Stereospecific Synthesis and NMR Conformational Studies of γ-Butyrolactones of Nucleosides as Chiral Synthons for the Preparation of 2′-*C*- and 3′-*C*-Branched-Chain Nucleosides

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A stereoselective method is described for the synthesis of [3.3.0] fused lactones (γ-butyrolactones) of ribonucleosides at the 2′ and 3′ positions of the furanose ring by intramolecular addition of radicals onto the α-position of α,β-unsaturated esters. A new chiral center is formed at an off-template site of the ribofuranose ring, with good diastereoselectivity. These γ-butyrolactones of nucleosides are useful chiral synthons for the preparation of branched-chain nucleosides. Opening of the lactone ring afforded highly functionalized 2′-*C*- and 3′-*C*-branched-chain nucleosides which are difficult to synthesize by currently available methods. Conformational analysis of the γ-butyrolactones of nucleosides has indicated an unusual ribose ring conformation, probably induced by the fused γ-lactone ring.

Introduction

Branched-chain sugar nucleosides are present in a wide range of both naturally occurring and synthetic products, some having biological activities such as antitumor,[1-4] antiviral,[5-8] or antibacterial.[9] The key step in the total synthesis of these branched-chain sugar nucleosides is the stereocontrolled formation of a new C–C bond at the branching point. This is a difficult task especially at position 2′ of nucleosides.

Free-radical cyclizations are widely used for stereo- and regiocontrolled C–C bond formation, and their utility is well recognized in natural product synthesis.[10] The formation of fused rings by cyclization of the hex-5-enyl radical is a particularly useful process. Substrates can be cyclized without difficulty by the tin hydride method.[11] *Cis*-ring fusion invariably predominates when fused 6,5- or 5,5-rings are constructed.[12] The factors affecting the rate of cyclization and the stereo- and regiochemical outcome of reactions of hex-5-enyl radicals are well understood, and excellent and detailed reviews are available.[10,13,14] However, very few successful radical cyclizations involving nucleosides have been reported.[15] We report here a facile and stereoselective method for the synthesis of fused [3.3.0] lactones (γ-butyrolactones) of nucleosides by intramolecular addition of alkyl radicals at the "anti-Michael" α-position of α,β-unsaturated esters by exclusive 5-*exo* cyclization. In these cyclizations a new stereocenter is formed with excellent diastereoselectivity at the "off-template" site of the ribofuranose ring.[16] γ-Butyrolactones are present in a wide range of natural products, many of which have important biological activities.[17] Moreover, these γ-butyrolactones can be considered useful chiral synthons for the preparation of branched-chain sugar nucleosides. Our research goal has been the synthesis of branched-chain nucleosides as potential anti-HIV agents.[18-20] Thus, here we report the ring opening and subsequent 3′-deoxygenation of the γ-butyrolactones of nucleosides previously mentioned, to give 3′-deoxy-2′-*C*- and 3′-*C*-branched nucleosides having

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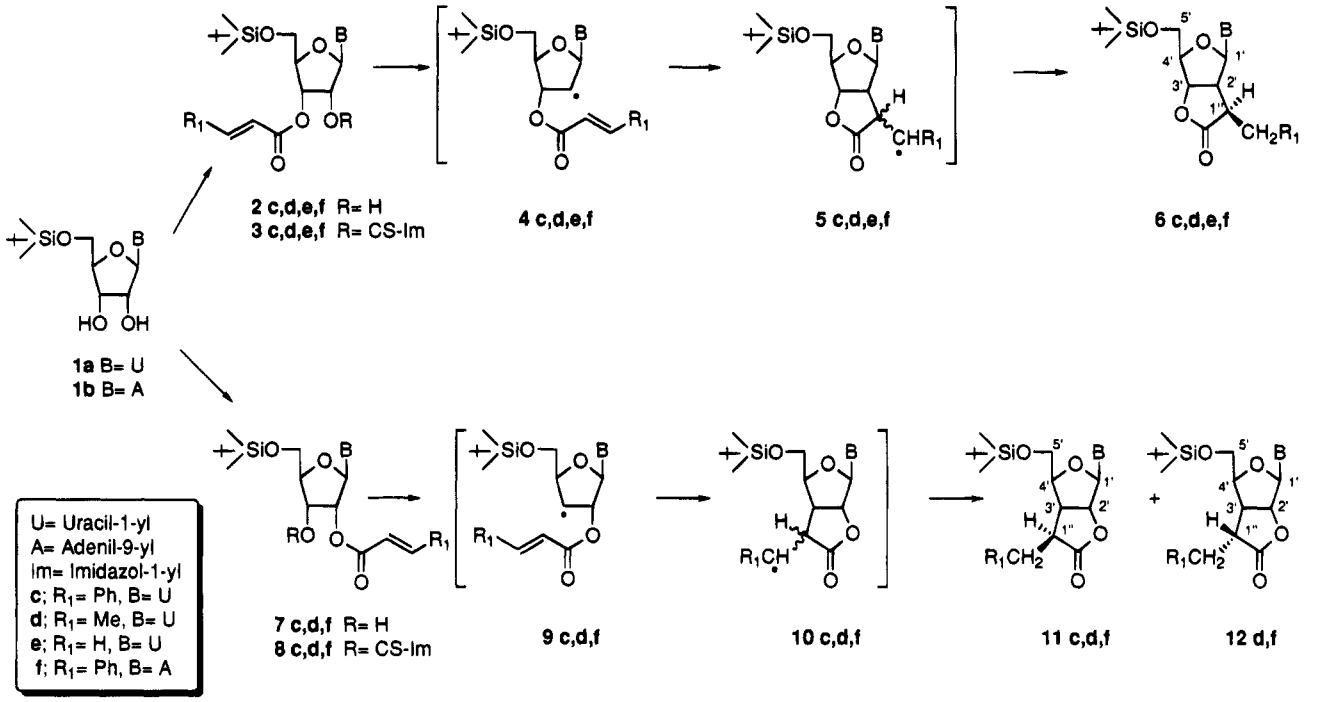
Scheme 1



a highly functionalized *C*-branch. These products are very difficult to obtain by more "classical" methods.

Results and Discussion

For the synthesis of the fused γ-butyrolactones we choose α,β-unsaturated esters differently substituted (R_1 = H, CH_3, Ph) as radical acceptors in order to study the effect of the different acceptor character of the double bond in the reaction. Furthermore, intramolecular additions of radicals into the double bond of α,β-unsaturated esters of nucleosides were unprecedented in the literature.[21] The general strategy is shown in Scheme 1. The conveniently 5′-*O*-protected nucleoside derivative **1** undergoes acylation by reaction with the corresponding α,β-unsaturated acid or acid chloride, to give α,β-unsaturated esters **2** and **7** which by reaction with 1,1′-(thiocarbonyl)-diimidazole afford the intermediates **3** and **8** ready for free-radical cyclization mediated by tributyltin hydride.

Radical precursors **3c−f** and **8c,d,f** were prepared by a two-step reaction sequence. Thus, reaction of the uridine nucleoside **1a** with 1 equiv of cynnamoyl chloride in dichloromethane/DMAP gave an isomeric mixture (1:1) of the respective 3′- and 2′-cinnamoyl derivatives **2c** and **7c** in 72% yield.

However, acylation of compound **1a** with crotonyl chloride or acryloyl chloride, under similar reaction conditions, gave poor yields of the desired products. It was found, however, that a satisfactory yield of the desired derivatives could be obtained via the cyclic stannylene method.[22] In both cases, the 3′-*O*-acyl derivative **2d** (60%) or **2e** (51%) was obtained, exclusively. Reaction of **1a** with crotonic acid according to the Mukaiyama procedure[23] gave a mixture (1:1) of the 3′- and 2′-crotonyl derivatives **2d** and **7d** (55% yield).

Similarly, treatment of the adenosine nucleoside **1b** with cinnamoyl chloride in dichloromethane/DMAP afforded a mixture (2:1) of the respective 3′- and 2′-cinnamoyl esters **2f** and **7f** in 73% yield.

Acyl derivatives **2c−f** and **7c,d,f** were not separated at this stage since it is known that trans acyl migration between position 2′ or 3′ may occur.[24] Reaction of the mixtures of 3′- and 2′-acyl derivatives **2c−f** and **7c,d,f** with 3 equiv of (thiocarbonyl)diimidazole in DMF[25] afforded the corresponding radical precursors **3c−f** and **8c,d,f** in good yields (80−90%), which were separated by column chromatography. Then, the radical precursors **3c−f** and **8c,d,f** (Scheme 1) were treated with Bu_3SnH in boiling benzene under an argon atmosphere. Addition of Bu_3SnH was very slow (syringe pump over 20−24 h) in order to favor cyclization over reduction. The radicals thus generated at C2′ or C3′ (**4c−f** or **9c,d,f**) were efficiently trapped by the double bond of the α,β-unsaturated ester to form the γ-lactones **6c−f**, **11c,d,f**, and **12d,f** in moderate yields (see Table 1) together with the reduction byproducts **13c−f** and **15c,d,f** (Scheme 2). It was found that in cyclization of the adenine intermediate **3f**, lactone **6f** was obtained together with a (1:1) mixture of the 2′-deoxynucleosides **13f** and **14f** in 15% yield, which was not chromatographically separable. Separation of the γ-lactones from the reduction products was rather laborious, and repeated chromatography was required to give the γ-lactones in the yields shown in Table 1.

Structures of the γ-butyrolactone nucleosides **6c−f**, **11c,d,f**, and **12d,f** were assigned on the basis of the corresponding analytical and spectroscopic data. The IR

(21) Our early paper was followed by another report on the synthesis of δ-lactones through the radical cyclization of α,β-unsaturated esters. See ref 15b.

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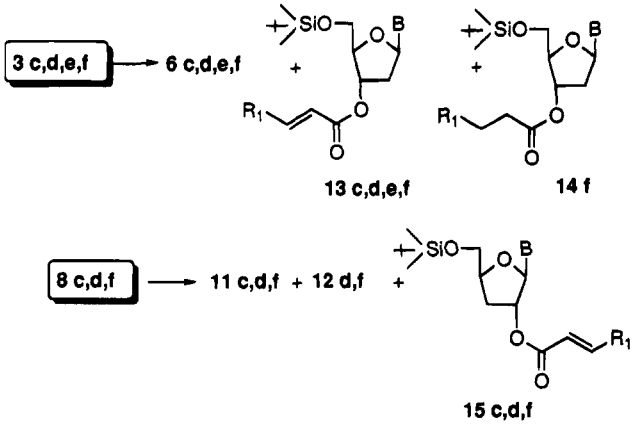
Table 1. Cyclization and Reduction Products from Nucleosides 3c–f and 8c,d,f

radical precursor	product (yield, %)[a] γ-butyrolactones	reduced
3c	**6c** (35)	**13c** (35)
3d	**6d** (20)	**13d** (50)
3e	**6e** (10)	**13e** (13)
3f	**6f** (30)	**13f** + **14f** (15)[b]
8c	**11c** (35)	**15c** (29)
8d	**11d** (25) + **12d** (17)	**15d** (40)
8f	**11f** (30) + **12f** (10)	**15f** (15)

[a] Yields after purification. [b] Yield of the mixture.

Scheme 2



spectra showed a band at 1770–1780 cm^{-1} corresponding to five-membered ring lactones. The ^1H NMR spectra (Table 2) showed the disappearance of the signals corresponding to the imidazole and the vinylic protons of the α,β-unsaturated ester and the presence of new multiplets around 1.3–1.4 ppm corresponding to the H-1″ and 1″-CH_2R[26] of the γ-lactone moiety.

The absolute stereochemistry at the newly formed stereocenter (C-1″) in **6c–f**, **11c,d,f**, and **12d,f** was unequivocally determined by NOE experiments[27,28] (Figure 1). Thus, irradiation of the anomeric proton of **6c–f** caused enhancements of the signal for H-1″ [**6c** (10%), **6d** (8%), **6e** (9%), **6f** (9%)], indicating that the stereochemistry at C-1″ was *R*. Similarly, irradiation of H-4′ in **11c,d,f** and **12d,f** influenced the signals for H-1″ [**11c** (8%), **11d** (8%), **11f** (8%)] and H-5′a [**11c** (4%), **11d** (4%), **11f** (3%)] for the major isomers **11c,d,f** and for CH_2-1″ [**12d** (5%), **12f** (5%)] and H-5′a [**12d** (3%), **12f** (2%)] for the minor isomers **12d,f**. Therefore, C-1″ was assigned as *S* in **11c,d,f** and as *R* in **12d,f**. Finally, irradiation of H-2′ in **6c–f**, **11c,d,f**, and **12d,f** induced NOE at the signal corresponding to H-3′ [**6c** (12%), **6d** (10%), **6e** (11%), **6f** (9%), **11c** (13%), **11d** (10%), **11f** (10%), **12d** (10%), **12f** (10%)], which indicated that for all compounds H-2′ and H-3′ are at the upper face of the furanose ring (β-face), establishing the cis fusion between the γ-lactone and the sugar ring.

The ratios of cyclized to reduced products could be explained by differences in acceptor character of the double bond.[13b] As seen from Table 1, the higher acceptor character of the double bond (R = Ph > R = H > R = CH_3), the higher the yields of the cyclized products and the lower the yields of the reduced products. The poor yield observed in the cyclization of the acryloyl ester precursor **3e** could be explained by the lower stability of the primary radical intermediate **5e** formed, which could lead to dimerization and other unwanted reactions.

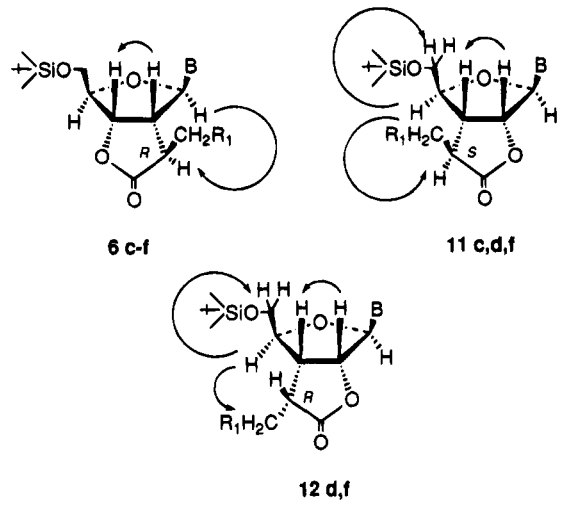


Figure 1. NOEs observed upon irradiation of the H-2′ and H-1′ protons in compounds **6c–f** and H-2′ and H-4′ protons in compounds **11c,d,f** and **12d,f**.

In cyclization of the radical precursors **3c–f** and **8c,d,f**, the γ-butyrolactones formed (**6c–f**, **11c,d,f**, and **12d,f**) were *cis*-fused and exclusively the 5-*exo* isomers were obtained.[29] These results indicate that the addition process is kinetically controlled[30] and that the radicals add to the "anti-Michael" α-position of the double bond.[31] Clearly, the stereoelectronic control of the cyclization strongly overrides the regioselectivity of β and "Michael addition".

In these cyclizations a new stereocenter is formed with good diastereoselectivity at an "off-template" site of the ribofuranose moiety. Thus, when prochiral radicals are generated at C-2′ (radical precursors **3c–f**), the addition of the radical to the double bond (Scheme 1) is diastereospecific, affording exclusively the *R* γ-butyrolactones (**6c–f**), whereas, when the radical is generated at C-3′ (radical precursors **8c,d,f**), the addition is diastereoselective, yielding a diastereomeric mixture of *S* (**11c,d,f**) and *R* (**12d,f**), with the latter isomers predominating. Therefore, this process is a good example of a reaction in which the sugar provides an ideal chiral template for achieving a good diastereoselection.[32]

Scheme 3 shows a possible rationale for the stereochemical results obtained in the cyclization of the radical precursors **3e–f**. Beckwith has proposed, for the addition of a radical to a double bond and hence for the cyclization, a transition state in which the three participating atoms (in this case the radical at C-2′ and the two carbons of the olefin) are situated at the vertices of an obtuse triangle. Therefore, the radical adopts a trajectory

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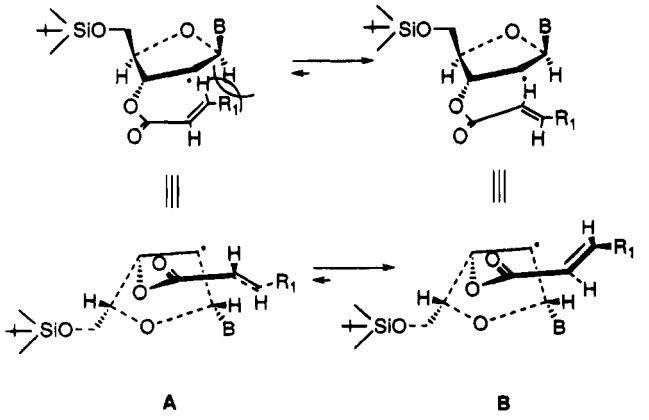
Table 2. Selected ^{1}H NNR Spectral Data of Nucleosides: Chemical Shifts (ppm), Multiplicity, and Coupling Constants (Hz)

compd	H-1′ ($J_{1',2'}$)	H-2′ ($J_{2',3'}$)	H-3′ ($J_{3',4'}$)	H-4′	H-5′ ($J_{4',5'}$)		H-1″ ($J_{2'(3'),1''}$)	others
3c[a]	6.65 d (7.4)	5.86 dd (5.5)	5.72 dd (1.3)	4.40 d	3.98 m			5.77 s (H-5), 6.44 d, 7.68 d (H-α, H-β),[b] 7.02 s, 7.59 s, 8.33 s (imidazole), 7.90 d (H-6)
3d[a]	6.60 d (7.6)	5.83–5.91 m (4.4)	5.64 dd (1.1)	4.35 d	3.96 s			1.91 dd, 5.87 m, 7.04 m (CH_3-β, H-α, H-β),[b] 5.78 d(H-5), 7.01 s, 7.60 s, 8.30 s (imidazole), 7.88 d (H-6)
3e[c]	*d*	*d*	*d*	4.30 m	4.00 m			5.80 d (H-5), 7.05 s, 7.60 s, 8.30 s (imidazole), 7.90 d (H-6)
3f[e]	6.67 d (7.0)	6.24 dd (5.5)	5.89 dd (2.0)	4.44 m	4.05 d (2.2, 2.0)			6.44 d, 7.80 d (H-α, H-β),[b] 7.07 s, 7.66 s, 8.33 s (imidazole), 8.23 s, 8.32 s (H-2, H-8)
6c[a]	5.80 d (5.9)	2.60 m (7.0)	4.31 m	4.31 m	3.65 dd (2.1)	3.81 dd (1.9)	3.29 m (2.3)	2.93 dd, 3.10 dd (Ph CH_2-1″), 5.56 d (H-5), 7.50 d (H-6)
6d[a]	5.94 d (5.6)	2.72 m (7.0)	4.97 dd (2.0)	4.45 m	3.85 dd (2.2)	3.98 dd (2.4)	2.96 m (2.5)	1.02 t, 1.80 m (CH_3-CH_2-1″), 5.72 d (H-5), 7.80 d (H-6)
6e[a]	5.89 d (5.3)	2.64 m (7.1)	5.01 dd (2.3)	4.45 m	3.70 dd (2.2)	3.85 dd (2.4)	2.64 m (3.0)	1.38 d (CH_3-1″), 5.75 d (H-5), 7.85 d (H-6)
6f[a]	5.97 d (5.1)	3.71 m (7.6)	4.98 dd (3.2)	4.29 m	3.84 dd (4.5)	3.89 dd (5.0)	3.38 m (4.5)	2.95 dd, 3.23 dd (Ph, CH_2-1″), 7.68 s, 8.21 s (H-2, H-8)
8c[e]	6.51 d (7.6)	5.20 dd (6.4)	6.05 dd (1.6)	4.55 m	4.05 m			5.80 d (H-5), 6.44 d, 7.70 d (H-α, H-β),[b] 7.05 s, 7.60 s, 8.40 s (imidazole), 7.80 d (H-6)
8d[a]	6.47 d (7.8)	5.42 dd (5.6)	6.00 dd (1.0)	4.51 m	3.98 dd (1.7)	4.08 dd (1.7)		1.91 dd, 5.84 m, 7.03 m (CH_3-β, H-α, H-β)[b] 5.78 d (H-5), 7.10 s, 7.65 s, 8.38 s (imidazole), 7.89 d (H-6)
8f[a]	6.50 d (7.3)	5.95 dd (5.4)	6.25 dd (1.8)	4.60 m	4.00 dd (2.2)	4.07 dd (2.4)		6.30 d, 7.80 d (H-α, H-β)[b] 7.05 s, 7.60 s, 8.30 s (imidazole), 8.20 s, 8.35 s (H-2, H-8)
11c[a]	5.88 d (1.8)	4.59 dd (7.1)	3.00 m (7.2)	3.85 m	3.40 dd (3.1)	3.75 dd (3.1)	2.84 m (2.3)	2.84 m, 3.18 d ($PhCH_2$-1″), 5.65 d (H-5), 7.54 d (H-6)
11d[E]	5.89 s	5.02 d (6.7)	3.00 m (8.1)	3.90 m	3.80 dd (1.4)	3.90 m	2.39 m (1.7)	1.02 t, 1.80 m (CH_3CH_2-1″), 5.70 d (H-5), 7.60 d (H-6)
11f[a]	6.10 d (1.6)	4.98 dd (6.7)	3.40 m (7.3)	3.96 m	3.50 dd (4.5)	3.65 dd (4.2)	2.90 (2.1)	2.98 m, 3.16 dd ($PhCH_2$-1″), 7.90 s, 8.30 s (H-2, H-8)
12d[e]	6.02 s	4.87 d (5.4)	3.36 m (6.6)	4.14 m	4.14 m	3.67 dd (2.7)	2.74 m (8.8)	1.02 t, 1.40 m, 1.90 m (CH_3CH_2-1″), 5.67 d (H-5), 7.81 d (H-6)
12f[a]	6.27 s	5.53 d (5.6)	3.70 m (6.9)	4.35 m	3.45 dd (4.1)	3.75 dd (3.7)	3.40 m (6.9)	2.78 dd, 3.40 m ($PhCH_2$-1″), 8.04 s, 8.30 s (H-2, H-8)
16c[a]	6.17 d (8.8)	2.34 m (5.1)	4.46 m	4.16 m	3.81 dd (2.0)	3.90 dd (2.0)	2.83 m (5.1)	0.73 d, 0.74 d, 1.61 m, 2.98 m (^{i}Bu), 2.83 m, 3.23 dd (CH_2Ph), 5.70 d (H-5), 7.12 t (NH^iBu), 7.99 d (H-6)
17c[f]	6.04 d (6.1)	2.75 m	2.16 m	4.24 m	3.75 dd (3.0)	3.93 dd (3.0)	2.75 m	0.70 d, 0.73d, 157 m, 2.75 m (^{i}Bu), 2.75 m (CH_2Ph), 5.60 d (H-5), 7.00 bs (NH^iBu), 7.96 d (H-6)
18c[a]	5.85 d (6.1)	3.05 ddd (8.3)	4.85 dd (3.4)	4.22 q	3.79 m		3.25 ddd (3.7)	2.91 dd, 3.19 dd ($PhCH_2$-1″), 5.50 d (H-5), 7.54 d (H-6)
19c[f]	6.27 d (9.7)	*g*	4.40 m	3.98 m	3.74 m		*g*	0.65 d, 0.67 d, 1.54 m (^{i}Bu), 5.62 m (H-5, OH), 7.11 m (NH^iBu, Ph), 7.99 d (H-6)
20c[h]	5.92 d (5.4)	*i*	1.94 m	4.10 m	3.60 m		*i*	0.60 d, 0.63 d, 1.44 m (^{i}Bu), 5.65 d (H-5), 7.64 bs (NH^iBu), 7.96 d (H-6)
21c[a]	5.07 s	4.31 d (10.0)	2.49 m (5.5)	4.27 d	3.81 dd (1.8)	4.15 d (0)	2.69 m (8.3)	0.74 d, 0.79 d, 1.41 m, 2.86 m (^{i}Bu), 2.69 m, 2.86 m (CH_2PH), 5.55 m (H-5, OH, NH^iBu), 8.05 d (H-6)

[a] $CDCl_3$ at 300 MHz. [b] Olefinic protons and substituents of the α,β-unsaturated ester are indicated as α and β. [c] $CDCl_3$ at 90 MHz. [d] 5.90–6.60 m (including H-1′, H-2′, H-3′, H-α′, and H-β). [e] $CDCl_3$ at 200 MHz. [f] $(CD_3)_2CO$ at 200 MHz. [g] 2.68–3.03 m (including H-2′, H-1″, CH_2Ph, $NHCH_2$). [h] $(CD_3)_2SO$ at 200 MHz. [i] 2.52–2.81 m (including H-2′, H-1″, CH_2PH, $NHCH_2$).

Scheme 3



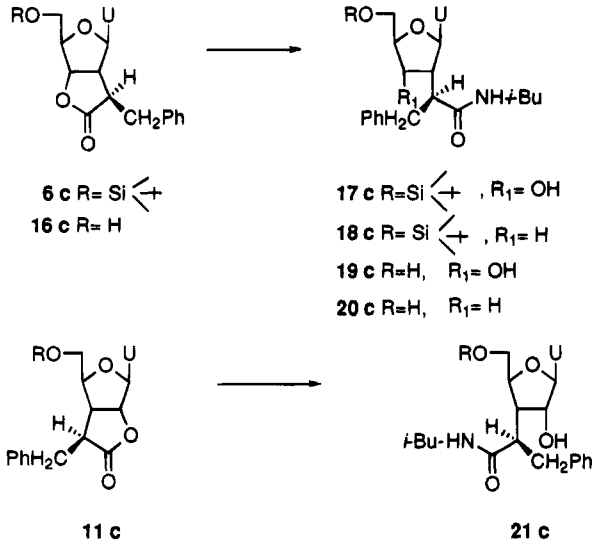
perpendicular to the nodal plane of the π system.[29a,33] The precursors **3e–f** are able to form such a transition state if the α,β-unsaturated ester moiety adopts either the *S-cis* (rotamer B) or *S-trans* (rotamer A) conformation. The unfavorable steric interactions between the anomeric proton and the double bond in the *S-trans* (rotamer A) drives the equilibrium to the right to the B rotamer (*S-cis*). Hence, γ-lactones **6c–f** with the *R* configuration are produced exclusively. Additionally, the transition state that gives rise to these γ-lactones (**6c–f**) would be an energetically more favorable chair-like conformation, whereas in the *S-trans* transition state only a boat-like conformation would be generated.

A similar rationale could be used for the cyclization of the radical precursors **8c,d,f**, where the unfavorable interactions between the double bond β-proton and the H-4′ in the intermediate would lead predominantly to the *S* isomers (**11c,d,f**). The fact that in the reaction the *R* isomers (**12d,f**) were also isolated as minor compounds seems to indicate that, although the steric interactions are important, the influence of other factors such as the different stereochemical environment at C-2′ or C-3′ or a different conformation of the C-2′ versus C-3′ radical[34] may also be of importance.

(33) Strubble, D. L.; Beckwith, A. L. J.; Gream, G. E. *Tetrahedron Lett.* **1968**, 3701–3704.

(34) De Mesmaeker, A.; Waldner, A.; Hoffmann, P.; Mindt, T.; Hug, P.; Winkler, T. *Synlett* **1990**, 687–690.

Scheme 4



The [3.3.0] fused lactones (γ-butyrolactones) of nucleosides described above can be considered useful chiral synthons for the synthesis of branched-chain nucleosides having a highly functionalized *C*-branch. Ring-opening of the γ-butyrolactones would provide convenient access to the desired branched-chain nucleosides.

Initial attempts to ring-open the γ-lactone moiety of **6c** by aminolysis with diluted ammonia, liquid ammonia, or primary amines following standard conditions[35,36] proved unsuccessful. The starting material was recovered unchanged. However, the γ-lactones **6c** and **11c** were readily opened by a recently described method which promoted aminolysis of lactones in the presence of aluminum chloride.[37,38] Thus, treatment of **6c** and **11c** (Scheme 4) with 2 equiv of isobuytylamine and 1 equiv of aluminum chloride gave the corresponding 2′-*C*- and 3′-*C*-branched nucleosides **17c** and **21c** in 81% and 62% yields, respectively.

3′-Deoxygenation[39] at the 3′ position of **17c** by treatment with *N,N′*-(thiocarbonyl)diimidazole followed by reaction with tributyltin hydride in the presence of AIBN afforded the 2′,3′-dideoxynucleoside **18c** in 44% yield. Finally, treatment of **6c**, **17c**, and **18c** with tetrabutylammonium fluoride gave the corresponding 5′-*O*-deprotected nucleosides **16c**, **19c**, and **20c** in 75%, 71% and 95% yields, respectively.

Conformational Analysis of the γ-Butyrolactones of Nucleosides 6c, 6f, 11c, 11f, and 12f. A detailed analysis of the ^{1}H NMR spectra (Table 2) showed that $^3J_{H1',H2'}$ and $^3J_{H3',H4'}$ for the 3′,2′-γ-butyrolactones (**6c**, **6f**) were different than those observed for the 2′,3′-γ-butyrolactones (**11c**, **11f**, and **12f**). These differences suggest a different conformation of the ribose moiety in both types of nucleosides.

The conformation of the ribose ring of **6c**, **6f**, **11c**, **11f**, and **12f** was determined from $^3J_{HH}$ values as described by Altona and co-workers.[40,41] The method uses the generalized Karplus equation which relates the vicinal

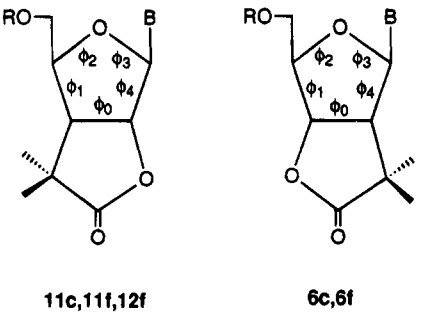


Figure 2. Definition of the endocyclic torsion angles (nomenclature as proposed by Altona[42]), where $\phi_j = \tau_{sugar} \cos(P_{sugar} + 4j(\pi/5))$ ($j = 0-4$).

proton–proton coupling constants with the corresponding proton–proton torsion angles from $^3J_{HH}$ values and takes into account the effect of substituent electronegativity and orientation.[42] Figure 2 shows the definition of the endocyclic torsion angles for the furanose ring in both types of nucleosides.

The geometry of the furanose ring is described by two pseudorotational parameters P (phase angle of pseudorotation) and τ (puckering amplitude). Equations to relate the proton–proton torsion angles ($\phi_{H,H}$) and the pseudorotational parameters (P_{sugar} and τ_{sugar}) have been parametrized empirically by Altona[42] for different sugar moieties.

It is known that, in general in solution, the furanoid rings exist as an N/S equilibrium of the two possible interconverting conformers N (north) and S (south) with P_N, τ_N and P_S, τ_S pseudorotational parameters for the N and S conformers, respectively.[43] Therefore, the experimental NMR coupling constant will be time-averaged and linearly related to the coupling of the individual conformers and their relative populations by the following equation: $J_{exp} = X_N J_N + (1 - X_N) J_S$, where X_N represents the mole fraction of the N conformer present.

From ^{1}H NMR spectra of compounds **6c**, **6f**, **11c**, **11f**, and **12f**, three coupling constants ($J_{1',2'}$, $J_{2',3'}$, and $J_{3',4'}$) for the ribose ring could be measured. However, considering that these spectra showed second-order effects, even at 500 MHz, accurate values for these coupling constants were obtained by spectral simulation using the iterative PANIC 86 program[44] (see Table 4).

A first calculation was performed to determine whether the experimental set of coupling constants for each compound was compatible with a single conformation. For **12f** the experimental $^3J_{HH}$ values were compatible with a single N-type conformation (rms = 0.19), whereas **11c** and **11f** showed an N-type preferred conformation and **6c** and **6f** a S-type preferred conformation with higher rms errors, which indicated the possibility of existence of S- and N-type minor conformers, respectively. In all cases the N-type conformations were in the range of 306° < P_N < 342° and 20° < τ_N < 40°, while the S-type conformations were in the range of 180° < P_S < 216° and 20° < τ_S < 40°. Then, the possibility of a N/S equilibrium was evaluated. We generated six dihedral angles ($\phi_{1',2'}$, $\phi_{2',3'}$, and $\phi_{3',4'}$), three for each conformer (N

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(36) Roshenthal, A.; Baker, D. A. *J. Org. Chem.* **1973**, *38*, 198–201.
(37) Lesimple, P.; Bigg, D. C. H. *Synthesis* **1991**, 306–308.
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(41) Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1973**, *95*, 2333–2344.
(42) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; de Leeuw, H. P. M.; Altona, C. *Org. Magn. Reson.* **1981**, *15*, 43–52.
(43) Fuschs, B. In *Topics in Stereochemistry*; Eliel, E., Allinger, N. L., Eds.; John Wiley and Sons: New York, 1987; Vol. 10, pp 1–94.
(44) PANIC 86. Bruker library, 1986.

Table 3. Pseudorotational Parameters Calculations for the Ribose Ring of Compounds 6c, 6f, 11c, 11f, and 12f

	6c		6f		11c		11f		12f	
	major	minor	major	minor	major	minor	major	minor	major	minor
P_{sugar}	202	336	193	347	324	90	324	90	325	
τ_{sugar}	29	29	27	23	35	20	34	29	39	
X[a]	0.8	0.2	0.6	0.4	0.8	0.2	0.9	0.1	1.0	
rms (Hz)[b]	0.02		0.02		0.08		0.04		0.19	

[a] Mole fraction. [b] Residual deviation in the calculated couplings.

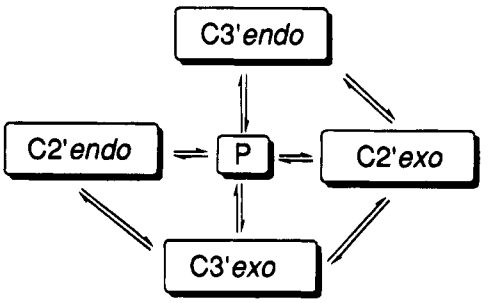
and S), and then we calculated the values of J_N and J_S for the three dihedral angles and compared them with the experimental coupling constant for different X_N values. Thus, while keeping P and τ pseudorotational parameters for the major conformers of **6c**, **6f**, **11c**, and **11f** fixed in the above-mentioned range, an optimization for P and τ values of the corresponding minor conformers was performed. Consequently, minor conformers for **6c** and **6f** were in the range of $324° < P < 360°$ and $20° < \tau < 30°$. Similarly, for **11c** and **11f**, P and τ were in the range of $72° < P < 108°$ and $20° < \tau < 30°$. Finally, an optimization to minimize the rms values for the calculated coupling constants varying P_N, P_S, τ_N, and τ_S within the mentioned range in steps of 1° for the phase angle (P) and steps of 1° for the puckering amplitude (τ) and the mole fraction (X_N) in steps of 0.1 was carried out. Table 3 shows the pseudorotational parameters obtained. These data indicated that the ribose moiety of nucleoside **12f** exists as a single N conformer, the energy minimum corresponding to a twist ($^1_2$T) conformation ($P = 325°$ and $\tau = 39°$), whereas in nucleosides **6c** and **6f**, the situation could be explained as a N/S equilibrium shifted to the S-type conformer, the energy minimum corresponding to a C-3′-*exo* envelope ($_3$E) conformer ($P = 202°$ and 193°; $\tau = 29°$ and 27°, respectively) and the minor conformers corresponding to a C-2′-*exo* envelope ($_2$E) ($P = 336°$, 347°; $\tau = 29°$, 23°, respectively). This unusual C-3′-*exo*/C-2′-*exo* equilibrium is reminiscent, in some way, to that observed for nonfused nucleosides[40,45] but located in the west region of the pseudorotational circuit. Finally, in compounds **11c** and **11f** the N/S equilibrium is shifted to an N-type conformer corresponding to a twist ($^1_2$T) conformation ($P = 324°$ and 324°; $\tau = 35°$ and 34°, respectively) and minor conformer corresponding to a O-1′-*endo* envelope (^{0}E) ($P = 90°$ and 90°; $\tau = 20°$ and 29°).

These compounds have an additional structural feature which is the presence of the fused γ-lactone ring. Since the C2′−C3′ bond is part of both fused rings (ribose and γ-lactone), an interdependence of the geometry of both rings may exist.

According to literature data,[46] replacement of a furanose ring sp^3 carbon by an sp^2 carbon causes considerable changes in ring conformation and dynamics. The planarity (or near-planarity) of the OC(O)C fragment restricts γ-lactone rings to two relatively small segments of the pseudorotational circuit.[40] Following the model proposed by Angelotti et al.,[46] in our study we considered the model shown in Scheme 5 for lactone ring conformational dynamics.

From ^{1}H NMR vicinal coupling constants, it is possible to discriminate between N and S conformers (i.e. C3′-*endo* and C3′-*exo*). However, discrimination between N or S conformers (i.e. C3′-*endo* and C2′-*exo*) is not possible due to the small differences in the NMR parameters of the two conformers.

Scheme 5



In our compounds only qualitative conclusions about the conformation of the lactone ring could be established. From the interprotonic torsion angles $\phi_{H2',H3'}$ [obtained from the conformational analysis of the ribose ring (see Table 4), some conformational features of the γ-lactone ring could be deduced. Thus, when $\phi_{H2',H3'} > 0$ the conformation of the lactone could be described by the equilibrium C2′-*endo* ⇄ C3′-*exo*, whereas when $\phi_{H2',H3'} < 0$ the conformation could be described by the equilibrium C3′-*endo* ⇄ C2′-*exo*. Finally, when $\phi_{H2',H3'} \cong 0$ the lactone ring should adopt the planar form. Therefore, the data shown in Table 4, for the major conformers of **6c** and **6f**, suggest that the lactone ring conformation could be described as a C3′-*endo* ⇄ C2′-*exo*. equilibrium, whereas in the minor conformers could correspond to a C3′-*exo* ⇄ C2′-*endo* equilibrium. Similarly, the 2′,3′-γ-butyrolactones (**11c**, **11f**, and **12f**) showed that in these compounds the conformation of the lactone ring for the major conformers of **11c**, **11f**, and **12f** could be described as a C3′-*exo* ⇄ C2′-*endo* equilibrium. Finally in the minor conformers of **11c** and **11f**, the lactone ring would adopt a planar form.

A molecular mechanics calculation[47] for the major and minor conformers of **6c**, **6f**, **11c**, **11f**, and **12f** gave values of the dihedral angles for the ribose ring very similar to those obtained from the ^{1}H NMR studies (see Table 4). Figure 3 shows a PLUTO representation of the conformers of **6c**, **6f**, **11c**, **11f**, and **12f** obtained by molecular mechanics minimization on the basis of dihedral angles calculated by Karplus−Altona equations from coupling constant values shown in Table 4.

Our NMR study has demonstrated that the γ-butyrolactones of nucleosides show rather unusual ribose ring conformations probably due to the fused γ-lactones ring. The base moiety (uracil or adenine) in these compounds seems to have little influence on the conformation of the ribose. However, the position of the γ-lactone moiety, 3′,2′-γ-butyrolactones (**6c**, **6f**) versus 2′,3′-γ-butyrolactones (**11c**, **11f**, **12f**) seems to be important in determining the conformation of the ribose ring. Thus, in **6c** and

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(46) Angelotti, T.; Krisko, M.; O'Connor, T.; Serianni, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 4464−4472.
(47) PCMODEL 1990, Serena Software, Bloomington, IN.

Table 4. Experimental and Calculated Coupling Constants (Hz) and Dihedral Angles for Nucleosides 6c, 6f, 11c, 11f, and 12f

	6c		6f		11c		11f		12f	
fragment	NMR[a]	MM[b]	NMR[a]	MM[b]	NMR[a]	MM[b]	NMR[a]	MM[b]	NMR[a]	MM[b]
$\phi_{H1',H2'}$	140.2 (92.0)	137.8 (106.2)	142.8 (100.0)	144.6 (102.7)	84.7 (136.2)	88.5 (146.7)	85.8 (142.1)	83.1 (144.4)	80.3	80.3
J_{exp}[c]	5.9		5.1		1.8		1.6		<1	
J_{calc}[d]	5.9		5.1		1.9		1.6		1.2	
$\phi_{H2',H3'}$	−29.1 (29.1)	−27.0 (26.5)	−28.5 (24.6)	−35.2 (25.6)	31.1 (0.2)	31.0 (9.3)	30.2 (0.2)	30.8 (9.0)	35.0	33.5
J_{exp}[c]	7.0		7.6		7.1		6.9		5.6	
J_{calc}[d]	7.0		7.6		7.1		6.9		5.7	
$\phi_{H3',H4'}$	−94.1 (−140.8)	−93.7 (−151.5)	−97.7 (−141.4)	−89.6 (−150.2)	−136.7 (−137.8)	−131.0 (−154.3)	−136.4 (−143.6)	(−129.9) (−154.1)	−138.8	−131.7
J_{exp}[c]	2.0		3.2		7.4		7.3		7.6	
J_{calc}[d]	2.0		3.2		7.3		7.3		7.3	
$\phi_{H2'(H3'),H1''}$	−106.0 (−153.1)		−96.3 (−152.7)		112.4 (119.3)		97.3 (120.1)		−41.1	
J_{exp}[c]	2.3		4.5		2.3		2.1		6.9	

[a] Calculated from NMR data (in parentheses values for minor conformer). [b] Obtained from molecular mechanics calculations (in parentheses values for minor conformer). [c] Obtained using iterative PANIC 86 program.[45] [d] Calculated using pseudorotational parameters.

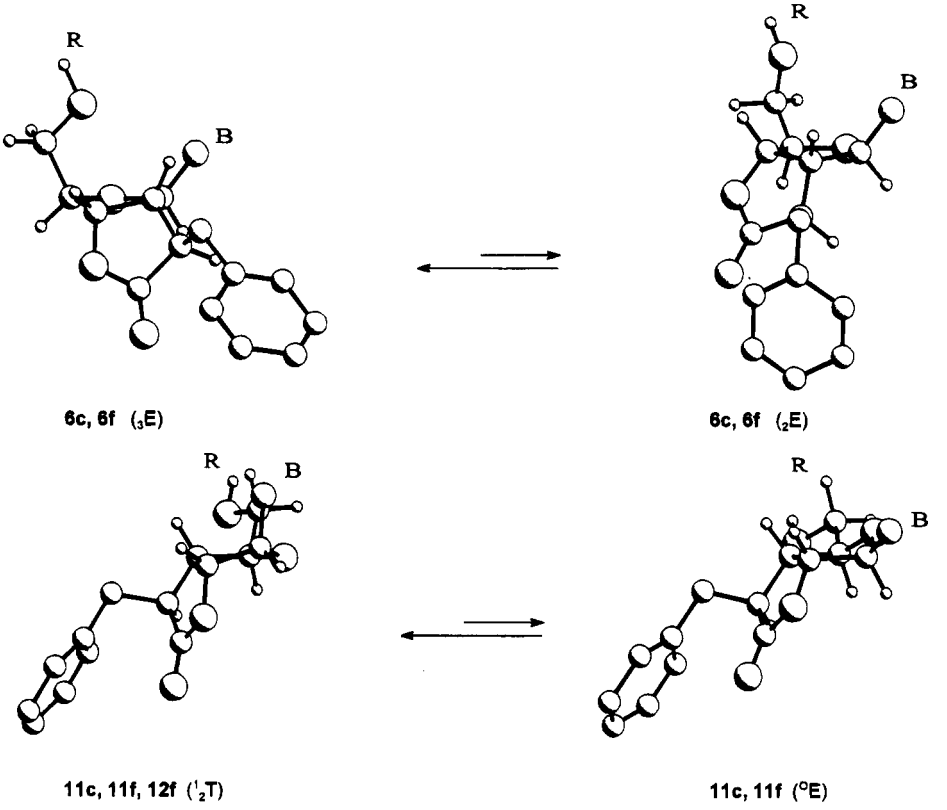

Figure 3. PLUTO representation of the conformational equilibrium of **6c**, **6f**, **11c**, **11f**, and **12f**. Structures are simplified (B = base moiety) and R = TBDMS.

6f the conformational equilibrium is shifted to an S-type ($_3$E) conformer, whereas in **11c** and **11f** this equilibrium is shifted to an N-type ($^1_2$T) conformer and **12f** exist as a single N-type conformer.

In summary, a stereoselective method for the preparation of [3.3.0] fused lactones (γ-butyrolactones) of nucleosides at positions 2′,3′ of the ribofuranose ring has been achieved. A new chiral center is formed at an "off-template" site of the ribofuranose ring with good diastereoselectivity. The moderate yield in the cyclization is counterbalanced by the good diastereoselectivity and the ready availability of the radical precursors. In the cyclizations of the radical precursors, a higher "off-template" stereoselectivity has been observed when the radical is generated at position 2′ of the ribose moiety, where enantiomerically pure γ-butyrolactones were isolated.

The overall result of the process described in this paper is the transformation of a 2′(3′)-*O*-acyl group to a highly functionalized 3′(2′)-*C*-branch through a free-radical cyclization.

Experimental Section

Microanalyses were obtained with a Heraeus CHN-O-RAPID instrument. ^{1}H NMR spectra were recorded with a Varian EM-390, a Varian XL-300, and a Bruker AM-200 spectrometer operating at 90, 300, and 200 MHz and ^{13}C NMR spectra with a Bruker AM-200 spectrometer operating at 50,

with Me_4Si as internal standard. IR spectra were recorded with a Shimadzu IR-435 spectrometer. Analytical TLC was performed on silica gel 60 F_{254} (Merck). Separations on silica gel were performed by preparative centrifugal circular thin layer chromatography (CCTLC) on a Chromatotron (Kiesegel 60 PF 254 gipshaltig (Merck)) (layer thickness 1 mm, flow rate 5 mL/min) or by flash column chromatography performed with silica gel 60 (230–400 mesh) (Merck). Proximities were established conventionally on the basis of NOE. For the NOE difference spectra the signals were irradiated during 3 s with γB_2 = 20 Hz of decoupling power.

All computations were carried out on a PC486 computer. Pseudorotational analysis were performed by using a PC version of the PSEROT program.[48] The geometries of nucleosides were optimized by the MMX method as implemented in the program PCMODEL.[47] Representation of the structures was performed using the PLUTO routine in the program (version 1.0).

1-[5′-*O*-(*tert*-Butyldimethylsilyl)-3′-*O*-cinnamoyl-β-D-ribofuranosyl]uracil and 1-[5′-*O*-(*tert*-butyldimethylsilyl)-2′-*O*-cinnamoyl-β-D-ribofuranosyl]uracil (2c and 7c). To a solution of **1a**[49] (4.0 g, 11.16 mmol) in a (4:1) mixture of dry dichloromethane:pyridine (170 mL) was slowly added a solution of cinnamoyl chloride (2.05 g, 12.3 mmol) in dichloromethane (20 mL), and the mixture was stirred at room temperature for 3 h. The solvent was evaporated to dryness. The residue was purified by flash column chromatography (hexane/ethyl acetate, 3:1) to afford 3.9 g (72% yield) of a (1:1) mixture of **2c** and **7c** as a white foam: IR (KBr) 3450 (OH), 1720 (CO), 1640 cm^{-1} (C=C). Anal. Calcd for $C_{24}H_{32}O_7N_2Si$: C, 58.99; H, 6.60; N, 5.73. Found: C, 59.30; H, 6.80; N, 5.87.

1-[5′-*O*-(*tert*-Butyldimethylsilyl)-3′-*O*-crotonyl-β-D-ribofuranosyl]uracil and 1-[5′-*O*-(*tert*-butyldimethylsilyl)-2′-*O*-crotonyl-β-D-ribofuranosyl]uracil (2d and 7d). Method A. Compound **1a** (2.0 g, 5.6 mmol) was dissolved in dry methanol (60 mL) containing dibutyltin oxide (1.4 g, 5.6 mmol). The mixture was heated to reflux under a stream of argon until it became clear. The solvent was removed at reduced pressure. The residue (the stannylene derivative) was suspended in dry dioxane (100 mL) containing NEt_3 (1.18 mL), and then a solution of freshly distilled crotonyl chloride (0.52 g, 5.7 mmol) in dry dioxane (2 mL) was added dropwise. The reaction was stirred at room temperature for 3 h and then evaporated to dryness. The residue was taken up in chloroform (25 mL), washed with water (2 × 15 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The residue was purified by column chromatography (hexane/ethyl acetate, 3:1) to give compound **2d** (1.4 g, 60%) as a white foam: IR (KBr) 1720 (CO), 1630 cm^{-1} (C=C). Anal. Calcd for $C_{19}H_{30}O_7N_2Si$: C, 53.50; H, 7.09; N, 6.57. Found: C, 53.20; H, 6.86; N, 6.23.

Method B. To a suspension of 2-choro-1-methylpyridinium iodide (0.85 g, 3.3.5 mmol) in dry dichloromethane (12 mL) was added a solution of **1a** (1.0 g, 2.79 mmol), crotonic acid (0.24 g, 2.79 mmol), and Bu_3N (1.23 g, 6.70 mmol) under an argon atmosphere. The reaction was heated to 70 °C for 5 h. After evaporation of the solvent, the residue was purified by column chromatography (hexane/ethyl acetate, 3:1) to give 0.65 g (55%) of a (1:1) mixture of **2d** and **7d** as a white foam: IR (KBr) 1720 (CO), 1640 cm^{-1} (C=C). Anal. Calcd for $C_{19}H_{30}O_7N_2Si$: C, 53.50; H, 7.09; N, 6.57. Found: C, 53.33; H, 6.84; N, 6.28.

1-[3′-*O*-Acryloyl-5′-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-uracil (2e). Following method A described for the synthesis of **2d**, compound **1a** (1.8 g, 5 mmol) was treated with dibutyltin oxide (1.25 g, 5 mmol) and acryloyl chloride (0.51 mL, 5.5 mmol). The oily residue, obtained after the workup, was purified by column chromatography (hexane/ethyl acetate, 7:3) to give 1.1 g (51%) of **2e** as a yellow foam; IR (KBr) 3440 (OH), 1720 (CO), 1640 cm^{-1} (C=O).

9-[5′-*O*-(*tert*-Butyldimethylsilyl)-3′-*O*-cinnamoyl-β-D-ribofuranosyl]adenine and 9-[5′-*O*-(*tert*-Butyldimethylsilyl)-2′-*O*-cinnamoyl-β-D-ribofuranosyl]adenine (2f and 7f). Following method B described for the synthesis of **2c** and **7c**, compound **1b** (1.9 g, 5.0 mmol) reacted with cinnamoyl chloride (0.87 g, 5.0 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated to dryness, and the residue was purified by column chromatography (hexane/ethyl acetate, 1:4) to give 1.85 g (73%) of a (2:1) mixture of **2f** and **7f** as a white foam: IR (KBr) 1720 (CO), 1630 cm^{-1} (C=C). Anal. Calcd for $C_{25}H_{33}O_5N_5Si$: C, 58.68; H, 6.50; N, 13.69. Found: C, 58.98; H, 6.82; N, 13.99

General Procedure for the Synthesis of the Radical Precursors. Synthesis of 2′(3′)-*O*-Acyl-5′-*O*-(*tert*-butyldimethylsilyl)-3′(2′)-*O*-[(imidazol-1-yl)thiocarbonyl]-β-D-ribofuranosyl]nucleosides (3c–f and 8c,d,f). To a solution of the 2′(3′)-*O*-acyl-5′-*O*-(*tert*-butyldimethylsilyl)nucleoside **2d–f** or **7c,d,f** (1 mmol) in dry DMF (15 mL), was added 1,1′-(thiocarbonyl)diimidazole (3 mmol), and reaction was stirred at room temperature overnight. The reaction mixture was treated with a (2:1) mixture of ethyl acetate:water (150 mL). The organic phase was separated, washed with water (2 × 50 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The residue was purified by column chromatography. Due to the instability of the compounds they were immediately used in the next step.

1-[5′-*O*-(*tert*-Butyldimethylsilyl)-3′-*O*-cinnamoyl-2′-*O*-[(imidazol-1-yl)thiocarbonyl]-β-D-ribofuranosyl]-uracil and 1-[5′-*O*-(*tert*-Butyldimethylsilyl)-2′-*O*-cinnamoyl-3′-*O*-[(imidazol-1-yl)thiocarbonyl]-β-D-ribofuranosyl]-uracil (3c and 8c). The general procedure was followed with a (1:1) mixture of **2c** and **7c** (2.3 g, 4.71 mmol). The residue was chromatographed (hexane/ethyl acetate, 4:1). The faster moving fractions afforded 1.15 g (41%) of **3c** as a white foam: IR (KBr) 1720 (CO), 1640 (C=C), 1180 cm^{-1} (C=S).

The slower moving fractions afforded 1.09 g (39%) of **8c** as a white foam: IR (KBr) 1710 (CO), 1640 (C=C), 1170 cm^{-1} (C=S).

1-[5′-*O*-(*tert*-Butyldimethylsilyl)-3′-*O*-crotonyl-2′-*O*-[(imidazol-1-yl)thiocarbonyl]-β-D-ribofuranosyl]uracil and 1-[5′-*O*-(*tert*-Butyldimethylsilyl)-2′-*O*-crotonyl-3′-*O*-[(imidazol-1-yl)thiocarbonyl]-β-D-ribofuranosyl]uracil (3d and 8d). In a similar manner treatment of a (1:1) mixture of **2d** and **8d** (0.75 g, 1.7 mmol) with *N,N′*-(thiocarbonyl)-diimidazole gave **3d** (0.40 g, 44%) after chromatography (hexane/ethyl acetate, 1:1) as a yellow foam: IR (KBr) 1720 (CO), 1690 (CONH), 1640 (C=C), 1175 cm^{-1} (C=S).

The slower moving fractions gave **8d** (0.33 g, 36%) as a yellow foam: IR (KBr) 1710 (CO), 1690 (CONH), 1640 (C=C), 1170 cm^{-1} (C=S).

1-[5′-*O*-(*tert*-Butyldimethylsilyl)-3′-*O*-acryloyl-2′-*O*-[(imidazol-1-yl)thiocarbonyl]-β-D-ribofuranosyl]uracil (3e). The general procedure was followed with **2e** (1.00 g, 2.42 mmol), and after column chromatography (hexane/ethyl acetate, 1:1) 1.13 g (89%) of **3e** was obtained as a yellow foam.

9-[5′-*O*-(*tert*-Butyldimethylsilyl)-3′-*O*-cinnamoyl-2′-*O*-[(imidazol-1-yl)thiocarbonyl]-β-D-ribofuranosyl]-adenine and 9-[5′-*O*-(*tert*-Butyldimethylsilyl)-2′-*O*-cinnamoyl-3′-*O*-[(imidazol-1-yl)thiocarbonyl]-β-D-ribofuranosyl]adenine (3f and 8f). Upon treatment of a (2:1) mixture of **2f** and **7f** (1.82 g, 3.5 mmol) with *N,N′*-(thiocarbonyl)diimidazole and after chromatography (dichloromethane/acetone, 3:1), 1.20 g (55%) of **3f** was obtained as a yellow foam: IR (KBr) 1720 (CO), 1690 (CONH), 1640 (C=C), 1180 cm^{-1} (C=S).

From the slower moving fractions 0.7 g (32%) of **8f** was isolated as a yellow foam: IR (KBr) 3500, 3400, 3200, 3100 (NH), 1720 (CO), 1640 (CONH), 1640 (C=C), 1180 cm^{-1} (C=S).

General Procedure for Free-Radical Cyclization of the Radical Precursors 3c–f and 8c,d,f. A 0.8 M solution of Bu_3SnH (1.5 equiv) and AIBN (cat.) in dry benzene was injected during 20–24 h (syringe pump), under argon, to a stirred 0.02 M solution of the radical precursor (**3c–f** or **8c,d,f**) in refluxing benzene, previously degassed with argon for 30 min. At the end of the addition, refluxing was continued for additional 2 h. The residue was diluted with dry acetonitrile (50 mL) and washed with hexane (2 × 25 mL). The acetonitrile phase was separated and evaporated to dryness.

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Repeated chromatography of the residue, first by flash column chromatography and then by preparative CCTLC on the chromatotron, is required to give the pure γ-lactones.

1-[5′-*O*-(*tert*-Butyldimethylsilyl)-2′-*C*-[(*R*)carboxybenzylmethyl]-2′-deoxy-β-D-ribofuranosyl]uracil 3′,2′-γ-Lactone (6c). According to the general procedure, compound **3c** (1.2 g, 2 mmol) was treated with Bu_3SnH/AIBN for 24 h. The residue was purified by flash column chromatography (chloroform/acetone, 9:1). The fastest moving fractions afforded 0.31 g (35%) of a white foam which was identified as **1-[5′-*O*-(*tert*-butyldimethylsilyl)-3′-*O*-cinnamoyl-2′-deoxy-β-D-ribofuranosyl]uracil (13c)**: IR (KBr) 1710 (CO), 1640 cm^{-1} (C=C). Anal. Calcd for $C_{24}H_{32}O_6N_2Si$: C, 60.99; H, 6.82; N, 5.93. Found: C, 61.15; H, 6.84; N, 6.03.

The slowest moving fractions afforded a syrup that was purified by preparative CCTLC (dichloromethane/methanol, 20:1) to give **6c** (0.33 g, 35%) as a white foam: IR (KBr) 1775 cm^{-1} (CO). Anal. Calcd for $C_{24}H_{32}O_6N_2Si$: C, 60.99; H, 6.82; N, 5.93. Found: C, 61.25; H, 7.00; N, 6.25.

1-[5′-*O*-(*tert*-Butyldimethylsilyl)-2′-*C*-[(*R*)carboxyethylmethyl]-2′-deoxy-β-D-ribofuranosyl]uracil 3′,2′-γ-Lactone (6d). In a similar manner **3d** (0.5 g, 0.93 mmol) afforded after flash column chromatography (hexane/ethyl acetate, 3:1) **1-[5′-*O*-(*tert*-butyldimethylsilyl)-3′-*O*-crotonyl-2′-deoxy-β-D-ribofuranosyl]uracil (13d)** (0.19 g, 50%) as a white foam: IR (KBr) 1710 (CO), 1640 cm^{-1} (C=C). Anal. Calcd for $C_{19}H_{30}O_6N_2Si$: C, 55.58; H, 7.36; N, 6.82. Found: C, 55.37; H, 7.24; N, 6.67.

The residue obtained from the slower moving fractions was purified by preparative CCTLC (dichloromethane/methanol, 20:1) to give **6d** (0.07 g, 20%) as a white foam: IR (KBr) 1780 cm^{-1} (CO). Anal. Calcd for $C_{19}H_{30}O_6N_2Si$: C, 55.58; H, 7.36; N, 6.82. Found: C, 55.37; H, 7.20; N, 6.55.

1-[5′-*O*-(*tert*-Butyldimethylsilyl)-2′-*C*-[(*R*)carboxymethylmethyl]-2′-deoxy-β-D-ribofuranosyl]uracil 3′,2′-γ-Lactone (6e). The general procedure was followed with **3e** (0.40 g, 0.76 mmol) for 20 h. The residue was purified by flash column chromatography (hexane/ethyl acetate, 3:2). The faster moving fractions afforded **1-[3′-*O*-acryloyl-5′-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-β-D-ribofuranosyl]uracil (13e)** (0.01 g, 13%) as a white foam: IR (KBr) 1720 (CO), 1630 cm^{-1} (C=C). Anal. Calcd for $C_{18}H_{28}O_6N_2Si$: C, 54.52; H, 7.12; N, 7.07. Found: C, 54.80; H, 7.24; N, 7.27.

The slower moving fractions gave a residue which was purified by preparative CCTLC (dichloromethane/methanol, 30:1) to give **6e** (0.03 g, 10%) as a white foam: IR (KBr) 1780 cm^{-1} (CO lactone). Anal. Calcd for $C_{18}H_{28}O_6N_2Si$: C, 54.52; H, 7.02; H, 7.07. Found: C, 54.27; H, 7.29; N, 6.90.

9-[5′-*O*-(*tert*-Butyldimethylsilyl)-2′-*C*-[(*R*)carboxybenzylmethyl]-2′-deoxy-β-D-ribofuranosyl]adenine 3′,2′-γ-Lactone (6f). Following the general procedure with **5d** (0.36 g, 0.57 mmol) gave after flash column chromatography (chloroform/acetone, 20:1) 0.03 g (15%) of a syrup from the faster moving fractions which was identified as a (1:1) mixture of **9-[5′-*O*-(*tert*-butyldimethylsilyl)-3′-*O*-cinnamoyl-2′-deoxy-β-D-ribofuranosyl]adenine and 9-[5′-*O*-(*tert*-Butyldimethylsilyl)-2′-deoxy-3′-*O*-(3-phenylpropionyl)-β-D-ribofuranosyl]adenine (13f and 14f)**: IR (KBr) 1735 (CO aliphatic esther), 1710 (CO conjugated esther), 1635 cm^{-1} (C=C).

The slower moving fractions afforded a syrup which was purified by preparative CCTLC (chloroform/methanol, 20:1) to give **6f** (0.06 g, 30%) as a white foam: IR (KBr) 1775 cm^{-1} (CO lactone). Anal. Calcd for $C_{25}H_{33}O_4N_5Si$: C, 60.58; H, 6.71; H, 14.13. Found: C, 60.43; H, 6.68; N, 14.00.

1-[5′-*O*-(*tert*-Butyldimethylsilyl)-3′-*C*-[(*S*)carboxybenzylmethyl]-3′-deoxy-β-D-ribofuranosyl]uracil 2′,3′-γ-Lactone (11c). According to the general procedure compound **8c** (0.34 g, 0.57 mmol) was treated with Bu_3SnH/AIBN for 20 h. The residue was flash column chromatographed (chloroform/acetone, 9:1). The faster moving fractions afforded 0.078 g (29%) of **1-[5′-*O*-(*tert*-butyldimethylsilyl)-2′-*O*-cinnamoyl-3′-deoxy-β-D-ribofuranosyl]uracil (15c)** as a white foam: IR (KBr) 1710 cm^{-1} (CO), 1630 cm^{-1} (C=C). Anal. Calcd for $C_{24}H_{32}O_6N_2Si$: C, 60.99; H, 6.82; N, 5.93. Found: C, 61.26; H, 7.10; N, 6.24.

The slower moving fractions afforded a syrup which was purified by preparative CCTLC (dichloromethane/methanol, 10:1) to give **11c** (0.09 g, 35%) as a white foam: IR (KBr) 1770 cm^{-1} (CO lactone). Anal. Calcd for $C_{24}H_{32}O_6N_2Si$: C, 60.99; H, 6.82; N, 5.93. Found: C, 61.25; H, 7.15; N, 6.30.

1-[5′-*O*-(*tert*-Butyldimethylsilyl)-3′-*C*-[(*S*)carboxyethylmethyl]-3′-deoxy-β-D-ribofuranosyl]uracil 2′,3′-γ-lactone and 1-[5′-*O*-(*tert* Butyldimethylsilyl)-3′-*C*-[(*R*)carboxyethylmethyl]-3′-deoxy-β-D-ribofuranosyl]uracil 2′,3′-γ-lactone (11d and 12d). The general procedure was followed with radical precursor **8d** (0.29 g, 0.54 mmol) for 24 h. After the workup, the residue was flash column chromatographed (hexane/ethyl acetate, 3:1). The faster moving fractions gave **1-[5′-*O*-(*tert*-butyldimethylsilyl)-2′-*O*-crotonyl-3′-deoxy-β-D-ribofuranosyl]uracil (15d)** (0.08 g, 40%) as a white foam: IR (KBr) 1700 (CO), 1630 cm^{-1} (C=O). Anal. Calcd for $C_{19}H_{30}O_6N_2Si$: C, 55.58; H, 7.36; H, 6.82. Found: C, 55.89; H, 7.50; H, 7.03.

The syrup obtained from the slower moving fractions was purified by preparative CCTLC (dichloromethane/methanol, 50:1). The fastest moving band afforded 0.05 g (25%) of **11d** as a white foam: IR (KBr) 1770 cm^{-1} (CO lactone). Anal. Calcd for $C_{19}H_{30}O_6N_2Si$: C, 55.58; H, 7.36; N, 6.82. Found: C, 55.93; H, 7.56; N, 7.14.

The slowest moving band gave **12d** (0.015 g, 7%) as a white foam: IR (KBr) 1780 cm^{-1} (CO) lactone). Anal. Calcd for $C_{19}H_{30}O_6N_2Si$: C, 55.58; H, 7.36; N, 6.82. Found: C, 55.96; H, 7.50; N, 7.13.

9-[5′-*O*-(*tert*-Butyldimethylsilyl)-3′-*C*-[(*S*)carboxybenzylmethyl]-3′-deoxy-β-D-ribofuranosyl]adenine 2′,3′-γ-Lactone and 9-[5′-*O*-(*tert*-Butyldimethylsilyl)-3′-*C*-[(*R*)-carboxybenzylmethyl]-3′-deoxy-2′,3′-γ-lactone-β-D-ribofuranosyl]adenine (11f and 12f). The general procedure was followed with precursor **8f** (0.62 g, 1.0 mmol) for 24 h. The residue was purified by flash column chromatography (hexane/ethyl acetate, 4:1). The faster moving fractions gave **9-[5′-*O*-(*tert*-Butyldimethylsilyl)-2′-*O*-cinnamoyl-3′-deoxy-β-D-ribofuranosyl]adenine (15f)** (0.08 g, 15%) as a white foam: IR (KBr) 1720 cm^{-1} (CO), 1635 cm^{-1} (C=O). Anal. Calcd for $C_{25}H_{33}O_4N_5Si$: C, 60.58; H, 6.71; N, 14.13. Found: C, 60.89; H, 7.00; N, 14.40.

The syrup obtained from the slower moving fractions was purified by preparative CCTLC (dichloromethane/methanol, 30:1). From the faster moving band, compound **11f** (0.14 g, 30%) was isolated as a white foam: IR (KBr) 1770 cm^{-1} (C=O lactone). Anal. Calcd for $C_{25}H_{33}O_4N_5Si$: C, 60.58; H, 6.71; N, 14.13. Found: C, 60.86; H, 6.98; N, 14.35.

From the slower moving band compound **12f** (0.05 g, 10%) was isolated as a white foam: IR (KBr) 1780 cm^{-1} (C=O lactone). Anal. Calcd for $C_{25}H_{33}O_4N_5Si$: C, 60.58; H, 6.71; N, 14.13. Found: C, 60.90; H, 6.95; N, 14.21.

1-[5′-*O*-(*tert*-Butyldimethylsilyl)-2′-deoxy-2′-*C*-[2″-phenyl-1″-(*N*-isobutylcarbamoyl)-1″(*R*)-ethyl]-β-D-ribofuranosyl]-uracil (17c). To an ice-bath cooled suspension of $AlCl_3$ (0.017 g, 0.13 mmol) in dry 1,2-dichloroethane (0.5 mL) was added dropwise a solution of isobutylamine (0.011 g, 0.15 mmol) in dry 1,2-dichloroethane (0.25 mL). The reaction mixture was allowed to reach room temperature, and then a solution of **6c** (0.03 g, 0.06 mmol) in 1,2-dichloroethane (0.25 mL) was added. The resulting mixture was stirred at room temperature for 16 h, and then ice water (10 mL) was added. The mixture was stirred for an additional hour and filtered through Celite, the organic phase was separated, and the aqueous phase was extracted with 1,2-dichloroethane (2 × 5 mL). The combined organic extracts were washed with water (2 × 5 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The residue was purified by preparative CCTLC (hexane/ethyl acetate, 2:1) to give **17c** (0.026 g, 81%) as a white foam: IR (KBr) 3375 (OH, NH), 1630 cm^{-1} (C=O amide). Anal. Calcd for $C_{28}H_{43}O_6N_3Si$: C, 61.62; H, 7.94; N, 7.70. Found: C, 61.35; H, 7.68; N, 7.65.

1-[5′-*O*-(*tert*-Butyldimethylsilyl)-3′-deoxy-3′-*C*-[2″-phenyl-1″-(*N*-isobutylcarbamoyl)-1″(*S*)-ethyl]-β-D-ribofuranosyl]-uracil (21c). Following the procedure described for the synthesis of **17c**, γ-lactone nucleoside **11c** (0.03 g, 0.06 mmol) was treated with isobutylamine (0.011 g, 0.15 mmol) and $AlCl_3$

(0.017 g, 0.13 mmol). The reaction mixture was stirred at room temperature for 16 h. After the workup the residue was purified by preparative CCTLC (hexane:ethyl acetate, 2:1) to give **21c** (0.02 g, 62%) as a white foam: IR (KBr) 3400 (OH, NH), 1640 cm^{-1} (C=O amide). Anal. Calcd for $C_{28}H_{43}O_6N_3Si$: C, 61.62; H, 7.94; N, 7.70. Found: C, 62.00; H, 7.69; N, 7.54.

1-[5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-dideoxy-2′-*C*-[2″-phenyl-1″-(*N*-isobutylcarbamoyl)-1″(*R*)-ethyl]-β-D-ribofuranosyl]uracil (18c). To a solution of **17c** (0.10 g, 0.18 mmol) in toluene (4 mL) was added *N,N′*-(thiocarbonyl)-diimidazole (0.048 g, 0.27 mmol). The mixture was heated at 80 °C for 4 h and then diluted with ethyl acetate (10 mL) and water (5 mL). The organic layer was separated, washed with water (2 × 5 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The residue was suspended in toluene (4 mL) and transferred to a three-necked flask, and AIBN (6 mg, 0.036 mmol) was added. Argon was bubbled through the suspension for 15 min, and then Bu_3SnH (0.09 mL, 0.36 mmol) was added. The flask was heated in an oil bath at 80 °C for 5 h, while argon bubbling was maintained. The reaction mixture was allowed to reach room temperature, and the solvent was evaporated to dryness. The residue was purified by CCTLC (hexane/ethyl acetate, 1:1) to give **18c** (0.03 g, 44%) as a white foam: IR (KBr) 3300 (NH), 1640 cm^{-1} (C=O amide). Anal. Calcd for $C_{28}H_{43}O_5N_3Si$: C, 63.48; H, 8.18; N, 7.93. Found: C, 63.37; H, 8.08; N, 7.89.

1-[2′-*C*-(*R*)Carboxybenzylmethyl]-2′-deoxy-β-D-ribofuranosyl]uracil 3′,2′-γ-Lactone (16c). Compound **6c** (0.045 g, 1 mmol) was dissolved in dry 1 M THF (11 mL), and then a 1 M solution of tetrabutylammonium fluoride in THF (0.11 mL, 1.1 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated to dryness, and the residue was purified by flash column chromatography (hexane/ethyl acetate, 1:2) to give **16c** (0.27 g, 75%) as a white foam: IR (KBr) 1780 cm^{-1} (C=O lactone). Anal. Calcd for $C_{18}H_{18}O_6N_2$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.53; H, 5.15; N, 7.91.

1-[2′-Deoxy-2′-*C*-[2″-phenyl-1″-(*N*-isobutylcarbamoyl)-1″(*R*)-ethyl]-β-D-ribofuranosyl]uracil (19c). The protected nucleoside **17c** (0.05 g, 0.09 mmol) was stirred with 0.1 M methanolic HCl (2 mL) at room temperature for 45 min. The solution was neutralized with 1 M NaOH–MeOH, and the solvent was evaporated to dryness. The residue was purified by column chromatography (chloroform/methanol, 40:1) to afford **19c** (0.028 g, 71%) as a white foam: IR (KBr) 3450 (NH, OH), 1645 cm^{-1} (C=O amide). Anal. Calcd for $C_{21}H_{27}O_6N_3$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.58; H, 6.50; N, 9.98.

1-[2′,3′-Dideoxy-2′-*C*-[2″-phenyl-1″-(*N*-isobutylcarbamoyl)-1″(*R*)-ethyl]-β-D-ribofuranosyl]uracil (20c). The protected nucleoside **18c** (0.02 g, 0.037 mmol) was stirred with 0.1 M methanolic HCl (1 mL) at room temperature for 45 min. The reaction was neutralized with 1 M NaOH–MeOH, and the solvent was evaporated to dryness. The residue was purified by column chromatography (ethyl acetate) to yield **20c** (0.014 g, 95%) as a white foam: IR (KBr) 3400 (NH, OH), 1640 cm^{-1} (C=O amide). Anal. Calcd for $C_{21}H_{27}O_5N_3$: C, 38.58; H, 4.16; N, 6.43. Found: C, 38.30; H, 3.85; N, 6.09.

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Supplementary Material Available: Compound characterization data, inclusive of NMR peak assignments (5 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.