correlations in **23**. (b) NOE correlations in **23**. Assignment of stereochemistry of the new stereogenic center created at C-4‴ and the double bond.

SCHEME 8. Reaction of 3 with Methyl Vinyl Ketone



CH proton (CH-4‴). In addition, the observed enhancement is an indication that the CH_3 of the stereogenic center is above the plane of the furanose ring, whereas the H proton is below the plane. This enhancement was not possible in the opposite configuration (CH_3 below the plane). On the other hand, irradiation at δ 4.24 ppm (H-5′ proton) and at δ 0.81 ppm (CH_3 of the stereogenic center) resulted in enhancements in the signal at δ 1.81 ppm (CH_2 of one of the ethyl moieties attached on the nitrogen of the pyrrolidine ring) confirming the structure proposed for **23**.

Formation of **23** can be explained through the iminium pathway (Scheme 7). In this case the iminium intermediate **24** can be formed. The oxygen (O^-) at the α position of the pyrrolidine ring may accept a proton from the neighboring ethyl group (γ position with respect to the OSO_2) to give **25**. Subsequently, a concerted intramolecular cyclization, promoted by iminium catalysis, might give **26** whose dehydration affords **23**.

Finally, reaction of **3** with 3-buten-2-one afforded the hydroxy tricyclic nucleoside **28** (59%) (Scheme 8). The ^{1}H NMR spectrum of **28** in benzene-d_6 is consistent with the structure proposed for this compound; however, in more polar solvents such as acetone-d_6, methanol-d_4, or acetonitrile-d_3, **28** was transformed into the substituted γ-lactam **29** showing that a spontaneous opening of the spiro sultone ring has taken place in these solvents (Scheme 8).

Stability of **28** in different solvents was analyzed by ^{1}H NMR and the results were summarized in Table 1. The ratio of **28** and **29** was determined from the values of their respective integrals.

TABLE 1. Rate of Conversion of 28 into 29 in Different Deuterated Solvents

entry	solvent	time	28[a] (%)	29[b] (%)
1	acetone-d_6	15 min	95	5
		30 min	90	10
		24 h	45	55
		48 h	40	60
		7 days	35	65
		14 days	75	25
		21 days	75	25
2	benzene-d_6	15 min	100	
		30 min	100	
		16 h	100	
		1 day	95	5
		> 3 days	95	5
3	acetonitrile-d_3	< 8 h		100
4	DMSO- d_6	< 6 h		100
5	methanol-d_4	within a few minutes		100

[a]The characteristic AB system at δ 2.88 and 2.89 ppm, corresponding to the protons adjacent to the SO_2, is integrated. [b]The singlet at δ 3.20 ppm, corresponding to the CH_3SO_2 methyl group, is integrated.

In a nonpolar aprotic solvent such as benzene-d_6, compound **28** was stable enough to allow its complete spectroscopic characterization (entry 2). In a polar solvent such as methanol-d_4, opening of the spiro sultone ring proceeded rapidly, within a few minutes (entry 5), while in less polar aprotic solvents, such as acetonitrile-d_3 and DMSO-d_6 (entries 3 and 4) quantitative opening requires hours. In acetone, opening was only partial and a mixture of **28** and **29** was obtained after 21 days. Thus, it might be concluded that the ring-opening depends on the polarity of the solvent. In a polar solvent such as methanol-d_4 the opening proceeds quickly, in a few minutes, while in less polar solvents such as acetonitrile-d_3 and DMSO-d_6 the opening requires hours.

The experimental result obtained with the α,β-unsaturated ketone also can be explained by the proposed mechanism. In this case, the 1,4 attack is favored over the 1,2 addition to give the enol **27** that tautomerizes to the keto derivative **28**. Consequently no iminium ion is formed and the subsequent attack of a second molecule of ketone to the adjacent position to the OSO_2 was not observed.

Conclusions

In summary, we report here the synthesis of a new α-hydroxy pyrrolidine tricyclic nucleoside **3**. The unexpected reaction of **3** with acetone allowed its efficient transformation into novel fused tetracyclic nucleosides **5** and **6** with rather unusual molecular skeletons in a complete regio- and stereoselective way. In this process, three new bonds, two of them novel carbon−carbon bonds, were spontaneously formed in a one-pot fashion. For the formation of **5** and **6** we propose an enamine−iminium mechanism involving carbinolamine, iminium ion, and enamine intermediates. The proton transfers that take place are mediated by the hydroxyl group at the α position of the pyrrolidine ring, suggesting that this OH is crucial for the progress of the reaction. Acetic acid and triethylamine promote the enamine pathway (formation of **5**) and accelerate the reaction rate. The combination of NMR and HPLC-ESI-MS techniques revealed that the reaction proceeds through an enamine−iminium mechanism that was supported by the presence of the iminium carbon signal at δ 191.2 ppm in the ^{13}C NMR spectrum. In addition, some of the proposed intermediates were trapped by using hydrogenation experiments.

The preliminary scope of the reaction was also examined concluding that the nature of the ketone (R^1COR^2) is critical for the attack of the NH of the pyrrolidine ring present in **3** and the subsequent cyclization. Different types of ketones can be attacked by the NH of the pyrrolidine ring present in **3**; however, this attack and the subsequent cyclization proceeds spontaneously only with acetone.

It can be concluded that the α-hydroxy pyrrolidine tricyclic nucleoside **3** can be an attractive synthetic intermediate for the efficient creation of molecular complexity.

Experimental Section

The names of some polycyclic furanoses in this section are given according to the IUPAC recommendations for polycyclic compounds (extension of the Von Baeyer system).[15] However, for easy comparison, the assignments of the signals of the NMR spectra follow standard nucleoside numbering (i.e., the furanose skeleton numbered 1′−5′ and the thymine nucleobase numbered 1−6). The spirosultone skeleton was numbered 1″−4″ starting from the oxygen. The novel fused ring was numbered 1‴−5‴ for compounds **5** and **6** and 1‴−7‴ for compounds **21**−**23**.

5′,$N^{4''}$-Cyclo[1-[2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-β-D-ribofuranosyl]thymine]-3′-spiro-5″-(4″-amino-4″-*S*-hydroxy-1″,2″-oxathiolane-2″,2″-dioxide) (3). A solution of enamino sultone **1**[4] (100 mg, 0.22 mmol) in a water/acetonitrile mixture (1:1) (4 mL) was acidified by addition of acetic acid until pH ∼5. The reaction mixture was then heated at 80 °C for 8 h. Volatiles were removed at reduced pressure and the crude was purified by CCTLC (polar gradient on elution, from hexane/EtOAc 1:1 up to hexane/EtOAc 1:10 as eluent) to afford **3** (100 mg, 93%) as a white amorphous foam. ^{1}H NMR [300 MHz, acetone-d_6, sample freshly prepared prior to analysis] δ 0.01 and 0.14 (2 s, 6H, $2CH_3$), 0.87 (s, 9H, *t*-Bu), 1.86 (s, 3H, CH_3-5), 3.21 (dd, 1H, H-5′a, $J_{4',5'a}$ = 2.2 Hz, $J_{5'a,5'b}$ = 11.9 Hz), 3.42 (dd, 1H, H-5′b, $J_{4',5'b}$ = 5.1 Hz, $J_{5'a,5'b}$ = 11.9 Hz), 3.61 (d, 1H, H-3″a, $J_{3''a,3''b}$ = 13.9 Hz), 3.85 (d, 1H, H-3″b, $J_{3''a,3''b}$ = 13.9 Hz), 4.56 (m, 1H, H-4′), 4.88 (d, 1H, H-2′, $J_{1',2'}$ = 6.9 Hz), 5.98 (d, 1H, H-1′, $J_{1',2'}$ = 6.9 Hz), 6.13 (br s, 1H, OH-4″), 7.58 (s, 1H, H-6), 10.24 (br s, 1H, NH).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 and 0.08 (2 s, 6H, $2CH_3$), 0.88 (s, 9H, *t*-Bu), 1.95 (s, 3H, CH_3-5), 3.27 (dd, 1H, H-5′a, $J_{4',5'a}$ = 1.1 Hz, $J_{5'a,5'b}$ = 9.6 Hz), 3.39 (dd, 1H, H-5′b, $J_{4',5'b}$ = 3.3 Hz, $J_{5'a,5'b}$ = 9.6 Hz), 3.53 (d, 1H, H-3″a, $J_{3''a,3''b}$ = 10.2 Hz), 3.62 (d, 1H, H-3″b, $J_{3''a,3''b}$ = 10.2 Hz), 4.56 (dd, 1H, H-4′, $J_{4',5'a}$ = 1.1 Hz, $J_{4',5'b}$ = 3.3 Hz), 5.12 (d, 1H, H-2′, $J_{1',2'}$ = 3.9 Hz), 5.32 (d, 1H, H-1′, $J_{1',2'}$ = 3.9 Hz), 7.08 (s, 1H, H-6), 8.78 (br s, 1H, NH). MS (ESI^+) *m*/*z* 476.1 $[M + H]^+$ (100%). Anal. Calcd for $C_{18}H_{29}N_3O_8SSi$: C, 45.46; H, 6.15; N, 8.84. Found: C, 45.54; H, 6.32; N, 8.68. HPLC: t_R = 8.3 min. TLC (EtOAc/MeOH, 9:1) R_f 0.33 (heating, vanillin).

In chloroform, **3** is a stable compound. However, its solubility in this solvent is very low, which precludes use for a long-time acquisition experiment such as ^{13}C NMR. For this purpose, deuterated acetonitrile was the solvent of choice, allowing a good solubility with slow decomposition. ^{1}H NMR (400 MHz, CD_3CN) δ 0.04 and 0.09 (2 s, 6H, $2CH_3$), 0.84 (s, 9H, *t*-Bu), 1.87 (d, 3H, CH_3-5, *J* = 1 Hz), 3.14 (dd, 1H, H-5′a, $J_{4',5'a}$ = 2.8 Hz, $J_{5'a,5'b}$ = 12 Hz), 3.31 (dd, 1H, H-5′b, $J_{4',5'b}$ = 5.4 Hz, $J_{5'a,5'b}$ = 12 Hz), 3.52 (d, 1H, H-3″a, $J_{3''a,3''b}$ = 14 Hz), 3.72 (d, 1H, H-3″b, $J_{3''a,3''b}$ = 14 Hz), 4.52 (dd, 1H, H-4′, $J_{4',5'a}$ = 2.8 Hz, $J_{4',5'b}$ = 5.5 Hz), 4.68 (d, 1H, H-2′, $J_{1',2'}$ = 7 Hz), 5.88 (d, 1H, H-1′, $J_{1',2'}$ = 7 Hz), 7.34 (s, 1H, H-6), 8.78 (br s, 1H, NH). ^{13}C NMR (100 MHz, CD_3CN) δ −4.8, −4.6, 12.36, 18.46, 25.8, 48.2 (CH_2), 56.9 (CH_2), 72.4 (CH), 84.9 (CH), 91 (C), 96.6 (C), 97.4 (CH), 112.4 (C-5), 136.5 (C-6), 151.5 (CO), 164.2 (CO).

(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 (4).[4]**.** To a solution of **3** (100 mg, 0.21 mmol) in acetonitrile (4 mL) was added potassium carbonate (3 mg, 0.021 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), 80 mg (80%) of **4**[4] as a white foam.

5′,$N^{4''}$-Cyclo[1-[2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-β-D-ribofuranosyl]thymine]-3′-spiro-5″-[4″-amino-4″-*S*-hydroxy-3″,$N^{4''}$-(4‴-methyl-2‴-penten-2‴,4‴-diyl)-1″,2″-oxathiolane-2″,2″-dioxide] (5) and 5′,$N^{4''}$-Cyclo[1-[2′-*O*-(*tert*-butyldimethylsilyl-)-5′-deoxy-β-D-ribofuranosyl]thymine]-3′-spiro-5″-[4″-amino-4″-*S*-hydroxy-3″,$N^{4''}$-(2‴-methylpentan-2‴,4‴,4‴-triyl)-1″,2″-oxathiolane-2″,2″-dioxide] (6). A solution of nucleoside **3** (100 mg, 0.21 mmol) in acetone (2 mL) was stirred at room temperature for 24 h. Then, the solvent was evaporated under reduced pressure and the residue was purified by CCTLC with (hexane/EtOAc, 1:1) as eluent. From the fastest moving band, 40 mg of **5** (35%) was isolated as a white solid. Mp 132−134 °C. ^{1}H NMR (300 MHz, acetone-d_6) δ 0.07 and 0.15 (2s, 6H, $2CH_3$), 0.88 (s, 9H, *t*-Bu), 1.35 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 1.80 (s, 3H, CH_3-5), 3.45 (s, 1H, H-3″), 3.62 (dd, 1H, H-5′a, $J_{4',5'a}$ = 5.7 Hz, $J_{5'a,5'b}$ = 11.4 Hz), 3.82 (d, 1H, H-5′b, $J_{5'a,5'b}$ = 11.4 Hz), 4.41 (s, 1H), 4.65 (d, 1H, H-4′, $J_{4',5'a}$ = 5.7 Hz), 5.01 (d, 1H, H-2′, $J_{1',2'}$ = 5.6 Hz), 5.91 (s, 1H, OH), 5.97 (d, 1H, H-1′, $J_{1',2'}$ = 5.6 Hz), 7.66 (s, 1H, H-6), 10.11 (br s, 1H, NH). ^{13}C NMR (75 MHz, acetone-d_6) δ −5.1 (CH_3), −4.6 (CH_3), 12.3 (CH_3), 18.6 (C), 19.3 (CH_3), 25.8 (CH_3), 26.1 (CH_3), 30.9 (CH_3), 32.3 (C), 53.0 (CH_2), 66.4 (CH), 72.9 (CH), 81.7 (CH), 91.7 (CH), 93.0 (C), 94.4 (C), 107.4 (C═), 112.1 (C-5), 134.7 (C═), 136.8 (C-6), 151.3 (CO), 163.7 (CO). MS (ESI^+) *m*/*z* 574 $[M + NH_4]^+$ (100%), 556.1 $[M + H]^+$ (85%). Anal. Calcd for $C_{24}H_{37}N_3O_8SSi$: C, 51.87; H, 6.71; N, 7.56. Found: C, 51.69; H, 6.86; N, 7.81. HPLC: t_R = 13.70 min. TLC (hexane/EtOAc, 1:2) R_f 0.54 (heating).

From the slowest moving band, 30 mg of **6** (30%) was isolated as a foam. ^{1}H NMR (300 MHz, acetone-d_6) δ 0.07 and 0.15 (2s, 6H, $2CH_3$), 0.89 (s, 9H, *t*-Bu), 1.26 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.86 (s, 3H, CH_3-5), 2.14 (s, 3H, CH_3), 2.34 (d, 1H, CH_2, *J* = 19.1 Hz), 2.48 (d, 1H, CH_2, *J* = 19.1 Hz), 2.67 (dd, 1H, H-5′a, $J_{4',5'a}$ = 4.5 Hz, $J_{5'a,5'b}$ = 11.7 Hz), 3.29 (d, 1H, H-5′b, $J_{5'a,5'b}$ = 11.7 Hz), 4.36 (d, 1H, H-4′, $J_{4',5'a}$ = 4.5 Hz), 4.92 (d, 1H, H-2′, $J_{1',2'}$ = 4.8 Hz), 5.39 (s, 1H, OH), 5.85 (d, 1H, H-1′, $J_{1',2'}$ = 4.8 Hz), 7.66 (s, 1H, H-6), 10.07 (br s, 1H, NH). ^{13}C NMR (75 MHz, acetone-d_6) δ −4.7 (CH_3), −4.6 (CH_3), 12.7 (CH_3), 18.6 (C), 19.3 (CH_3), 26.1 (CH_3), 29.0 (CH_3), 31.4 (CH_3), 40.0 (CH_2), 50.4 (CH_2), 53.3 (C), 75.1 (CH), 82.1 (CH), 91.5 (CH), 92.1 (C), 96.1 (C), 110.7 (C-5), 126.7 (C═), 136.9 (C-6), 147.8 (C═), 151.5 (CO), 164.1 (CO). MS (ESI^+) *m*/*z* 556.1 $[M + H]^+$. Anal. Calcd for $C_{24}H_{37}N_3O_8SSi$: C, 51.87; H, 6.71; N, 7.56. Found: C, 51.73; H, 6.88; N, 7.74 . HPLC: t_R = 13.21 min. TLC (hexane/EtOAc, 1:2) R_f 0.33 (heating).

Selective Method for the Synthesis of 5. (A) In the presence of acetic acid: Acetic acid was added over acetone (2 mL) until pH ∼5. Hydroxynucleoside **3** (100 mg, 0.21 mmol) was allowed to dissolve in this acidified solution and the mixture was efficiently stirred at room temperature for 24 h. After that, volatiles were eliminated at reduced pressure and the crude was purified by CCTLC with hexane/EtOAc, 1:1, as eluent to afford 99 mg of **5** (85%). **(B) In the presence of triethylamine:** A solution of the hydroxynucleoside **3** (50 mg, 0.1 mmol) in acetone (2.5 mL) and triethylamine (0.05 mL) was stirred at room temperature for 4 h. Then, the solvent was evaporated under reduced pressure and

(15) IUPAC nomenclature home page: http://www.chem.qmul.ac.uk/iupac/.

the residue was purified by CCTLC with (hexane/EtOAc, 1:1) as eluent to afford 46 mg of **5** (80%).

5′,$N^{4''}$-Cyclo[1-[2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-β-D-ribofuranosyl]thymine]-3′-spiro-5″-(4″-amino-4″*S*-methoxy-1″, 2″-oxathiolane-2″, 2″-dioxide) (7). A solution of **1**[4] (0.1 g, 0.23 mmol) in methanol (3 mL) was heated in a sealed tube at 80 °C for 16 h. After evaporation of the solvent, the residue was purified by CCTLC (hexane:EtOAc, 1:2) to give 0.06 g (58%) of **7** as a white foam. ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ 1.85 (s, 3H), 3.20 (m, 1H, H-5′a), 3.43 (s, 3H, OCH_3), 3.45 (m, 1H, H-5′b), 3.62 (d, 1H, H-3″a, $J_{3''a,3''b}$ = 13.6 Hz), 3.77 (t, NH), 3.97 (d, 1H, H-3″b), 4.64 (dd, 1H, H-4′, $J_{4',5'a}$ = 4.6 Hz, $J_{4',5'a}$ = 6.1 Hz), 4.88 (d, 1H, H-2′), 6.03 (d, 1H, $J_{1',2'}$ = 6.7 Hz), 7.54 (s, 1H), 10.2 (br s, 1H, NH). ^{13}C NMR [75 MHz, $(CD_3)_2CO$] δ 12.5 (CH_3), 49.5 (CH_2), 51.8 (CH_2), 54.5 (OCH_3), 72.9 (CH), 85.5 (CH), 92.1 (CH), 99.4 (C), 99.9 (C), 111.9 (C-5), 137.6 (C-6), 152.4 (CO), 166.1 (CO). MS (ES+) m/z 502.6 $(M + Na)^+$. Anal. Calcd for $C_{19}H_{31}N_3O_8SSi$: C, 46.61; H, 6.38; N, 8.58. Found: C, 46.76; H, 6.75; N, 8.33.

(1*R*,3*R*,4*R*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-7-isopropyl-5-mesyloxy-6-oxo-3-(thymin-1′-yl)-7-aza-2-oxabicyclo[3.3.0]-octane (18). A solution of the hydroxynucleoside **3** (104 mg, 0.2 mmol) in acetone (25 mL) containing Pd/C (10%) (50 mg) was hydrogenated under atmospheric hydrogen pressure for 6 h. The reaction mixture was filtered, and the filtrate was evaporated to dryness under reduced pressure. The crude material is purified by CCTLC (polar gradient on elution, from dichloromethane 100% up to dichloromethane/MeOH, 9:1), isolating 91 mg (80%) of **18** as a white waxy solid. ^{1}H NMR (500 MHz, acetone-d_6) δ 0.01 and 0.20 (2s, 6H, $2CH_3$), 0.87 (s, 9H, *t*-Bu), 1.17 (d, 3H, CH_3 isopropyl, J = 6.8 Hz), 1.21 (d, 3H, CH_3 isopropyl, J = 6.8 Hz), 1.83 (s, 3H, CH_3-5), 3.33 (s, 3H, CH_3SO_2), 3.45 (dd, 1H, H-5′a, $J_{4',5'a}$ = 6.6 Hz, $J_{5'a,5'b}$ = 11.2 Hz), 3.80 (dd, 1H, H-5′b, $J_{4',5'b}$ = 1.6 Hz, $J_{5'a,5'b}$ = 11.2 Hz), 4.27 (sextuplet, 1H, CH isopropyl, J = 6.8 Hz), 4.60 (d, 1H, H-2′, $J_{1',2'}$ = 7.6 Hz), 4.94 (dd, 1H, H-4′, $J_{4',5'a}$ = 6.6 Hz, $J_{4',5'b}$ = 1.6 Hz), 5.93 (d, 1 H, H-1′, $J_{1',2'}$ = 7.6 Hz), 7.49 (s, 1 H, H-6), 10.21 (br s, 1H, NH). ^{13}C NMR (75 MHz, acetone-d_6) δ −4.3 (CH_3), −3.3 (CH_3), 13.3 (CH_3), 19.5 (C), 19.7 (CH_3), 20.6 (CH_3), 26.8 (3 CH_3), 42.4 (CH_3), 45.5 (CH), 47.3 (CH_2), 77.5 (CH), 80.2 (CH), 90.1 (C), 90.6 (CH), 113.0 (C-5), 137.6 (C-6), 152.4 (CO), 164.8 (CO), 168.5 (CO). MS (ESI^+) m/z 518.2 $[M+H]^+$ (100%), 540.2 $[M + Na]^+$ (18%). HPLC: t_R = 10 min. TLC (CH_2Cl_2/MeOH, 9:1) R_f 0.58 (heating). Anal. Calcd for $C_{21}H_{35}N_3O_8SSi$: C, 48.72; H, 6.81; N, 8.12. Found: C, 48.76; H, 6.84; N, 8.16.

5′,$N^{4''}$-Cyclo[1-[2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-β-D-ribofuranosyl]thymine]-3′-spiro-5″-[3″-isopropyl-4″-isopropylamino-1″,2″-oxathiole-2″,2″-dioxide] (20). A solution of the hydroxynucleoside **3** (50 mg, 0.1 mmol) in acetone (20 mL) was stirred at room temperature for 7 h. Then, Pd/C (10% Pd) (25 mg) was added and the reaction mixture was hydrogenated under atmospheric hydrogen pressure overnight. The reaction mixture was filtered, and the filtrate was evaporated to dryness under reduced pressure. The crude material is purified by CCTLC (polar gradient on elution, from dichloromethane 100% up to dichloromethane/MeOH, 10:1), isolating 24 mg (30%) of **20** as a white waxy solid. ^{1}H NMR (300 MHz, $CDCl_3 + D_2O$) δ 0.07 and 0.15 (2s, 6H, $2CH_3$), 0.79 (s, 9H, *t*-Bu), 1.26 (d, 3H, CH_3 isopropyl, J = 7.0 Hz), 1.28 (d, 3H, CH_3 isopropyl, J = 7.0 Hz), 1.33 (d, 3H, CH_3 isopropyl, J = 6.6 Hz), 1.35 (d, 3H, CH_3 isopropyl, J = 6.6 Hz), 1.92 (s, 3H, CH_3-5), 2.87−3.05 (m, 3H, 2H-5′ and CH isopropyl), 3.16 (sextuplet, 1H, CH isopropyl), 4.58 (m, 1H, H-4′), 5.07 (d, 1H, H-2′, $J_{1',2'}$ = 8.3 Hz), 5.17 (d, 1H, H-1′, $J_{1',2'}$ = 8.3 Hz), 6.98 (s, 1H, H-6). ^{13}C NMR (100 MHz, $CDCl_3 + D_2O$) δ −5.5 (CH_3), 4.6 (CH_3), 12.0 (CH_3), 17.8 (C), 19.3 (CH_3), 19.6 (CH_3), 21.1 (CH_3), 21.4 (CH_3), 24,1 (CH), 25.4 (CH_3), 46.0 (CH_2), 49.9 (CH), 70.0 (CH), 81.8 (CH), 90.4 (CH), 96.8 (CH), 106.4 (C═), 112.3 (C-5), 141.1 (C-6), 150.8 (CO), 159.9 (C═), 162.3 (CO). MS (ESI^+) m/z 560.5 $[M + NH_4]^+$ (100%), 542.5 $[M + H]^+$ (85%). Anal. Calcd for $C_{24}H_{39}N_3O_7SSi$: C, 53.21; H, 7.26; N, 7.76. Found: C, 53.43; H, 7.16; N, 7.81. HPLC: t_R = 10.4 min. TLC (hexane/EtOAc, 1:2) R_f 0.49 (heating).

Compounds **3** and **18** were also isolated in very low yields (< 5%).

5′,$N^{4''}$-Cyclo[1-[2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-β-D-ribofuranosyl]thymine]-3′-spiro-5″-[4″-amino-4″-*S*-hydroxy-3″, $N^{4''}$-(5‴-*S*-methyl-3‴-hepten-3‴,5‴-diyl)-1″,2″-oxathiolane-2″, 2″-dioxide] (21) and 5′,$N^{4''}$-Cyclo[1-[2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-β-D-ribofuranosyl]thymine]-3′-spiro-5″-[4″-amino-4″-*S*-hydroxy-3″,$N^{4''}$-(5‴-*R*-methyl-3‴-hepten-3‴,5‴-diyl)-1″,2″-oxathiolane-2″,2″-dioxide] (22). A solution of nucleoside **3** (50 mg, 0.1 mmol) in 2-butanone (2.5 mL) and triethylamine (0.05 mL) was stirred at room temperature for 24 h. Then the solvent was evaporated under reduced pressure and the residue was purified by CCTLC with hexane/EtOAc, 3:1, as eluent.

From the fastest moving band, 7.5 mg of **21** (14%) was isolated as a foam. ^{1}H NMR (300 MHz, acetone-d_6) δ 0.09 and 0.17 (2s, 6H, $2CH_3$), 0.90 (s, 9H, *t*-Bu), 1.09 (t, 3H, CH_3), 1.10 (m, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.74 (m, 1H, CH_2 CH_3), 1.81 (s, 3H, CH_3-5), 2.00 (m, 1H, CH_2 CH_3), 2.12 (q, 2H, CH_2CH_3), 3.54 (s, 1H, H-3″), 3.64 (dd, 1H, H-5′a, $J_{4',5'a}$ = 5.8 Hz, $J_{5'a,5'b}$ = 11.1 Hz), 3.82 (d, 1H, H-5′b, $J_{5'a,5'b}$ = 11.1 Hz), 4.48 (s, 1H), 4.68 (d, 1H, H-4′, $J_{4',5'a}$ = 5.8 Hz), 5.06 (d, 1H, H-2′, $J_{1',2'}$ = 5.4 Hz), 5.81 (s, 1H, OH), 5.98 (d, 1H, H-1′, $J_{1',2'}$ = 5.4 Hz), 7.64 (s, 1H, H-6), 10.26 (br s, 1H, NH). ^{13}C NMR (125 MHz, acetone-d_6) δ −5.3 (CH_3), −4.5 (CH_3), 7.9 (CH_3), 12.1 (CH_3), 18.6 (C), 21.7 (CH_3), 25.8 (CH_3), 27.2 (CH_3), 34.7 (C), 35.1 (CH_2), 49.6 (CH_2), 53.0 (CH_2), 63.9 (CH), 72.9 (CH), 81.9 (CH), 91.6 (CH), 93.1 (C), 94.5 (C), 105.6 (C═), 112.2 (C-5), 136.8 (C═), 140.4 (C-6), 151.4 (CO), 163.6 (CO). MS (ESI^+) m/z $[M + H]^+$ 584.7. Anal. Calcd for $C_{26}H_{41}N_3O_8SSi$: C, 53.49; H, 7.08; N, 7.20. Found: C, 53.59; H, 7.05; N, 7.21. TLC (hexane/EtOAc, 2:1) R_f 0.59 (heating).

From the intermediate band, 7.6 mg of **22** (14%) was isolated as a foam. ^{1}H NMR (300 MHz, acetone-d_6) δ 0.09 and 0.17 (2s, 6H, $2CH_3$), 0.91 (s, 9H, *t*-Bu), 0.92 (m, 3H, CH_3), 1.02 (dt, 6H, CH_3), 1.32 (s, 3H, CH_3), 1.62 (dd, 1H, CH_2CH_3), 1.80 (s, 3H, CH_3-5), 1.90 (m, 1H, CH_2CH_3), 2.12 (q, 2H, CH_2CH_3), 3.52 (s, 1H, H-3″), 3.63 (dd, 1H, H-5′a, $J_{4',5'a}$ = 5.8 Hz, $J_{5'a,5'b}$ = 11.1 Hz), 3.83 (d, 1H, H-5′b, $J_{5'a,5'b}$ = 11.1 Hz), 4.52 (s, 1H), 4.66 (d, 1H, H-4′, $J_{4',5'a}$ = 5.8 Hz), 5.02 (d, 1H, H-2′, $J_{1',2'}$ = 5.4 Hz), 5.80 (s, 1H, OH), 5.96 (d, 1H, H-1′, $J_{1',2'}$ = 5.4 Hz), 7.64 (s, 1H, H-6), 10.23 (br s, 1H, NH). ^{13}C NMR (125 MHz, acetone-d_6) δ −5.3 (CH_3), −4.5 (CH_3), 8.9 (CH_3), 12.6 (CH_3), 18.9 (C), 26.0 (CH_3), 27.1 (CH_3), 31.7 (C), 35.6 (CH_2), 49.8 (CH_2), 52.7 (CH_2), 63.9 (CH), 72.9 (CH), 81.9 (CH), 92.1 (CH), 93.2 (C), 94.5 (C), 104.1 (C═), 112.2 (C-5), 137.0 (C═), 140.5 (C-6), 151.4 (CO), 163.8 (CO). MS (ESI^+) m/z $[M + H]^+$ 584.7. Anal. Calcd for $C_{26}H_{41}N_3O_8SSi$: C, 53.49; H, 7.08; N, 7.20. Found: C, 53.59; H, 7.05; N, 7.21. TLC (hexane/EtOAc, 2:1) R_f 0.57 (heating).

From the slowest moving band, 7.5 mg of **4**[4] (16%) was isolated as a foam.

5′,$N^{4''}$-Cyclo[1-[2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-β-D-ribofuranosyl]thymine]-3′-spiro-5″-[4″-amino-3″,$N^{4''}$-(4‴-*S*-methyl-2‴-hepten-3‴,5‴-diyl)-1″,2″-oxathiole-2″,2″-dioxide] (23). A solution of nucleoside **3** (50 mg, 0.1 mmol) in 3-pentanone (10 mL) was stirred at room temperature for 24 h and then heated at 80 °C for an additional 24 h. Then the solvent was evaporated under reduced pressure and the residue was purified by CCTLC with hexane/EtOAc, 1:2, as eluent to afford **23** (18.8 mg, 30%) as a white foam. ^{1}H NMR (300 MHz, acetone-d_6) δ 0.09 and 0.17 (2s, 6H, $2CH_3$), 0.81 (d, 3H, CH_3, J = 1.9 Hz), 0.91 (s, 9H, *t*-Bu), 0.92 (t, 3H, CH_3), 0.96 (t, 3H, CH_3), 0.98 (m, 3H, CH_3), 1.45−1.50 (m, 4H, 2 CH_2), 1.88 (s, 3H, CH_3), 1.89 (d, 3H, CH_3, J = 7.8 Hz), 2.27 (q, 1H, CH, J = 7 Hz), 4.24 (dd, 1H,

H-5′a, $J_{4',5'a}$ = 8.8 Hz, $J_{5'a,5'b}$ = 10.5 Hz), 4.30 (dd, 1H, H-5′b, $J_{4',5'b}$ = 6.1 Hz, $J_{5'a,5'b}$ = 10.5 Hz), 5.09 (dd, 1H, H-4′, $J_{4',5'a}$ = 6.1 Hz, $J_{5'a,5'b}$ = 8.8 Hz), 5.47 (br s, 1H, H-2′), 5.48 (qt, 1H, J = 7 Hz), 5.80 (br s, 1H, H-1′), 7.60 (d, 1H, H-6, J = 1.2 Hz), 10.20 (br s, 1H, NH). ^{13}C NMR (125 MHz, acetone-d_6) δ −3.3 (CH_3), −4.3 (CH_3), 8.4 (CH_3), 8.5 (CH_3), 12.8 (CH_3), 15.4 (CH_3), 16.1 (CH_3), 22.8 (CH_2), 26.8 (CH_3), 28.8 (CH_2), 40.2 (CH), 57.5 (CH_2), 65.6 (C), 73.9 (CH), 83.5 (CH), 91.5 (C), 97.9 (C), 112.4 (C-5), 120.5 (C═), 123.9 (C═), 130.5 (C-6 and C═), 151.9 (CO), 155.7 (C═), 164.5 (CO). MS (ESI$^+$) m/z MS (ESI$^+$) m/z [M + H]$^+$ 594.5. Anal. Calcd for $C_{28}H_{43}N_3O_7SSi$: C, 56.63; H, 7.30; N, 7.08. Found: C, 56.59; H, 7.05; N, 7.21. TLC (hexane/EtOAc, 1:2) R_f 0.47 (heating).

5′,$N^{4''}$-Cyclo[1-[2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-β-D-ribofuranosyl]thymine]-3′-spiro-5″-(4″-methylcarbonylethylamino-4″-*S*-hydroxy-1″,2″-oxathiolane-2″,2″-dioxide) (28). A solution of nucleoside **3** (50 mg, 0.1 mmol) and methyl vinyl ketone (0.8 mL, 10 mmol) in dry acetonitrile (2 mL) was stirred at room temperature for 24 h. Then the solvent was eliminated in vacuo and the resulting crude material was purified by CCTLC with dichloromethane/hexane, 6:4, as eluent until elimination of the unreacted methyl vinyl ketone, then with a polar gradient from dichloromethane 100% up to dichloromethane/MeOH 7:3, affording 32 mg of **28** (59%) as a white foam. ^{1}H NMR (400 MHz, benzene-d_6) δ 0.08 and 0.30 (2s, 6H, $2CH_3$), 1.00 (s, 9H, *t*-Bu), 1.40 −1.50 (m, 1H, CHaN), 1.45 (s, 3H, CH_3), 1.65−1.85 (m, 2H, CH_2CO), 1.76 (s, 3H, CH_3-5), 2.40 (dd, 1H, H-5′b, J = 10.8 Hz, J = 4.4 Hz), 2.50 (m, 1H, CHbN), 2.60 (d, 1H, H-5′a, J = 10.8 Hz), 2.88 (d, 1H, H-3″a, J = 13.8 Hz), 2.89 (d, 1H, H-3″b, J = 13.8 Hz), 4.10 (d, 1H, H-4′, J = 4.2 Hz), 4.95 (d, 1H, H-2′, J = 6.2 Hz), 5.50 (s, 1 H, OH), 5.91 (d, 1 H, H-1′, J = 6.2 Hz), 6.62 (s, 1H, H-6), 8.83 (br s, 1H, NH). ^{13}C NMR (100 MHz, benzene-d_6) δ −5.02 (CH_3), −4.6 (CH_3), 12.4 (CH_3), 18.3 (C), 25.8 (CH_3), 29.8 (CH_3), 40.0 (CH_2), 41.0 (CH_2), 50.8 (CH_2), 51.6 (CH_2), 72.9 (CH), 81.4 (CH), 92.2 (CH), 94.6 (C), 99.0 (C), 111.8 (C-5), 136.0 (C-6), 150.5 (CO), 162.9 (CO), 209.3 (CO). MS (ESI$^+$) m/z 546 [M + H]$^+$. HPLC: t_R = 8.8 min. TLC (CH_2Cl_2/MeOH, 9:1) R_f 0.33 (heating). Anal. Calcd for $C_{22}H_{35}N_3O_9SSi$: C, 48.42; H, 6.46; N, 7.70. Found: C, 48.76; H, 6.44; N, 7.76.

(1*R*,3*R*,4*R*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-7-methylcarbonylethyl-5-mesyloxy-6-oxo-3-(thymin-1′-yl)-7-aza-2-oxabicyclo[3.3.0]octane (29). To isolate **29** a solution of **28** in methanol was stirred for 15 min. The solvent was eliminated in vacuo and the resulting crude material was purified by CCTLC with dichloromethane/hexane, 6:4, as eluent to give **29** as a foam. ^{1}H NMR (400 MHz, acetonitrile-d_3) δ −0.02 and 0.20 (2s, 6H, $2CH_3$), 0.80 (s, 9H, *t*-Bu), 1.90 (s, 3H, CH_3-5), 2.20 (s, 3H, CH_3), 2.80 (t, 2H, CH_2N, J = 7.2 Hz), 3.20 (s, 3H, CH_3SO_2), 3.40 (dd, 1H, H-5′a, J = 11.4 Hz, J = 1.6 Hz), 3.42 (m, 1H, CHaCO), 3.60 (dt, 1H, CHbCO, J = 14.0 Hz, J = 7.2 Hz), 3.75 (dd, 1H, H-5′a, J = 11.6 Hz, J = 6.8 Hz), 4.20 (d, 1H, H-2′, J = 8.0 Hz), 4.90 (dd, 1H, H-4′, J = 6.8 Hz, J = 1.6 Hz), 5.90 (d, 1H, H-1′, J = 8.0 Hz), 7.30 (s, 1H, H-6), 9.10 (br s, 1H, NH). ^{13}C NMR (100 MHz, acetonitrile-d_3) δ −5.4 (CH_3), −4.4 (CH_3), 12.2 (CH_3), 18.4 (C), 25.7 (CH_3), 30.1 (CH_3), 38.9 (CH_2), 40.4 (CH_2), 41.5 (CH_3), 51.4 (CH_2), 77.0 (CH), 78.9 (CH), 87.6 (CH), 88.3 (C), 112.6 (C-5), 135.8 (C-6), 151.5 (CO), 163.9 (CO), 168.2 (CO), 208.2 (CO). MS (ESI$^+$) m/z 546 [M + H]$^+$. HPLC: t_R = 8.8 min. TLC (CH_2Cl/MeOH, 9:1) R_f 0.33 (heating). Anal. Calcd for $C_{22}H_{35}N_3O_9SSi$: C, 48.42; H, 6.46; N, 7.70. Found: C, 48.51; H, 6.56; N, 7.69.

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Supporting Information Available: General experimental methods, NMR procedures, and copies of spectra for **3**, **5**, **6**, **7**, **18**, **20**, **21**, **22**, **23**, **28**, and **29**, as well as gHSQC of the reaction of **3** with acetone after 7 h. This material is available free of charge via the Internet at http://pubs.acs.org.