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[4 + 2] and [3 + 2] Cycloaddition Reactions of 2′,3′-Dideoxy-3′-nitro-2′,3′-didehydrothymidine with Ethyl Vinyl Ether

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Cycloaddition reaction of 1-(5′-*O*-(monomethoxytrityl)-2′,3′-dideoxy-3′-nitro-β-D-*glycero*-pent-2′-enofuranosyl)thymine (**1a**) with ethyl vinyl ether gave a diastereomeric mixture of [3.4.0]sugar-fused bicyclic (**2a**) (27%) and (**3**) (12%) and the tricyclic (**4a**) (47%) derivatives. An identical reaction with (2′,3′-dideoxy-3′-nitro-β-D-*glycero*-pent-2′-enofuranosyl)thymine (**1b**) gave only bicyclic **2b** (40%) and tricyclic **4b** (43%) in a stereospecific manner. Chemical evidence has been presented which suggests that only one of the diastereomeric nitronates (i.e., **2a**) formed as a result of [4 + 2] addition reaction across a 4π heterodiene system undergoes the second [3 + 2] cycloaddition reaction across its nitronate function by a second molecule of the reagent to give the tricyclic product **4a**. The configurations of new chiral centers have been assigned as C2′-*R*/C8-*R* in **2a** and **2b**, C2′-*R*/C8-*S* in **3**, and C2′-*R*/C3′-*S*/C8-*R*/C12-*S* in **4a** and **4b** by detailed 500-MHz NMR studies. Detailed analysis of $^3J_{HH}$ coupling constants at 500 MHz and estimation of interproton distances by 1D ^{1}H difference NOE and the NOESY spectra have enabled us to define the conformation of novel thymidine derivatives **2b**, **3**, and **4b**: (i) The pentose sugars in **2b** and **3** are 2′-endo-3′-exo (P = 142°, Ψ_m = 34° for **2b** and P = 140°, Ψ_m = 33° for **3**), and the constituent six-membered ring are in the half-chair/half-boat conformation. (ii) For tricyclic nucleoside **4b**, the pentose sugar moiety adopts 2′-endo conformation (P = 161°, Ψ_m = 40°) with the fused six-membered ring in $^{09}C_{C2'}$ conformation, whereas the conformation of its fused-spiro isoxazolidine ring can be described by P = 188°, Ψ_m = 40°.

Nitroolefins[1] possess unique chemical reactivity toward both nucleophilic and cycloaddition reactions because of their highly reactive double bond. These facile reactions and the free-radical induced denitration reactions[2] have prompted us to use nitroolefins[3] (**1a** and **1b**) as attractive general intermediates[3] for the preparation of various 2′- and 3′-modified nucleoside analogues intended as potential anti-HIV agents. Although Michael-type addition reactions can be performed easily with 2′,3′-unsaturated nucleosides in which the sugar double bond is conjugated with electron-withdrawing groups[4–7] (CN, $PhSO_2$, $PhSeO_2$, etc.), but their cycloaddition reactions[7] are generally very sluggish, taking several days to weeks for completion. In contrast, the cycloaddition reactions of the heteroatom-containing π system, as in a nitroolefin,[8–10] take place in a facile manner in simple alicyclic or carbocyclic systems. These cycloaddition reactions have been shown to be a powerful means[8–10] to access new heterocycles which can, under appropriate conditions, produce acyclic functional subunits on the carbon framework of the parent compound. These facile cycloaddition reactions in nucleoside chemistry involving the pentose sugar residue were heretofore unknown.

We herein report the cycloaddition reaction of (3′-nitro-2′,3′-dideoxy-β-D-*glycero*-pent-2′-enofuranosyl)nucleosides[3] **1a** or **1b** with ethyl vinyl ether (Scheme I). The reaction of 5′-protected nitroolefin **1a** with ethyl vinyl ether in CH_2Cl_2 at ~20 °C for 24 h gave a diastereomeric mixture of two pentose sugar [3.4.0]-fused bicyclic nucleosides **2a** (27%) and **3** (12%) and a tricyclic (**4a**) (47%) nucleoside. Clearly, bicyclic products **2a** and **3** are formed as a result of [4 + 2] addition reaction across a 4π heterodiene by an activated dienophile[9,10] and then undergo the second [3 + 2] cycloaddition reaction[8] across the nitronate function by a second molecule of ethyl vinyl ether to give the tricyclic product **4a** in which four new chiral centers are formed simultaneously in one step. In order to confirm this, we have attempted to perform cycloaddition reactions with pure nitronates **2a** or **3** with ethyl vinyl ether separately. To our surprise, only one of the diastereomeric nitronates (i.e., **2a**) reacted with ethyl vinyl ether to give the tricyclic nucleoside **4a** in 89% yield. This means that the stereoelectronic properties of the two nitronates **2a** and **3** that dictate the formation of the transition state with ethyl vinyl ether in the cycloaddition reaction are clearly different. We have subsequently performed the reaction of 5′-hydroxy-3′-nitroolefin **1b** with ethyl vinyl ether in ethanol (at ~20 °C for 24 h) to give only bicyclic nucleoside **2b** (40%) and the tricyclic nucleoside **4b** (43%). The ratio of bicyclic (**2b**) and tricyclic (**4b**) nucleosides formed in the latter reaction was dependent upon the reaction period suggesting that **4b** is presumably formed through **2b**. The fact that the reaction of pure **2b** with ethyl vinyl ether in ethanol at ~20 °C for 48 h gave only **4b** in a high yield (76%) also proved, in conjunction with NMR evidence, that the chiralities at $C_{2'}$ and C_8 in both **2b** and **4b** are identical. The structures of **2a**, **2b**, **3**, and **4a**,**b** have been

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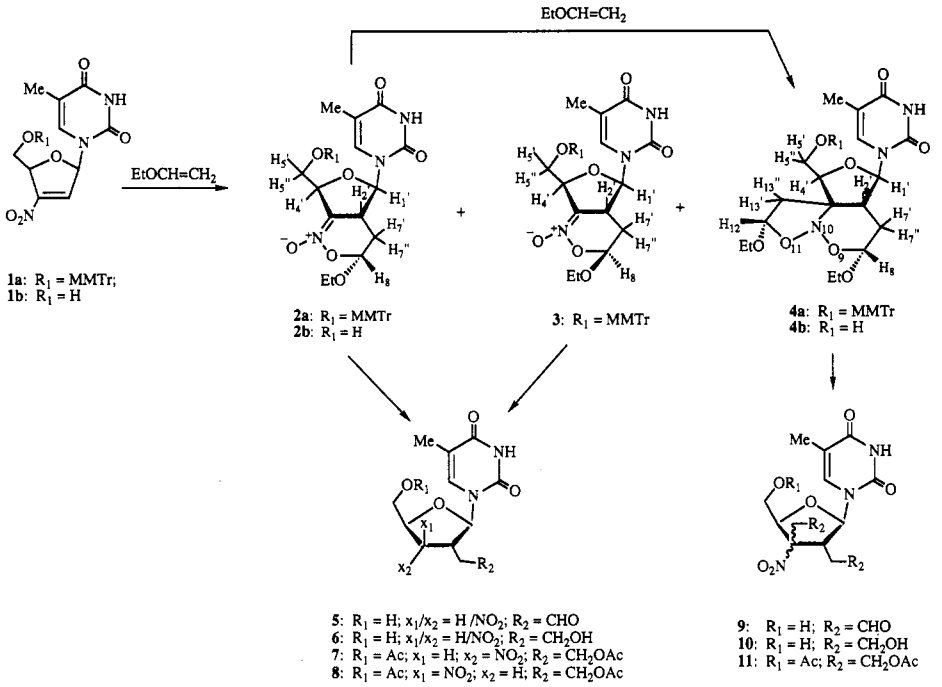
(11) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; de Leeuw, H. P. M.; Altona, C. *Recl. Trav. Chim. Pays-bas* **1979**, *98*, 576. Limiting values for $J_{4'5'}$ and $J_{4'5''}$ in the staggered C4′–C5′ rotamers are as follows: γ^+, $J_{4'5'}$ = 2.4 Hz, $J_{4'5''}$ = 1.3 Hz. Rotamer γ^t: $J_{4'5'}$ = 2.6 Hz, $J_{4'5''}$ = 10.5 Hz. Rotamer γ^-: $J_{4'5'}$ = 10.6 Hz, $J_{4'5''}$ = 3.8 Hz.

0022-3263/93/1958-2874$04.00/0

Scheme I



confirmed by detailed spectroscopic studies. The diastereomeric nature of **2a** and **3** has been further confirmed by converting each of the pure diastereomers independently to an identical diastereomeric mixture of 2′-C-branched acetates **7**/**8** (2:1) through acidic hydrolysis, reduction with $NaBH_4$ followed by acetylation (**2a** or **3** → **5** → **6** → **7**/**8**). In an identical manner, the chemical proof for the structure of tricyclic nucleoside **4a** was corroborated by its conversion to the diastereomeric mixture of 2′,3′-bis-C-branched acetate **11** by the sequential acidic hydrolysis, reduction, and acetylation (**4a** → **9** → **10** → **11**) (Scheme I).

Detailed conformational studies on **2a**, **2b**, **3**, and **4a**,**b** by 500-MHz NMR have been performed on the basis of all $^3J_{HH}$ coupling constants and distances derived using NOESY spectra (two-proton approximation), which also provided evidence for the assigned configurations at the newly generated chiral centers (vide infra).

Assignment of Configurations and Conformation of Tricyclic Nucleoside 4b. The observed $^3J_{H,H}$ coupling constants were translated into the respective torsion angles ($\Phi_{H,H}$) using the Karplus–Altona equation (1), which

$$^3J_{H,H} = P_1 \cos^2 \Phi_{H,H} + P_2 \cos \Phi_{H,H} + P_3 + \sum \Delta\chi i\{P_4 + P_5 \cos^2(\zeta i\varphi + P_6|\Delta\chi i)\} \ldots \quad (1)$$

includes a correction term to take into account the influence of the electronegativities of various substituents.[12,13] $\Phi_{H,H}$ is a proton–proton torsion angle, $\Delta\chi i$ is a difference in Huggins electronegativity between the substituent and hydrogen, and ζ_i denotes the orientation of the substituent relative to the coupling protons in the HCCH fragment. The parameters P_1–P_6 were determined empirically with a large coupling constant data set.[12,13]

The $\Phi_{H,H}$ for **4b** derived from $^3J_{H,H}$ presented in the footnotes of Table I enabled us to build structural models of compound **4b**. The generalized AMBER force field parameters as implemented in the computer program MacroModel V3.5a were used.[15] Energy minimizations with constraints on $\Phi_{H,H}$ were used (Table I and footnotes) to build structures[15,16] (Table II) that fulfill all torsion angles[16] derived from NMR-derived $^3J_{H,H}$ values. The $\Phi_{1',2'}$ in Table II show that the sugar ring is in the South conformation.[13,14] There are four $\Phi_{2',7'}$ values that resulted from Karplus–Altona equation (1),[12,13] but only the value of $\Phi_{2',7'} = 42°$ is mutually consistent with the value of $\Phi_{2',7''} = 280°$, and such a conformer fulfills NOE-derived distance information ($H_{1'}$ is spatially closer to $H_{7''}$ than to $H_{7'}$). Assuming the *R* configuration at C_8, the consistent values for $\Phi_{7',8}$ and $\Phi_{7'',8}$ are 313° and 86°, respectively. Two computer models of **4b** with C_8-*R* configuration were constructed (conformers 1 and 2 in Table II), and both of them fulfill the five torsion angles ($\Phi_{1',2'}$, $\Phi_{2',7'}$, $\Phi_{2',7''}$, $\Phi_{7',8}$, $\Phi_{7'',8}$) obtained through analysis of $^3J_{H,H}$ coupling constants. Conformers 1 and 2 of **4b** (Table II) differ slightly in the geometry of the sugar ring as assessed by their $\Phi_{1',2'}$ values. In both conformers 1 and 2, the sugar ring is locked in a C2′-endo conformation [phase angle of pseudorotation (*P*) = 161°, the puckering amplitude (Ψ_m) = 40° in conformer 1, and *P* = 151° and Ψ_m = 45° (Table II) in conformer 2]. In both conformers the six-membered ring adopts $^{O9}C_{C2'}$ chair conformation. With the assumption of C_8-*S* con-

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(16) The experimental coupling constants were translated by eq 1 into torsion angles, which were the basis for defining torsional constraints used in the building of the computer models of **2b**, **3**, and **4b** (see Table I). The estimated error in the experimental value of $^3J_{HH}$ of ±0.1 Hz was used to determine the flat region of the torsion angles (±2°). Note that inside this region (see footnote to Table I) no energy penalty is paid, while the constraint energy outside this allowed region is calculated by $E = V_1[1 - \cos(\text{deviation})]$, where V_1 is a force constant (1000 kJ/mol·rad), in accordance with AMBER force-field parameters in MacroModel 3.5. No evaluation of energies of the minimized conformers was attempted due to the absence of high-quality force constants, especially for C=N⁺O⁻ fragments in **2b** and **3**.

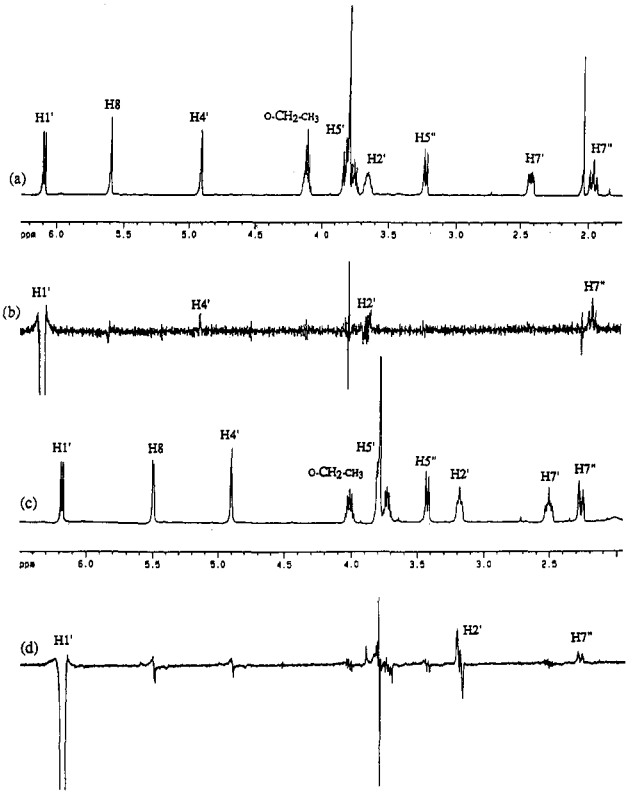

Figure 1. (a) 1D ^{1}H spectrum of **3** recorded at 298 K in $CDCl_3$ at 500 MHz. (b) 1D NOE difference spectrum of **3** upon irradiation of H1′. The observed NOE between H1′ and H7″ leads to the assignment of H7′ and H7″ in **3**. (c) 1D ^{1}H spectrum of **2a** recorded at 298 K in $CDCl_3$ at 500 MHz. (d) 1D NOE difference spectrum of **2a** upon irradiation of H1′. The observed NOE between H1′ and H7″ leads to the assignment of H7′ and H7″ in **2a**.

figuration (i.e., –OEt "up"), mutually consistent values for $\Phi_{1',2'}$, $\Phi_{2',7'}$, $\Phi_{2',7''}$, $\Phi_{7',8}$, and $\Phi_{7'',8}$ are possible that would fulfill all the information derived from $^3J_{H,H}$ (isomer 4; Table II). In isomer 4, however, $d_{7'13''}$ = 3.1 Å, which is not in agreement with the NOE-derived distance of 2.3 Å. Note that in both conformers 1 and 2 with C_8-*R* configuration (i.e., –OEt "down"), $d_{7',13''}$ = 2.5 Å, which is in close agreement with the experimental data (Table II).

The experimentally determined distance, $d_{7',13''}$ = 2.3 Å, also enables the determination of the configuration at C_{12}. In the model of compound **4b** with C_{12}-*S* configuration $d_{7',13''}$ = 2.5 Å (conformers 1 and 2), whereas in the compound with C_{12}-*R* configuration $d_{7'13''}$ = 4.2 Å (isomer 3 in Table II). Note that $H_{7'}$ is in closer spatial proximity to $H_{13''}$ than to $H_{13'}$, while $H_{5''}$ is closer to $H_{13'}$ than to $H_{13''}$ in conformers 1 and 2 (C_{12}-*S*), which was also observed in the NOESY experiment (Table II).

In compound **4b**, there are two more chiral centers that were formed in the cycloaddition reaction. The configuration at $C_{2'}$ is determined through the observation of $^3J_{1',2'}$ = 9.6 Hz, which can only be a transoid coupling, and thus the configuration at $C_{2'}$ should be *R* (i.e., H2′ 'up'). The largest $^3J_{1',2'}$ which is possible in cisoid orientation (i.e., $C_{2'}$-*S* configuration with H2′ down) was found by using the Karplus–Altona equation (1)[12,13] with values of electronegativities of substituents found around the H1′C1′C2′H2′ fragment at $\Phi_{H,H}$ = 0° is 8.1 Hz, which is 1.5 Hz less than what was observed in the ^{1}H NMR spectrum (Table I).

The configuration at $C_{3'}$ in **4b** was examined by building the model with $C_{2'}$-*R*, $C_{3'}$-*R* (i.e., N_{10} would be "up"), C_8-*S* and C_{12}-*R* configurations (isomer 5 in Table II). The isomer 5 presented in Table II does not fulfill $d_{7',13''}$ = 2.3 Å and $d_{5'',13'}$ = 2.4 Å found by NOE measurements (in the model of isomer 5, $d_{7',13''}$ = 4.0 Å and $d_{5'',13'}$ = 4.3 Å). Note, however, that the models with $C_{3'}$-*S* (and $C_{2'}$-*R*, C_8-*R*, C_{12}-*S*) configuration (i.e., N_{10} "down") fulfil all *J* and NOE data (conformers 1 and 2, Table II, Figure 2). The populations of the γ^+ rotamer across C4′–C5′ was calculated from $^3J_{4',5'}$ and $^3J_{4',5''}$. The observed $^3J_{4',5'}$ and $^3J_{4',5''}$ are weighted time-averaged coupling constants related to the couplings of individual conformers (γ^+, γ^t and γ^-) and their respectively populations.[11] The population of γ^+ rotamer is found to be 96% and is independent of the assignment of H5′ and H5″. The conformation around the glycosidic bond (χ) in **4b** was considered (Figure 2) on the basis of $d_{6,1'}$ = 2.2 Å and $d_{6,2'}$ = 3.4 Å measured in the NOESY spectrum which suggest a χ [$O_{4'}$–$C_{1'}$–N_1–C_2] = 0° (syn conformation).

Table I. $^3J_{HH}$ Coupling Constant (Error ± 0.1 Hz) of Cycloaddition Products 2a–4b at 500 MHz in $CDCl_3$ at 25 °C[a]

coupling constant	2a	2b	3	4a	4b
$J_{1',2'}$	8.2	8.6	8.5	9.4	9.6
$J_{2',4'}$	2.6	2.2	1.4		
$J_{2',7'}$	10.2	10.3	6.3	5.5	5.9
$J_{2',7''}$	3.2	3.5	13.1	1.1	1.1
$J_{7',7''}$	14.5	14.7	13.1	14.8	15.0
$J_{7',8}$	4.8	4.9	2.2	4.5	4.5
$J_{7'',8}$	0.8	1.5	2.5	0.0	0.0
$J_{4',5'}$	1.8	1.8	1.7	2.9	1.8
$J_{4',5''}$	2.2	2.2	1.5	1.5	2.2
$J_{5',5''}$	10.9	12.3	10.6	11.3	10.9
$J_{12,13'}$				0.0	0.0
$J_{12,13''}$				6.5	6.5
$J_{13',13''}$				13.3	13.6

[a] For bicyclic nucleoside **2b**, $^3J_{HH}$ can be translated into the following possible dihedral angles [$\Phi_{H,H}$] using the Karplus equation (1): (1) $J_{1',2'}$ = 8.6 Hz gives $\Phi_{H,H}$ = 155° and 199°; (2) $J_{2',7'}$ = 10.3 Hz gives $\Phi_{H,H}$ = 6°, 155°, 206°, and 355°; (3) $J_{2',7''}$ = 3.5 Hz gives $\Phi_{H,H}$ = 56°, 116°, 243°, and 302°; (4) $J_{7',8}$ = 4.9 Hz gives $\Phi_{H,H}$ = 43°, 125°, 233°, and 315°; (5) $J_{7'',8}$ = 1.5 Hz gives $\Phi_{H,H}$ = 80°, 95°, 266°, and 283°. For bicyclic nucleoside **3**, $^3J_{HH}$ can be translated into the following possible dihedral angles [$\Phi_{H,H}$] using the Karplus equation (1): (1) $J_{1',2'}$ = 8.5 Hz gives $\Phi_{H,H}$ = 154° and 200°; (2) $J_{2',7'}$ = 6.3 Hz gives $\Phi_{H,H}$ = 39°, 131°, 227°, and 319°; (3) $J_{2',7''}$ = 13.1 Hz indicates perfect trans coupling with $\Phi_{H,H}$ = 180°; (4) $J_{7',8}$ = 2.2 Hz gives $\Phi_{H,H}$ = 69°, 106°, 256°, and 294°; (5) $J_{7'',8}$ = 2.5 Hz gives following $\Phi_{H,H}$ = 63°, 108°, 251°, and 295°. For tricyclic nucleoside **4b**, $^3J_{HH}$ can be translated into the following possible dihedral angles [$\Phi_{H,H}$] using the Karplus equation (1): (1) $J_{1',2'}$ = 9.6 Hz gives $\Phi_{H,H}$ = 165° and 188°; (2) $J_{2',7'}$ = 1.1 Hz gives $\Phi_{H,H}$ = 42°, 130°, 229°, and 317°; (3) $J_{2',7''}$ = 5.9 Hz gives $\Phi_{H,H}$ = 82°, 94°, 267°, and 280°; (4) $J_{7',8}$ = 4.5 Hz gives $\Phi_{H,H}$ = 48°, 125°, 237°, and 313°; (5) $J_{7'',8}$ = 0.0 Hz gives $\Phi_{H,H}$ = 86° and 272°; (6) $J_{12,13'}$ = 0.0 Hz gives $\Phi_{H,H}$ = 88° and 274°; (7) $J_{12,13''}$ = 6.5 Hz gives $\Phi_{H,H}$ = 31°, 136°, 222°, and 327°.

Assignment of Configurations and Conformations of Diastereomeric Bicyclic Nucleosides 2b and 3. The $^3J_{H,H}$ of compounds **2b** and **3** and their corresponding proton–proton torsion angles obtained through analysis by the Karplus–Altona equation (1) are presented in Table I. Since compound **4b** was obtained from **2b** and during this transformation no change in configuration at $C_{2'}$ and C_8 is likely, we have assumed $C_{2'}$-*R* (i.e., H2′ "up") and C_8-*R* (i.e., –OEt "down") configuration in our conformational study of **2b**. The values of $\Phi_{1',2'}$ obtained from $J_{1',2'}$ established the south conformation of the pentofuranose ring (Table III). The large coupling constant of 10.3 Hz was observed between H2′ and one of the protons at C_7 (H7′, H7″). As shown in Table I, this value can fit either a cisoid or a transoid arrangement of two coupled protons.

Table II. Various Stereoisomers and Conformers of Compound 4b with Different Possible Configurations at $C_{2'}$, $C_{3'}$, and C_{12}

conformational param (deg) and dist (Å)	distances from NOE expt	conformer 1 $C_{2'}$-*R*, $C_{3'}$-*S*, C_8-*R*, C_{12}-*S*	conformer 2 $C_{2'}$-*R*, $C_{3'}$-*S*, C_8-*R*, C_{12}-*S*	isomer 3 $C_{2'}$-*R*, $C_{3'}$-*S*, C_8-*R*, C_{12}-*R*	isomer 4 $C_{2'}$-*R*, $C_{3'}$-*S*, C_8-*S*, C_{12}-*S*	isomer 5 $C_{2'}$*R*, $C_{3'}$-*R*, C_8-*R*, C_{12}-*S*
$\Phi_{1'2'}$		167	185	162	188	167
P		161	151	90	151	175
ψ_m		40	45	45	47	54
$\Phi_{2',7'}$		44	43	39[b]	37[b]	38[b]
$\Phi_{2',7''}$		−77	−78	−83	−85	−83
$\Phi_{7',8}$		−43	−47	−45	−51	−44
$\Phi_{7'',8}$		81	81	80	76	81
$\Phi_{12,13'}$		−88	−88	−80	−80	
$\Phi_{12,13''}$		33	34	36	39	
P^a		188	186	−47	146	
$\psi_m{}^a$		40	39	47	37	
$d_{1'7'}$		3.8	3.9	3.7	3.9	4.0
$d_{1',7''}$	3.0	2.8	3.0	2.5	2.6	3.0
$d_{5'',13'}$	2.4	2.4	2.4	2.3	2.2	4.3[b]
$d_{5'',13''}$		3.7	3.9	3.7	3.8	4.9
$d_{7',13'}$		3.8	3.7	4.8	4.4	4.1
$d_{7',13''}$	2.3	2.5	2.5	4.2[b]	3.1[b]	4.0[b]

[a] *P* and ψ_m for isoxazolidine ring were calculated assuming the following definitions of endocyclic torsions: τ_0 [N10–O11–C12–C13], τ_1 [O11–C12–C13–C3′], τ_2 [C12–C13–C3′–N10], τ_3 [C13–C3′–N10–O11], τ_4 [C3′–N10–O11–C12]. [b] Denotes at least small discrepancy with NMR derived torsion angles or proton–proton distances. Note that both conformers 1 and 2 are in agreement with $\Phi_{H,H}$ obtained from vicinal $J_{H,H}$ and distance information based on the NOESY experiment. The conformer 1 with $C_{2'}$-*R*, $C_{3'}$-*S*, C_8-*R*, and C_{12}-*S* configurations is presented in Figure 2a.

If the cisoid arrangement is considered the mutually consistent values of $\Phi_{2'7'}$ and $\Phi_{2',7''}$ are 5° and −115°, respectively (Table III). Note that the upfield H7″ showed NOE enhancement in the 1D NOE difference spectrum (Figure 1), whereas no enhancement was observed for downfield H7′. The values of $d_{1',7'}$ = 3.6 Å and $d_{1',7''}$ = 2.4 Å (Table III) are in agreement with the fact that the downfield H7′ shows a larger $J_{2',7'}$ but is not in close proximity to H1′. This agreement cannot be fulfilled if the coupling constant of 10.3 Hz is attributed to transoid arrangement of H2′ with respect to H7′ or H7″ (i.e., the assignment of H7′ and H7″ is reversed). In the computer model, the proton with the larger coupling constant to H2′ (J = 10.3 Hz) is closer to H1′ (2.5 Å) than the proton with the smaller coupling constant (J = 3.5 Hz, d = 3.1 Å), which is not observed through 1D ^{1}H difference NOE measurements (Figure 1). The six-membered ring of **2b** is in the half-chair/half-boat conformation (Table III, Figure 2).

In compound **3**, the H7″ is more upfield than H7′ and shows NOE enhancement upon saturation of H1′ and a large $J_{2',7''}$ of 13.1 Hz. The analysis by Karplus–Altona equation (1) showed that $J_{2',7''}$ can only be attributed to trans orientation of the coupled protons. In fact, the largest J that was obtained by the use of eq 1 with consideration of all four substituent electronegativities at $\Phi_{2',7''}$ = 180° was 12.4 Hz (if $\Phi_{2',7''}$ = 0° predicted $J_{2'7''}$ = 10.4 Hz). The six-membered ring of compound **3** is in the half-chair/half-boat conformation (Table III, Figure 2).

Experimental Section

^{1}H-NMR spectra were (in δ scale) recorded at 90, 270, and 500 MHz using TMS (0.0 ppm). ^{13}C-NMR were recorded at 67.5 MHz using both ^{1}H-coupled and ^{1}H-decoupled or INEPT modes. TLC was carried out using Merck precoated silica gel F_{254} plates. The column chromatographic separations were carried out using Merck G60 silica gel.

Reaction of 5′-*O*-(4-Monomethoxytrityl)-3′-nitro-2′,3′-dideoxy-2′,3′-didehydrothymidine (1a) with Ethyl Vinyl Ether. Compound **1a** (230 mg, 0.442 mmol) in CH_2Cl_2 (2 mL) was treated with ethyl vinyl ether (4 mL) at room temperature for 24 h. The solvent was removed in vacuo, and the mixture was separated on a silica gel column in hexane–ethyl acetate to give **4a** (136 mg, 47%), **2a** (68 mg, 27%), **3** (30 mg, 12%), and initial **1a** (18 mg, 8%). Compound **4a**. ^{1}H-NMR ($CDCl_3$) δ: 8.43 (brs, 1 H), NH; 7.90 (q, J = 1.1 Hz, 1 H) H-6; 7.43–7.21 (m, 12 H) arom; 6.95 (d, $J_{1',2'}$ = 9.4 Hz, 1 H) H-1′; 6.84 (m, 2 H) arom; 5.47 (d, $J_{12,13''}$ = 6.5 Hz, 1 H) H-12; 4.96 (d, $J_{7',8}$ = 4.5 Hz, 1 H) H-8; 4.11 (m, 1 H), H-4′; 3.99 (m, 1 H) OCH_2CH_3; 3.84 (dd, $J_{4',5'}$ = 2.9 Hz, $J_{5',5''}$ = 11.3 Hz, 1 H) H-5′; 3.79 (s, 3 H) OCH_3; 3.59 (dd, $J_{4',5''}$ = 1.5 Hz, 1 H) H-5″; 3.52 (m, 1 H) OCH_2CH_3; 3.25 (m, 1 H) OCH_2CH_3; 3.25 (m, 1 H), OCH_2CH_3; 2.84 (m, 1 H) H-2′; 2.68 (dd, $J_{13',13''}$ = 13.3 Hz, 1 H) H-13″; 1.99 (d, 1 H) H-13′; 1.95 (ddd, $J_{7',7''}$ = 14.8 Hz, $J_{2',7'}$ = 5.5 Hz, 1 H) H-7′; 1.75 (dd, $J_{2',7''}$ = 1.1 Hz, 1 H) H-7″; 1.31 (t, J = 7.0 Hz, 3 H) OCH_2CH_3; 1.17 (d, 3 H) 5-CH_3; 0.94 (t, J = 7.0 Hz, 3 H) OCH_2CH_3. ^{13}C-NMR ($CDCl_3$) δ: 163.7 (s) C-4; 150.5 (s) C-2; 135.9 (d, J_{CH} = 178.7 Hz) C-6; 111.4 (s) C-5; 108.6 (d, J_{CH} = 176.0 Hz) C-12; 98.4 (d, J_{CH} = 169.5 Hz) C-8; 86.2 (d, J_{CH} = 178.7 Hz) C-1′; 82.7 (d, J_{CH} = 150.3 Hz) C-4′; 77.6 (s) C-3′; 65.0 (t, J_{CH} = 142.5 Hz) OCH_2CH_3; 63.3 (t, J_{CH} = 145.2 Hz) C-5′; 62.9 (t, J_{CH} = 143.0 Hz) OCH_2CH_3; 55.0 (q, J_{CH} = 143.9 Hz) OCH_3; 42.1 (d, J_{CH} = 130.1 Hz) C-2′; 33.3 (t, J_{CH} = 135.2 Hz) C-13; 22.4 (t, J_{CH} = 129.2 Hz) C-7; 15.0 (q, J_{CH} = 126.5 Hz) OCH_2CH_3; 14.6 (q, J_{CH} = 126.8 Hz) OCH_2CH_3; 10.9 (q, J_{CH} = 129.22 Hz) 5-CH_3. MS (FAB⁻): calcd for $(M-H)^-$ 684.2921 for **4a**, found 684.2935. Compound **2a**. ^{1}H-NMR ($CDCl_3$) δ: 8.61 (brs, 1 H) NH; 7.67 (q, 1 H) H-6; 7.39–7.21 (m, 12 H) arom; 6.86 (m, 2 H) arom; 6.18 (d, $J_{1',2'}$ = 8.2 Hz, 1 H) H-1′; 5.49 (dd, $J_{7'',8}$ = 0.8 Hz, $J_{7',8}$ = 4.8 Hz, 1 H) H-8; 4.90 (dd, $J_{4',5'}$ = 1.8 Hz, $J_{4',5''}$ = 2.2 Hz, 1 H) H-4′; 4.01 (m, 1 H) OCH_2CH_3; 3.80 (dd, $J_{5',5''}$ = 10.9 Hz, 1 H) H-5′; 3.78 (s, 3 H) OCH_3; 3.72 (m, 1 H) OCH_2CH_3; 3.42 (dd, 1 H) H-5″; 3.18 (m, $J_{2',4'}$ = 2.6 Hz, 1 H) H-2′; 2.50 (ddd, $J_{7',7''}$ = 14.5 Hz, $J_{2',7'}$ = 10.2 Hz, 1 H) H-7′; 2.26 (ddd, $J_{2',7''}$ = 3.2 Hz, 1 H) H-7″; 1.40 (d, J = 1.2 Hz, 3 H) 5-CH_3; 1.24 (t, J = 7.0 Hz, 3 H) OCH_2CH_3; ^{13}C-NMR ($CDCl_3$) δ: 163.6 (s) C-4; 150.5 (s) C-2; 134.6 (d, J_{CH} = 185.1 Hz) C-6; 112.1 (s) C-5; 101.5 (d, J_{CH} = 174.1 Hz) C-8; 87.2 (s) Ph_3C; 86.7 (d, J_{CH} = 178.7 Hz) C-1′; 76.4 (d, J_{CH} = 156.7 Hz) C-4′; 65.5 (t, J_{CH} = 144.3 Hz) OCH_2CH_3; 62.5 (t, J_{CH} = 145.7 Hz) C-5′; 55.0 (q, J_{CH} = 143.9 Hz) OCH_3; 39.3 (d, J_{CH} = 140.2 Hz) C-2′; 28.2 (t, J_{CH} = 133.3 Hz) C-7; 14.6 (q, J_{CH} = 126.8 Hz) OCH_2CH_3; 11.4 (q, J_{CH} = 129.5 Hz) 5-CH_3. MS (FAB⁻): calcd for $(M-H)^-$ 612.2346 for **2a**, found 612.2380. Compound **3**. ^{1}H-NMR ($CDCl_3$) δ 8.40 (brs, 1 H) NH; 7.67 (q, J = 1.2 Hz, 1 H) H-6; 7.41–7.22 (m, 12 H) arom; 6.86 (m, 2 H) arom; 6.18 (d, $J_{1',2'}$ = 8.5 Hz, 1 H) H-1′; 5.60 (dd, $J_{7',8}$ = 2.2 Hz, $J_{7'',8}$ = 2.5 Hz, 1 H) H-8; 4.90 (dd, $J_{4',5'}$ = 1.7 Hz, $J_{4',5''}$ = 1.5 Hz, 1 H) H-4′; 4.11 (m, 1 H) OCH_2CH_3; 3.80 (dd, $J_{5',5''}$ = 10.6 Hz, 1 H) H-5′; 3.80 (s, 3 H) OCH_3; 3.76 (m, 1 H) OCH_2CH_3; 3.18 (m, $J_{2',4'}$ = 1.4 Hz, 1 H) H-2′; 3.42 (dd, 1 H) H-5″; 2.43 (ddd, $J_{7',7''}$ = 13.1 Hz, $J_{2',7'}$ = 6.3 Hz, 1 H) H-7′; 1.97 (ddd, $J_{7',7''}$ = $J_{2',7''}$ = 13.1 Hz, 1 H) H-7″; 1.29 (d, 3 H) 5-CH_3; 1.12 (t, J = 7.1, 3 H) OCH_2CH_3. ^{13}C-NMR ($CDCl_3$) δ: 163.2 (s) C-2;

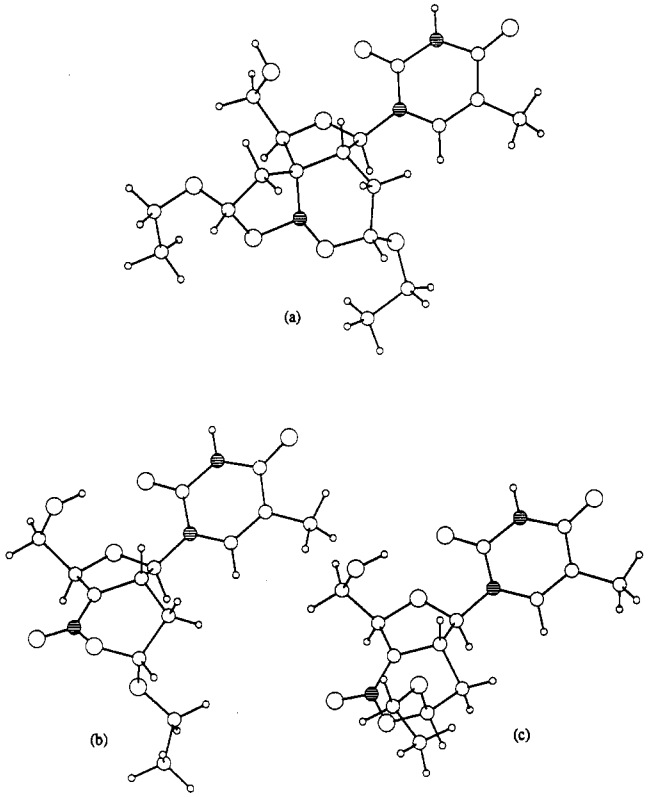

Figure 2. Conformations of **4b** (panel a), **2b** (panel b), and **3** (panel c) were obtained through energy minimization (the generalized AMBER force field parameters as implemented in the computer program MacroModel V3.5a were used) with constraints on $\Phi_{H,H}$ to build structures that fulfill all torsional angles derived from $^3J_{H,H}$ (ref 16). The configurations at four chiral centers in **4b** (panel a) were established as $C_{2'}$-*R*, $C_{3''}$-*S*, C_8-*R*, C_{12}-*S* through the use of distance information derived from NOESY experiments. The pentofuranose ring in **4b** is in the south conformation ($P = 161°$, $\Psi_m = 40°$), the six-membered ring adopts a $^{09}C_{C2'}$ chair conformation ($\Phi_{2',7'} = 44°$, $\Phi_{2',7''} = -77°$, $\Phi_{7',8} = -43°$, $\Phi_{7'',8} = 81°$) (panel a). The $P = 188°$ and $\Psi_m = 40°$ for the isoxazoline ring in **4b** were calculated assuming the following definitions of endocyclic torsion angles: τ_0 [N_{10}–O_{11}–C_{12}–C_{13}], τ_1 [O_{11}–C_{12}–C_{13}–$C_{3'}$], τ_2 [C_{12}–C_{13}–$C_{3'}$–N_{10}], τ_3 [C_{13}–$C_{3'}$–N_{10}–O_{11}], and τ_4 [$C_{3'}$–N_{10}–O_{11}–C_{12}] (Figure 2a). The distances $d_{1',7''} = 2.8$ Å, $d_{5'',13'} = 2.4$ Å and $d_{7',13''} = 2.5$ Å in the model of **4b** presented in Figure 2a are in close agreement with the experimentally determined values ($d_{1',7''} = 3.0$ Å, $d_{5'',13'} = 2.4$ Å and $d_{7',13''} = 2.3$ Å). Since the compound **2b** yields **4b** and during this transformation no change in configuration at C2′ and C8 is likely, we have assumed C2′-*R* and C8-*R* configuration in our conformational study of **2b**. The pentofuranose ring in **2b** is in the south conformation ($P = 142°$, $\Psi_m = 34°$), while the six-membered ring adopts the half-chair/half-boat conformation as shown in Figure 2b. In compound **3** (C2′-*R*, C8-*S*) the sugar ring is in the south conformation ($P = 140°$, $\Psi_m = 33°$) and the six-membered ring is in the half-chair/half-boat conformation as shown in Figure 2c.

158.8 (s) C-4; 134.9 (d, J_{CH} = 183.3 Hz) C-6; 112.2 (s) C-5; 101.6 (d, J_{CH} = 172.2 Hz) C-8; 87.4 (s) Ph_3C; 86.4 (d, J_{CH} = 174.1 Hz) C-1′; 77.0 (d, J_{CH} = 154.0 Hz) C-4′; 65.1 (t, J_{CH} = 142.9 Hz) OCH_2CH_3; 62.4 (t, J_{CH} = 146.6 Hz) C-5′; 55.1 (q, J_{CH} = 143.6 Hz) OCH_3; 38.6 (d, J_{CH} = 137.5 Hz) C-2′; 25.1 (t, J_{CH} = 134.7 Hz) C-7; 14.9 (q, J_{CH} = 126.5 Hz) OCH_2CH_3; 11.3 (q, J_{CH} = 129.5 Hz) 5-CH_3. MS (FAB⁻): calcd for (M – H)⁻ 612.2346 for **3**, found 612.2338.

Reaction of 3′-Nitro-2′,3′-dideoxy-2′,3′-didehydrothymidine (1b) with Ethyl Vinyl Ether. Compound **1b** (174 mg, 0.646 mmol) was treated in EtOH (2 mL) with ethyl vinyl ether (4 mL) at rt for 24 h. The solvent was removed in vacuo, and the mixture was separated on a silica gel column using CH_2Cl_2–EtOH to give **4b** (114 mg, 43%), **2b** (88 mg, 40%), and initial **1b** (17 mg, 10%). Compound **4b**. ^{1}H-NMR ($CDCl_3$) δ: 8.88 (brs, 1 H) NH; 7.12 (q, J = 0.8 Hz, 1 H) H-6; 6.16 (d, $J_{1',2'}$ = 9.6 Hz, 1 H) H-1′; 5.69 (d, $J_{12,13''}$ = 6.5 Hz, 1 H) H-12; 4.95 (d, $J_{7',8}$ = 4.5 Hz, 1 H) H-8; 4.01 (dd, $J_{4',5'}$ = 1.8 Hz, $J_{5',5''}$ = 10.9 Hz, 1 Hz) H-5′; 4.06 (m, 1 H) H-4′; 4.0 (m, 1 H) OCH_2CH_3; 3.91 (dd, $J_{4',5''}$ = 2.2 Hz, 1 H) H-5″; 3.78 (m, 1 H) OCH_2CH_3; 3.55 (m, 1 H) OCH_2CH_3; 3.51 (m, 1 H) OCH_2CH_3; 3.39 (m, 1 H) H-2′; 3.75 (dd, $J_{13',13''}$ = 13.6 Hz, 1 H) H-13″; 2.47 (d, 1 H) H-13′; 1.93 (ddd, $J_{7',7''}$ = 15.0 Hz, $J_{2',7'}$ = 5.9 Hz, 1 H) H-7′; 1.93 (d, 3 H) 5-CH_3; 1.57 (dd, $J_{2',7''}$ = 1.1 Hz, 1 H) H-7″; 1.29 (t, J = 7.0 Hz, 3 H) OCH_2CH_3; 1.19 (t, J = 7.1 Hz, 3 H) OCH_2CH_3. ^{13}C-NMR ($CDCl_3$) δ: 163.8 (s) C-4; 150.6 (s) C-2; 140.2 (d, J_{CH} = 179.6 Hz) C-6; 111.0 (s) C-5; 108.9 (d, J_{CH} = 176.0 Hz) C-12; 98.8 (d, J_{CH} = 168.6 Hz) C-8; 94.3 (d, J_{CH} = 171.4 Hz) C-1′; 84.0 (d, J_{CH} = 152.1 Hz) C-4′; 77.6 (s) C-3′; 65.2 (t, J_{CH} = 143.0 Hz) C-5′; 62.9 (t, J_{CH} = 143.0 Hz) OCH_3CH_3; 62.6 (t, J_{CH} = 144.8 Hz) OCH_2CH_3; 38.6 (d, J_{CH} = 138.4 Hz) C-2′; 33.1 (t, J_{CH} = 136.1 Hz) C-13; 22.6 (t, J_{CH} = 129.2 Hz) C-7; 15.0 (q, J_{CH} = 126.5 Hz) OCH_2CH_3; 14.8 (q, J_{CH} = 126.5 Hz) OCH_2CH_3; 12.3 (q, J_{CH} = 129.2 Hz) 5-CH_3. MS (FAB)⁻: calcd for (M – H)⁻ 412.1720 for **4b**, found 412.1736. Compound **2b**. ^{1}H-NMR ($CDCl_3$ + CD_3OD) δ: 7.76 (q, J = 1.2 Hz, 1 H) H-6; 6.06 (d, $J_{1',2'}$ = 8.6 Hz, 1 H) H-1′; 5.46 (dd, $J_{7'',8}$ = 1.5 Hz, $J_{7',8}$ = 4.9 Hz, 1 H) H-8; 4.85 (m, 1 H) H-4′; 4.04 (dd, $J_{4',5'}$ = 1.8 Hz, $J_{5',5''}$ = 12.3 Hz, 1 H) H-5′; 3.99 (m, 1 H) OCH_2CH_3; 3.95 (dd, $J_{4',5''}$ = 2.2 Hz, 1 H) H-5″; 3.71 (m, 1 H) OCH_2CH_3; 3.10 (m, $J_{2',4'}$ = 2.2 Hz, 1 H) H-2′; 2.38 (ddd, $J_{2',7''}$ = 3.5 Hz, $J_{7',7''}$ = 14.7 Hz, 1 H) H-7″; 2.13 (ddd, $J_{2',7'}$ = 10.3 Hz, 1 H) H-7′; 1.94 (d, 3 H) 5-CH_3; 1.25 (t, J = 7.0 Hz) OCH_2CH_3. ^{13}C-NMR ($CDCl_3$ + CD_3OD) δ: 135.2 (d, J_{CH} = 179.6 Hz) C-6; 111.5 (s) C-5; 101.5 (d, J_{CH} = 173.2 Hz) C-8; 86.3 (d, J_{CH} = 171.4 Hz) C-1′; 77.6 (d, J_{CH} = 151.2 Hz) C-4′; 65.2 (t, J_{CH} = 144.3 Hz) OCH_2CH_3; 59.9 (t, J_{CH} = 144.3 Hz) C-5′; 38.6 (d, J_{CH} = 140.2 Hz) C-2′; 27.3 (t, J_{CH} = 132.9 Hz) C-7; 14.1 (q, J_{CH} = 127.1 Hz) OCH_2CH_3; 11.6 (q, J_{CH} = 130.4 Hz) 5-CH_3. MS (FAB⁻): calcd for (M – H)⁻ 340.1145 for **2b**, found 340.1149.

Conversion of Tricyclic Nucleoside 4a to 11. Compound **4a** (60 mg, 0.09 mmol) was treated with 90% aqueous acetic acid (2 mL) at 40 °C for 3 h. The volatiles were evaporated, and the residue was dissolved in water (5 mL), filtered, and evaporated in vacuo. The residue (30 mg) was dissolved in EtOH (3 mL) and treated with $NaBH_4$ (40 mg, 1.3 mmol) at 0 °C for 30 min, acetic acid (0.5 mL) was added, and the mixture was evaporated to dryness and coevaporated with toluene. The residue was dissolved in pyridine (5 mL) and treated with acetic anhydride (1 mL) at rt for 2 h. The reaction mixture was poured slowly with stirring into ice–water, and the product was extracted with CH_2Cl_2 (2 × 10 mL). The organic phase was washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated. The residue was separated on a silica gel column in CH_2Cl_2–EtOH (9.5:0.5, v/v) to give compound **11** (25 mg, 59%). ^{1}H-NMR ($CDCl_3$) δ: 9.07 (brs, 1 H) NH; 7.25 (q, J = 0.8 Hz, 1 H) H-6; 5.87 (d, $J_{1',2'}$ = 6.3 Hz, 1 H) H-1′; 4.40–4.34 (m, 3 H) H-4′, CH_2CH_2OAc; 4.23–4.12 (m, 4 H) H-5′, H-5″, CH_2CH_2OAc; 3.00 (ddd, $J_{2',7'}$ = 8.7 Hz, $J_{2',7''}$ = 3.4 Hz, 1 H) H-2′; 2.78–2.73 (m, 2 H) H-7′, H-7″; 2.33–2.25 (m, 1 H) H-13′; 2.28 (s, 3 H) Ac; 2.09 (s, 3 H) Ac; 2.06 (s, 3 H) Ac; 1.98–1.93 (m, 1 H) H-13″; 1.96 (d, 3 H) 5-CH_3. ^{13}C-NMR δ: 163.2 (s) C-4; 150.2 (s) C-2; 134.5 (d, J_{CH} = 179.5 Hz) C-6; 111.5 (s) C-5; 91.0 (d, J_{CH} = 167.7 Hz) C-1′; 82.8 (d, J_{CH} = 149.4 Hz) C-4′; 71.0 (t, J_{CH} = 150.3 Hz) C-5′; 62.2 (t, J_{CH} = 148.5 Hz) CH_2CH_2OAc; 59.3 (t, J_{CH} = 149.4 Hz) CH_2CH_2OAc; 45.2 (d, J_{CH} = 136.4 Hz) C-2′; 29.9 (t, J_{CH} = 127.8 Hz) CH_2CH_2OAc; 28.8 (t, J_{CH} = 127.4 Hz) CH_2CH_2OAc; 20.7 (q, J_{CH} = 129.8 Hz) Ac; 20.6 (q, J_{CH} = 130.1 Hz) Ac; 17.9 (q, J_{CH} = 131.7 Hz) Ac; 12.4 (q, J_{CH} = 129.2 Hz) 5-CH_3. IR: 1550 cm^{-1} ($-NO_2$). MS (FAB⁻): calcd for (M – H)⁻ 484.1567 for **11**, found (M – H_3O)⁻ 466.1437, (M – $CH_3CO_2H_2$)⁻ 424.1339.

Conversion of Bicyclic Nucleoside 2a to a Diastereomeric Mixture of 7 and 8. Compound **2a** (80 mg, 0.13 mmol) was converted to a mixture of **7** and **8** using a reaction condition described for **4a** to give the mixture of compounds **7** and **8** (32 mg, 62%). NMR showed this to be an inseparable mixture (2:1) of the ribo and xylo isomers. Compound **7**. ^{1}H-NMR ($CDCl_3$) δ: 8.97 (brs, 1 H) NH; 7.55 (q, J = 1.2 Hz) H-6; 5.98 (d, $J_{1',2'}$ = 6.7 Hz, 1 H) H-1′; 5.12 (dd, $J_{2',3'}$ = 3.4 Hz, $J_{3',4'}$ = 5.9 Hz, 1 H) H-3′; 4.44 (ddd, $J_{4',5'}$ = 1.0 Hz, $J_{4',5''}$ = 4.3 Hz, 1 H) H-4′; 4.37–4.17 (m, 4 H) H-5′, H-5″, CH_2CH_2OAc; 3.12 (m, $J_{2',7'}$ = 5.1 Hz, $J_{2',7''}$ = 9.7 Hz, 1 H) H-2′; 2.16–2.04 (m, 2 H), H-7′, H-7″; 2.10 (s, 3 H)

Table III. Conformers of Compounds 2b and 3[a]

compd	$\Phi_{1'2'}$ (deg)	P (deg)	ψ_m (deg)	$\Phi_{2',7'}$ (deg)	$\Phi_{2',7''}$ (deg)	$\Phi_{7',8}$ (deg)	$\Phi_{7'',8}$ (deg)	$d_{1',7'}$ (Å)	$d_{1',7''}$ (Å)
2b	158	142	34	5	−115	−42	78	3.6	2.4
3	157	140	33	−44	−177	−64	61	3.2	2.4

[a] The conformations of **2b** and **3** with $C_{2'}$-*R* and C_8-*R* configurations are presented in Figure 2b,c.

Ac; 2.02 (s, 3 H) Ac; 2.00 (d, 3 H) 5-CH_3. Compound **8**. ^{1}H-NMR ($CDCl_3$) δ: 8.88 (brs, 1 H) NH; 7.19 (q, J = 1.2 Hz, 1 H) H-6; 6.28 (d, $J_{1',2'}$ = 9.3 Hz, 1 H) H-1'; 5.20 (dd, $J_{2',3'}$ = 7.3 Hz, $J_{3',4'}$ = 1.8 Hz, 1 H) H-3'; 4.77 (dt, $J_{4',5'} = J_{4',5''}$ = 3.9 Hz, 1 H) H-4'; 4.44 (dd, $J_{5',5''}$ = 12.9 Hz, 1 H) H-5'; 4.31 (dd, 1 H) H-5''; 4.12–4.00 (m, 2 H) CH_2CH_2OAc; 2.75 (ddd, $J_{2',7'}$ = 7.2 Hz, $J_{2',7''}$ = 14.6 Hz, 1 H) H-2'; 2.04 (s, 3 H) Ac; 2.17 (s, 3 H) Ac; 1.87–1.80 (m, 2 H) H-7', H-7''; 1.95 (d, 3 H) 5-CH_3. IR (Nujol): 1550 cm^{-1} ($-NO_2$). MS (FAB$^-$): calcd for $(M - H)^-$ 398.1200 for **7/8**, found 398.1218.

Conversion of Bicyclic Nucleoside 3 to a Diastereomeric Mixture of 7 and 8. Compound **3** (50 mg, 0.08 mmol) was subjected to the reaction conditions described for **4a** to give a mixture of **7** and **8** (2:1 mixture (NMR), 17 mg, 53%).

Conversion of Bicyclic Nucleoside 2a to a Tricyclic Nucleoside 4a. Compound **2a** (15 mg, 0.025 mmol) was treated in dichloromethane (0.5 mL) with ethyl vinyl ether (1 mL) at room temperature for 48 h. The solvent was removed in vacuo, and the substance was separated on a silica gel column using a linear gradient of 0–20% of ethyl acetate in hexane to give **4a** (15 mg, 89%).

Conversion of Bicyclic Nucleoside 2b to a Tricyclic Nucleoside 4b. Compound **2b** (13 mg, 0.038 mmol) in ethanol (0.5 mL) was treated with ethyl vinyl ether (1 mL) at room temperature for 48 h. The solvent was removed in vacuo, and the product was separated on a silica gel column using a linear gradient of 0–20% of ethyl acetate in hexane to give **4b** (12 mg, 76%).

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Supplementary Material Available: COSY, NOESY, and ^{13}C–^1H correlation spectra (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.