C-1′ Radical-Based Approaches for the Synthesis of Anomeric Spironucleosides

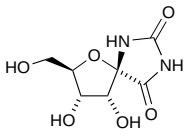
Chryssostomos Chatgilialoglu,*[a] Thanasis Gimisis,[a] and Gian Piero Spada[b]

Abstract: Efficient methodologies based on radical cascade reactions for the preparation of anomeric spironucleosides of general structure **3** and **4** are reported. The reactions were performed on modified uridine and 2′-deoxyuridine substrates. The protected derivatives **6** and **28** afforded the anomeric spironucleosides **7** and **29**, respectively, in a stereospecific manner and in moderate yields (35–50%). In the 2′-deoxyribo series, the efficiency increased considerably (yields higher than 70%) with a concomitant decrease in stereoselectivity. In fact, the protected derivatives **13** and **21** gave mixtures of the anomeric products **11**/**14** and **22**/**23**, respectively. Chemical transformations of some of these spironucleosides were successfully performed. The circular dichroism spectra of the anomeric spironucleosides displayed some striking features which can be attributed to the restricted rotation of the glycosidic bond. The reaction mechanism, which has been studied in some detail, comprises of a cascade of radical reactions in which the key step is the 1,5-radical translocation from an alkoxyl or vinyl radical, conveniently situated on the base moiety in the vicinity of the anomeric position. After the translocation, the alkoxyl radical **15**, generated photolytically from an in situ prepared hypoiodite, afforded spironucleosides which possess an unusual orthoamide structure at the anomeric position. Alternatively, the vinyl radical **30**, generated by the reaction of vinyl bromides with tributyltin radical, undergoes a 5-*endo-trig* cyclization followed by a bromine atom elimination after the 1,5-radical translocation step.

Keywords: cascade reactions · nucleosides · radicals · spiro compounds

Introduction

Anomeric spironucleosides are useful modifications of natural nucleosides as they contain the base unit in a fixed conformation around the *N*-glycosidic bond. This property has made them excellent candidates for structure–activity relationship studies to determine the ideal torsion angle around the *N*-glycosidic bond for optimal biological activity.[1] In recent years, they have gained considerable importance with the discovery of hydantocidin (**1**),[2] a natural spiro compound with herbicidal and plant growth regulatory activities, and generally, with the notion that important pharmaceutical lead structures can be found among modified nucleoside analogues. The first anomeric spironucleosides to be synthesized were derivatives of psiconucleosides such as 6,1′-anhydro-6-hydroxy-psicocytosine (**2**),[3] locked in the *syn* conformation or O^2,1′-anhydro-psicouridine,[4] locked in the *anti* conformation. With one exception, in which the anionically induced formation of anomeric spironucleosides from 1′-C-cyano-2′-deoxyuridine has been reported,[5] all recent results on the synthesis of anomeric spironucleosides are based on free-radical chemistry. The carbon analogues have been synthesized by a multistep procedure in which the key step is the formation of a carbon–carbon bond either by a 6-*exo-trig* radical cyclization to a nucleobase double bond[3b, 6] or by a 5-*exo-trig* radical cyclization on the 1′,2′-anhydro-2′-deoxynucleosides.[7] Modifications of the anomeric position of nucleosides can also be envisaged by C-1′ radical intermediates.[8] However, the presence of the nucleobase in the anomeric position of a nucleoside complicates any synthetic



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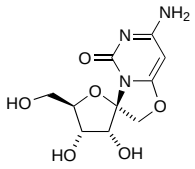

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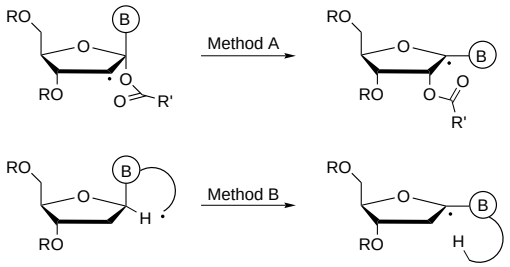
plan for direct modifications on that position, which can serve as precursors of C-1′ radicals.[9] This is probably the main reason for the disparity between the relatively small number of reported studies involving the C-1′ position and the more extensive literature covering the chemistry of C-2′, C-3′, C-4′, and C-5′ positions. This overall picture has prompted us to undertake a systematic investigation on the indirect formation of C-1′ radicals. One of our first attempts to generate such radicals involved a β-(acyloxy)alkyl radical rearrangement of a C-2′ radical into the anomeric position (Scheme 1, Method A). This successful methodology led to the formation of model C-1′ ribouridyl and riboadenyl radicals, which were found to be stabilized substantially by the presence of the nucleobase with the degree of stabilization being similar to purine and pyrimidine moieties.[10]



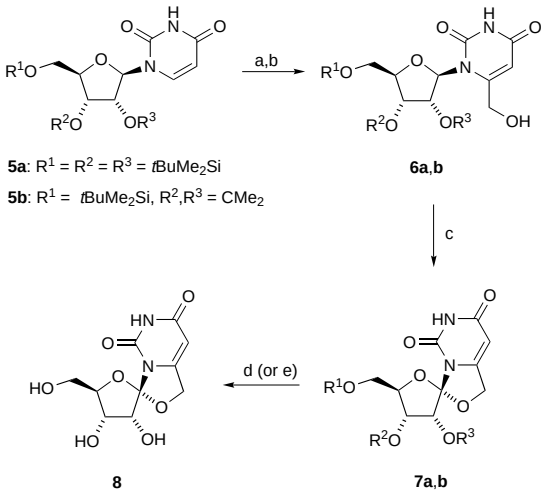
Scheme 1. Indirect methods of formation of C-1′ radicals.

In our preliminary communications, we reported the first examples of a [1,5]-hydrogen transfer (Scheme 1, Method B) used as a protocol to access C-1′ radical intermediates in model 2′-deoxyribonucleosides.[11, 12] We report herein a full account of this kind of transformations aimed at the synthesis of anomeric spironucleosides of general formulas **3** and **4** (both ribo and 2′-deoxyribo analogues) through alkoxyl and vinyl radicals, respectively.

3 **4**

Results and Discussion

Spironucleosides of type 3: Protected 6-hydroxymethylribouridine **6a** and **6b** were prepared from the corresponding protected uridines[13] by the fine tuning of literature procedures.[14] Subsequently, these compounds were subjected to photolysis with visible light in the presence of (diacetoxyiodo)benzene and iodine in cyclohexane at room temperature (standard Suárez conditions[15]) in order to generate the corresponding alkoxyl radicals. When compound **6a** was treated under these conditions one major product was obtained after flash column chromatography in moderate yield (36%) (Scheme 2). The structure of the product could be assigned to compound **7a** based on the ^{1}H NMR spectrum,

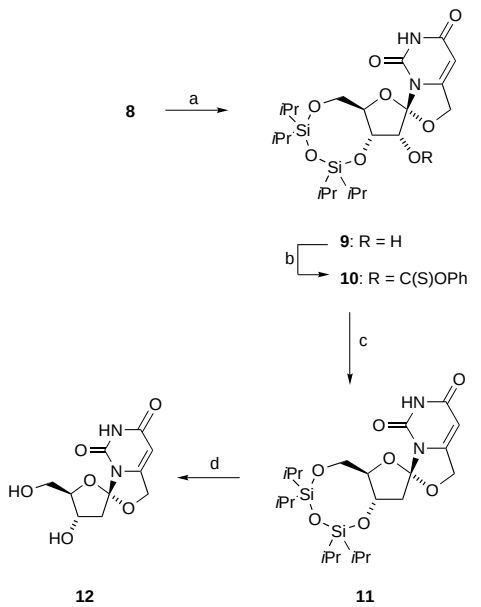


Scheme 2. a) LDA, THF, $-70\,^\circ$C, 3 h; HCO_2Et, $-60\,^\circ$C, 2 h; b) $NaBH_4$, MeOH, RT, 30 min, 68% based on recovered **5a**, 94% based on recovered of **5b**; c) $PhI(OAc)_2$, I_2, cyclohexane, hν, 28 °C, 6 h, 36% from **6a**, 49% from **6b**; d) TBAF on SiO_2, THF, RT, 2 h, 90% from **7a**; e) 1N HCl/THF (1:1), 20 °C, 82% from **7b**.

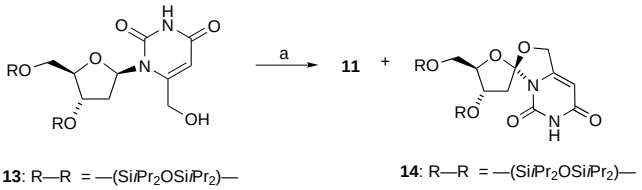
in which 2′-H appeared as a doublet and the 7-Hs appeared as a well-resolved AB quartet. This fact together with the lack of a 1′-H or 7-OH signal corroborated the assignment of an orthoamide function to the product nucleoside, although the configuration of the anomeric center remained ambiguous. When compound **6a** was replaced by compound **6b**, the analogous product **7b** was obtained in 49% yield. Deprotection[13] of the silyl groups in **7a** as well as the acetal function in **7b** provided the same water-soluble compound **8** (m.p. 172–173 °C). A single crystal of this compound, grown in methanol/H_2O was subjected to X-ray structure analysis to determine unambiguously the stereochemistry of the C-1′ position.[16] The absolute (*R*) configuration of the C-1′ center was determined based on the known absolute configuration of the C-2′, C-3′, and C-4′ centers of the starting nucleosides, which were not altered during the synthesis.

In order to prepare the 2-deoxy analogue of the spironucleoside **8**, the four-step chemical transformation outlined in Scheme 3 was considered. Standard regioselective protection of the 3′ and 5′ position with the tetraisopropyldisiloxanyl group afforded **9**.[13] The deoxygenation of the secondary alcohol was achieved in 79% yield following a modified Barton–McCombie radical deoxygenation. Thus, the phenxythiocarbonyl derivative **10**[17] reacted with $(TMS)_3SiH$[18] under normal free radical conditions to produce the protected 2′-deoxyspironucleoside **11**. Deprotection of the silyl groups provided the water-soluble compound **12** in 90% yield.

When the Suárez conditions[15] were applied to the 2′-deoxynucleoside **13**, two spironucleoside products were isolated in a combined 71% yield after flash column chromatography (Scheme 4). The chromatographically less polar stereoisomer is identical to compound **11**. On the other hand, the structure of the more polar stereoisomer was assigned to compound **14**, based on the similarity of the ^{1}H NMR spectra, in which the two diastereotopic 2′-Hs appeared as well-resolved doublets of doublets and the 7-Hs appeared as an AB quartet. The stereochemical distribution of the products



Scheme 3. a) $(i\mathrm{Pr_2SiCl)_2O}$, pyridine, RT, overnight, 61%; b) PhOC(S)Cl, DMAP, CH_2Cl_2, 1 h, RT, 84%; c) $(TMS)_3SiH$, AIBN, toluene, 80°C, 6 h, 94%; d) TBAF on SiO_2, THF, RT, 2 h, 90%.

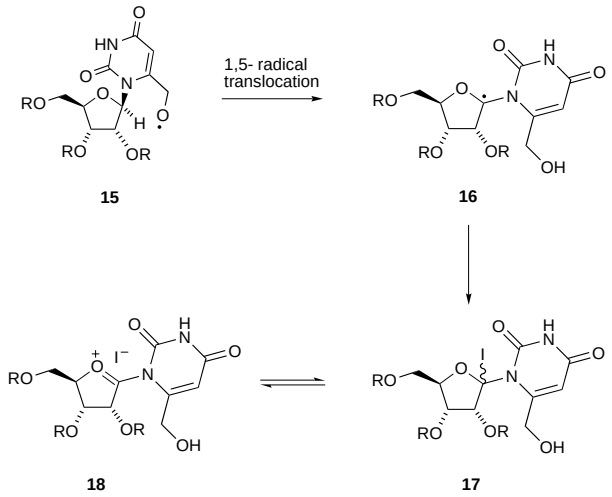


Scheme 4. a) $PhI(OAc)_2$, I_2, cyclohexane, hν, 28°C, 5 h, 71%, **11**:**14** = 1.1:1.

depended considerably on small variations of the reaction temperature and varied from a 2:1 to 1:1 ratio in favor of β-anomer **11** for temperature ranges between 25 and 35°C. Below 25°C the reaction was extremely slow, whereas above 35°C extensive decomposition led to decreased product yields.[19] Therefore, the final stereochemical distribution could be a result of the relative stability of the isomeric intermediates rather than any stereoselectivity.

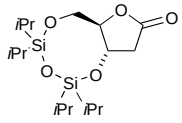
The mechanism that we conceived for the formation of the spironucleoside structure is outlined in Scheme 5. Photolysis of the hypoiodite formed under the Suárez conditions generates the alkoxy radical intermediate **15**, which undergoes a Barton-type hydrogen migration[20] to generate the anomeric C-1′ radical **16**, which reacts in turn with iodine to generate the unstable C-1′ iodo derivative **17**. Compound **17** should exist in equilibrium with the corresponding oxonium salt **18** and can readily undergo an anionic cyclization reaction on the proximal hydroxyl with elimination of HI and generation of the observed product.[22d, 23] Noteworthy, the steric hindrance induced by the C-2′ substituent is most probably responsible for the stereospecificity of the cyclization in the ribo series.

We proceeded to test the stability of this new class of compounds. The orthoamide structure in compound **11** proved to be stable towards hydrolysis or isomerization when



Scheme 5. Proposed mechanism for the formation of anomeric spironucleosides of type **3**.

heated in ethanol or ethanol:water at 80°C, or when heated in a sealed tube in benzene at 80°C (4 h) or at 140°C (1 h). The silyl protection was more susceptible to acidic hydrolysis than the orthoamide function and slowly led to compound **12** with acetic acid in ethanol (12 h at 80°C) or faster with 1N HCl in THF (1 h at 50°C). However, the orthoamide function was susceptible to nucleophilic attack at 7-position and led to the formation of protected 2′-deoxyribonolactone **19** in 65% yield upon treatment with Me_3SiBr in toluene (4 h, RT). Slow epimerization of the C-1′ center was observed, when **11** was treated in the presence of a Lewis acid ($BF_3\cdot Et_2O$ in benzene). This reaction requires opening and reclosure of the orthoamide structure. It was faster in the unprotected spironucleoside **12** and could be effected by simply heating a methanol solution of **12** at 50–60°C.



Spironucleosides of type 4: The radical precursor, the protected 6-(2,2-dibromovinyl)-2′-deoxyuridine (**21**), was prepared from **20** by the Corey–Fuchs protocol[24] to introduce the dibromovinyl function on the appropriate carboxaldehyde[14b] in 42% yield. We obtained two products upon reaction of compound **21** with photogenerated tributyltin radicals, which were isolated in a combined 78% yield and in a 2:1 ratio. Based on the NMR experiments, the structures of the anomeric spironucleosides **22** and **23** were assigned, the former being predominant (Scheme 6). We were aided in their structure determination by a report of Tanaka and co-workers on the preparation of some similar anomeric spironucleosides by a different route.[7a] Deprotection of the silyl groups in **22** with Bu_4NF in THF led to the known free nucleoside 2′-deoxy-6,1′-ethenouridine (**24**) in complete agreement of the spectroscopic data with the reported data.[7a] Furthermore, compounds **22** and **23** were converted to spironucleosides **25** and **26** in 75 and 68% yield, respectively, by selective hydrogenation of the double bond with 5% Rh/Al catalyst in methanol.[7a]

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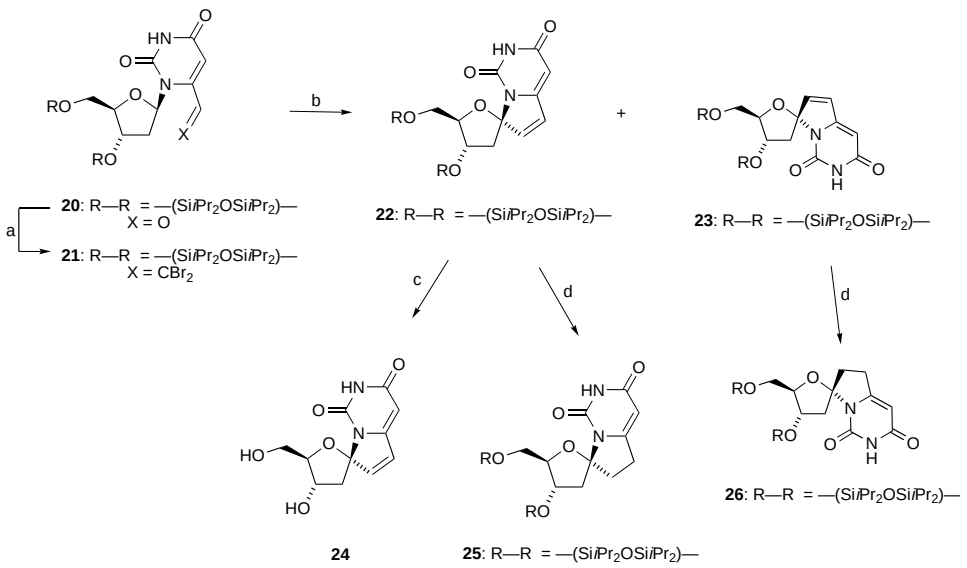
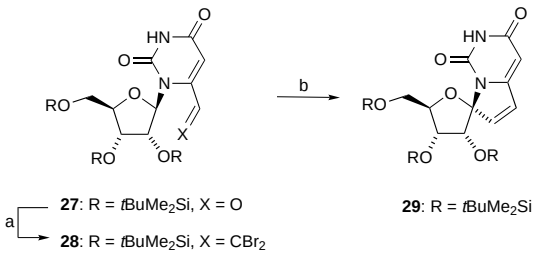


Scheme 6. a) $Ph_3P{=}CBr_2$, CH_2Cl_2/DMF, RT, 2 h, 42%; b) $Bu_3SnSnBu_3$, benzene, hν, 80 °C, 12 h, 78%, **22**:**23** = 2:1; c) Bu_4NF, THF, CH_3CO_2H, RT, 24 h, 90%; d) Et_3N, 5% Rh/Al, MeOH, H_2, RT, 5 h, 68%.

The protected 6-(2,2-dibromovinyl)uridine (**28**) was prepared similarly from **27** by a modification of the Corey–Fuchs protocol[24, 25] in 70% yield. When compound **28** reacted with photogenerated tributyltin radicals one major product was obtained in moderate yield (37%) after flash column chromatography (Scheme 7). The structure of the product could be assigned to compound **29**, based on the ^{1}H NMR spectrum in which the characteristic 2′-H appeared as a doublet at $\delta = 5.43$ in analogy to the ^{1}H NMR spectrum of **7b**, where 2′-H appeared as a doublet at $\delta = 5.46$.



Scheme 7. a) $Ph_3P{=}CBr_2$, CH_2Cl_2/DMF, RT, 3 h, 70%; b) $Bu_3SnSnBu_3$, toluene, hν, 90 °C, 32 h, 37%.

In order to obtain further mechanistic information the cyclization reaction of substrate **21** was performed under a variety of free radical conditions with Group 14 hydrides. In particular, Bu_3SnH, $(TMS)_3SiH$, and Bu_3SnD were utilized. A summary of these results is shown in Table 1. When the reaction was performed with Bu_3SnH (1.5 equiv, direct addition), we obtained four products which were isolated by preparative TLC and characterized (80% combined yield) (Entry 1). While the two more polar products ($R_f = 0.14, 0.20$; 40% ethyl acetate in hexanes) corresponded to the spironucleosides **22** and **23** (2:1 ratio), the two less polar products ($R_f = 0.33, 0.38$; 40% ethyl acetate in hexanes) were assigned to the structures of the monoreduced vinyl bromides (*E*)-**31** and (*Z*)-**31** (Scheme 8), respectively. The structure and anomeric composition of these last products were deduced from a combination of NMR experiments including ^{1}H, ^{13}C, homonuclear decoupling, and 1D-NOE,[26] as well as from a comparison of the analytical data with those of similar reported compounds.[27] Entry 2 shows an experiment analogous to entry 1 with 2.5 equiv of tributyltin deuteride with the same four compounds being obtained. However, about 90% deuterium incorporation in the C-8 position of (*E*)-**31** and (*Z*)-**31** was observed, but no measurable (<4%) deuterium incorporation in the anomeric C-1′ position of either compound. Furthermore, no deuterium incorporation was observed in spironucleoside **22** or **23**. The results in entries 3 and 4 (Table 1) show that by decreasing the hydrogen donation ability of the reducing agent, either by slow addition of Bu_3SnH or by using $(TMS)_3SiH$,[18] the amount of vinyl bromides **31** decreases substantially in favor of spironucleosides **22** and **23**.

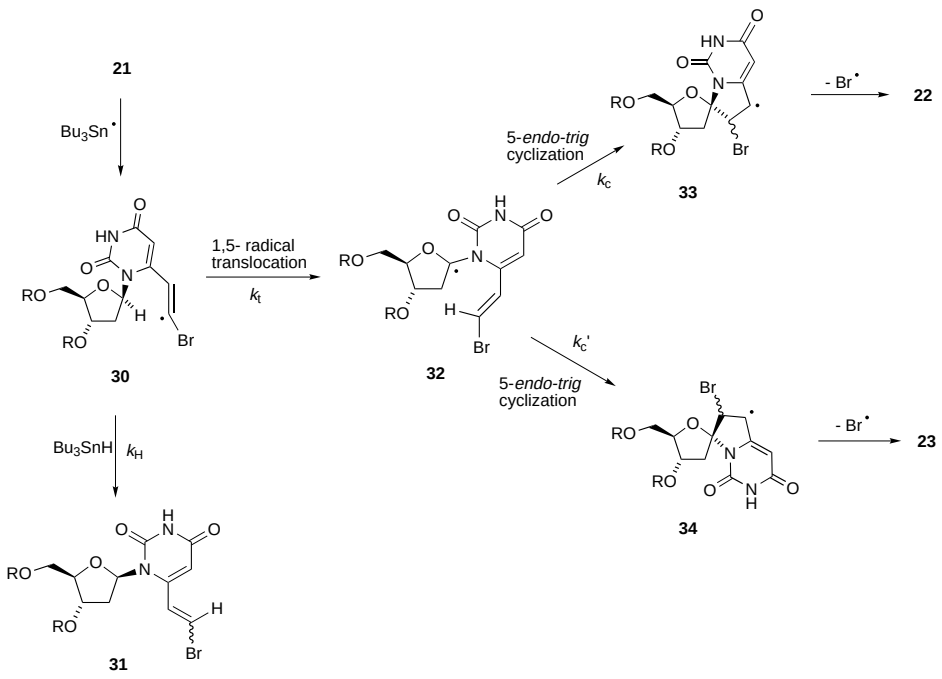
Table 1. Reaction of compound **21** with some hydrides at 80 °C under a variety of conditions[a]

Entry	Reagent (equiv)	yield[b] [%] **31** (*E*:*Z*)	**22**+**23** (**22**:**23**)
1	Bu_3SnH (1.5)	44 (1:2)	36 (2:1)
2	Bu_3SnD (2.5)	42 (1:2)[c]	32 (2:1)
3	Bu_3SnH (1.2)[d]	26 (1:2)	52 (2:1)
4	$(TMS)_3SiH$ (4.0)[e]	25 (1:2)	57 (2:1)

[a] Starting concentration of **21** was 0.05 M in benzene. The reactions were run (1.5–5 h) until no starting material was detected by TLC. AIBN (10 mol%) was used as radical initiator; a second portion of AIBN (10 mol%) was added after 1.5 h. [b] Yields after isolation of pure compounds. [c] The deuterium incorporation was ca. 90%. [d] Syringe-pump addition in 3 h followed by an additional 1 h reflux. [e] 7% of starting material was recovered.

On the other hand, by increasing the concentration of Bu_3SnH (3 equiv), the vinyl bromides **31** were consumed giving rise to two new spironucleosides **25** and **26** ($R_f = 0.24$, 0.29; 40% ethyl acetate in hexanes), which were formed along with the expected spironucleosides **22** and **23**. The anomeric ratio of the two new spironucleosides was again 2:1. An experiment utilizing an excess of Bu_3SnD (5 equiv) provided the two dideuterated compounds **40** and **41** (Scheme 9) in 36% yield. Noteworthy, in all experiments reported with various hydrides the stereochemical ratios of either the product vinyl bromides or the two pairs of anomeric spironucleosides remained constant at (*E*)-**31**:(*Z*)-**31** = 1:2, **22**:**23** = 2:1, and **25**:**26** = 2:1, respectively.

The mechanism that we propose for the reaction of **21** in the presence of either hexabutylditin or relatively low concentration of reducing agent is outlined in Scheme 8. The pathway comprises a cascade of free radical reactions involv-



Scheme 8. Proposed mechanism for the formation of anomeric spironucleosides of type **4**.

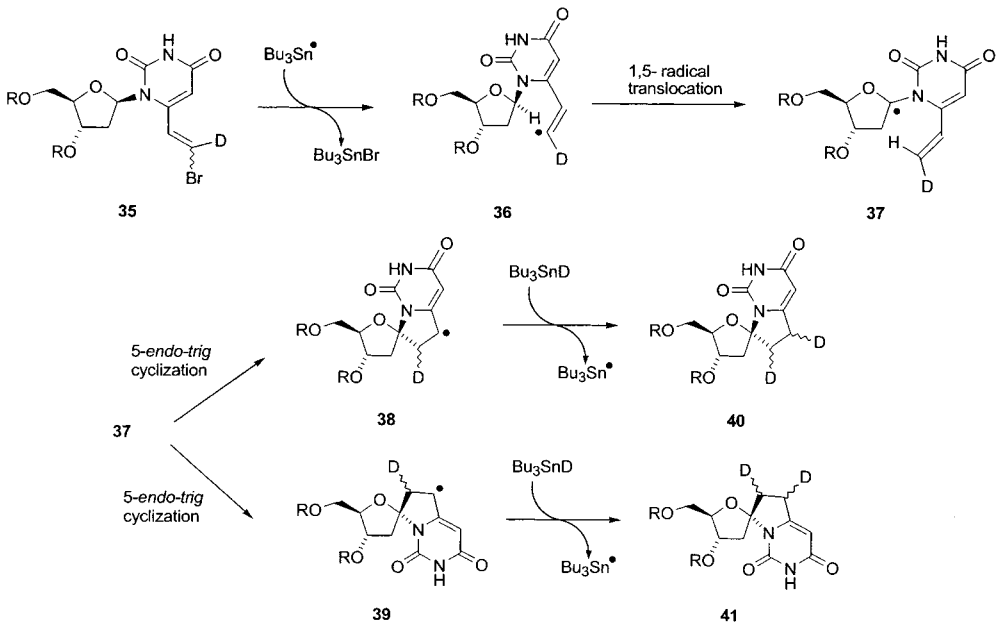
ing bromine abstraction from C-8 by stannyl or silyl radical to generate the vinyl radical species **30**,[18c] followed by a 1,5-radical translocation to the anomeric position,[28] a 5-*endo-trig* cyclization of the anomeric radical **32** onto the proximal double bond,[29] and finally product formation by bromine atom elimination.[34–37] The bimolecular homolytic substitution of a bromine atom with hexabutylditin [Eq. (1)] or the hydrogen abstraction from the tin hydride [Eq. (2)], or silane completes the cycle of these chain reactions. In the presence of a hydride or deuteride, radical intermediate **30** can also undergo reduction to the vinyl bromides **31** or **35**, respectively.

$$Br^{\bullet} + Bu_3SnSnBu_3 \longrightarrow Bu_3SnBr + Bu_3Sn^{\bullet} \quad (1)$$

$$Br^{\bullet} + Bu_3SnH \longrightarrow HBr + Bu_3Sn^{\bullet} \quad (2)$$

On the other hand, when an excess of tributyltin hydride or deuteride is employed, the vinyl bromides **31** and **35** undergo another cascade reaction to yield (**25**,**26**) and (**40**,**41**), respectively.[38] The reaction mechanism involving Bu_3SnD, where products **40** and **41** incorporate deuterium in two adjacent carbon atoms, is illustrated in Scheme 9. The regioselectivity of deuterium incorporation indicates that the 1,5-radical translocation step is followed by a 5-*endo-trig* cyclization prior to deuterium abstraction.

Kinetic information for some of the reactions shown in Scheme 8 can be deduced from Table 1. Since the relative amounts of the vinyl bromides and spironucleosides are similar in entries 1 and 2, a deuterium isotope effect $k_H/k_D = 1.7$ can be calculated, where k_H and k_D are the rate constants for the reaction of radical **30** with Bu_3SnH and Bu_3SnD, respectively. By applying free-radical clock methodology[39] in entry 1 (Table 1, second-order kinetics), we were able to determine $k_t/k_H = 0.045$ M. By assuming $k_H > 10^7\ M^{-1}\,s^{-1}$,[40] we estimate the radical translocation (k_t) to be larger than $4 \times 10^5\ s^{-1}$.[41] On the other hand, the lack of hydrogen abstraction from the hydrides by radical **32** to give anomeric mixtures of bromides **31** suggests that the 5-*endo-*



Scheme 9. Proposed mechanism for the formation of anomeric spironucleosides **40** and **41**.

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trig cyclization is a relatively fast process. We should mention in particular a recent synthetically useful application by Sato et al. of a 5-*endo-trig* radical cyclization of *N*-vinylic-α,α-bis(phenylthio)acetamides,[32] which bear a geometric resemblance to our system. The correct geometric arrangement coupled with the stability of the C-7-produced radical could account for the success of this exceptional cyclization.[42]

The factors controlling the stereoselectivity in these cyclizations deserve some comments. C-1′ radicals are shown both by EPR spectroscopy and theoretical calculations to be pyramidal (the C1′–N1 bond is about 30° out of the plane OC1′C2′).[45] Therefore, the inversion of configuration at C-1′ radical (see Scheme 10) is expected to be the main factor

42 **43**

Scheme 10. Inversion of configuration in C-1′ radicals.

controlling the outcome of the stereochemistry. Thus, when a bulky substituent is present in C-2′ position (X = $OSiMe_2tBu$), the equilibrium between **42** and **43** is expected to lie on the left side, where the two substituents on the ring are in *trans* arrangement.[46] This is most likely the reason, why a single stereoisomer is observed in the reaction of the ribo system **28** (Scheme 7). In the 2′-deoxyribo series (X = H) presumably the intermediate C-1′ radical is rapidly inverting and the product distribution is controlled only by the difference between the total free energy of activation for each pathway (Curtin–Hammett principle).[47, 48] It can also be confirmed by the ^{1}H NMR spectra of **40** and **41** that there is a lack of stereoselectivity in the deuterium incorporated in both positions; this indicates that not only the final deuterium abstraction step is not stereoselective, as expected, but also the 6-vinyl substituent is flexible enough to allow for the scrambling of the initially stereospecifically incorporated deuterium during the cyclization step.

Circular dichroism: Nucleic acid bases give several intense π–π^* transitions in the UV spectrum. The asymmetric sugar induces a CD in each electronic transition.[49] Although a complete quantitative understanding of the origin of the CD bands in mononucleosides is still missing, they can be interpreted in the coupled oscillator approach: the CD bands result from the nondegenerate interaction of the transition dipoles that correspond to each electronic transition of the base with the electronic transitions of the asymmetric sugar.

Since CD is mostly affected by the restricted rotation around the *N*-glycosidic bond, this technique has been used empirically to determine whether modified nucleosides are *anti* or *syn* in solution.[50] In cyclonucleosides the chromophore attached to the anomeric position is fixed by the bridge and the CD pattern reflects the glycosidic torsion angle. In particular, the sign of the Cotton effect in the low-energy band of *C*-cyclouridines changes from positive to negative, when the glycosidic torsion angle passes through two "critical" values at around $-117°$ (*anti* region) and 63° (*syn* region).[6] *O*-Cyclouridine exhibits similar behavior.[51]

We present and discuss here the CD spectra of a few selected spironucleosides in order to evaluate the versatility of the empirical approach proposed for discussion on the glycosidic torsion angle and to test the possibility of assigning the configuration of C-1′ from the sign of the main dichroic signal. The CDs presented are not directly related to those described in the literature.[6, 51] In fact, i) the five-membered oxazole ring in type **3** compounds creates a different strain with respect to the published compounds, and ii) in the case of type **4** compounds, the chromophore is different.

The most striking feature of the CD spectra of anomeric compounds **11** and **14** (Figure 1) is that they are almost mirror immages of each other in the entire region despite the fact that they are diastereomers and not enantiomers. These spectra are dominated by an intense band at 265 nm positive for the β-anomer (**11**) and negative for the α-anomer (**14**) followed by a shoulder at 240 nm and a maximum at 215 nm of opposite sign with respect to the low-energy band. The CD spectrum of the α-anomer *C*-cyclouridine **26** is quite similar,

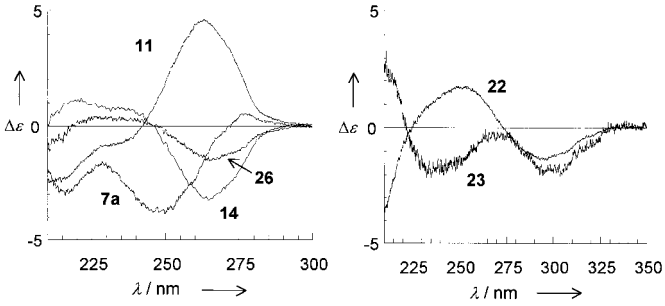

Figure 1. CD spectra of compounds **11, 14, 7a**, **26** (left) and of compounds **22** and **23** (right) in THF at room temperature.

though weaker, to that of the corresponding *O*-cyclouridine **14**; this is indicative of a similarity in their chromophores. On the other hand, the importance of the conformation of the sugar in the actual shape of CD is not negligible. Compounds **11** and **7a** in which C-1′ has the same configuration (β-anomer) show different spectra. In fact, **7a** exhibits the same pattern of positive–negative–negative bands (from the low-energy extreme) observed for **11**, although the relative intensities are different and the spectrum is dominated by the negative band at 250 nm. These differences suggest that it is not yet safe to draw conclusions on the configuration of C-1′ only from the sign of the main dichroic signal. As already reported[6] for other spirouridines, this dependence of the CD pattern on relatively subtle conformational changes could be attributed to the fact that the actual value of the glycosidic angle is near the critical value (estimated around 63°).[6]

On the other hand, anomeric compounds **22** and **23** show CDs that are not quasispecular. The CD corresponding to the low-energy absorption at about 290 nm is negative for both compounds, while only at a higher energy the spectra are quasimirror images of each other with negative–positive bands for **23** and the opposite for **22**. The presence of a more extended conjugation in derivatives **22** and **23** severely modify the chromophoric part of the molecule and this prevents a reliable assignment of the relative configuration by means of an empirical comparison of the CD spectra.

Conclusion

We have disclosed two short and efficient synthetic sequences, based on consecutive radical reactions, for the preparation of anomeric spironucleosides. The C-1′ radicals generated through an 1,5-hydrogen transfer from an alkoxyl or vinyl radical linked on the base moiety (Scheme 1, Method B) are the key intermediates in these transformations. The presence of the C-2′ substituent in the sugar ring plays an important role in the stereoselectivity of these reactions. Consequently, a single diastereoisomer is produced in the ribo series.

The research described in this article has demonstrated the feasibility of the radical cascade strategy for the preparation of presumably inaccessible compounds starting from easily available modified pyrimidine nucleosides.[52] We envisage that this approach can be extended to other nucleobase-modified nucleosides giving anomeric spironucleosides with new types of fused heterocyclic systems.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded on a Varian model VXR-200 FT-NMR spectrometer at 200 MHz and 50 MHz, respectively. Chemical shifts are given in δ and coupling constants in Hertz (Hz). Infrared (IR) spectra were recorded on a Nicolet model 205 FT-IR spectrometer with KBr pellets. CD spectra were recorded at room temperature using a Jasco J-710 Spectropolarimeter. Melting points (M.p.) were determined on a Büchi model 510 or SMP-20 apparatus and are uncorrected. Column chromatography was performed by the method of Still on Merck 230–400 mesh ASTM silica gel 60. Analytical (TLC) and preparative (PLC) thin layer chromatography was performed with Merck 60 F_{254} 0.2 and 1 mm precoated silica gel plates, respectively. Compounds were visualized with ultraviolet light, iodine vapor, or by heating plates previously immersed in a ammonium molybdate/ceric ammonium sulfate/sulfuric acid mixture. Solvents were freshly distilled prior to use. Diethyl ether (Et_2O) was distilled from $LiAlH_4$. Triethylamine (Et_3N) was distilled from calcium hydride. Benzene and toluene were distilled from sodium metal. Water content in organic solvents was measured by a Prolabo model Hydromat 2 colorimetric Karl Fischer titration apparatus. All other reagents were used as received. All air- or moisture-sensitive reactions were conducted in oven- or flame-dried glassware, and under an atmosphere of nitrogen or argon. Moisture-sensitive reagents were transferred with syringes or cannulas through rubber septa.

2′,3′,5′-Tri-*O*-(*tert*-butyldimethylsilyl)-6-(hydroxymethyl)uridine (6a):[14] *n*BuLi (2.0 M solution in hexanes, 75 mL, 150 mmol) was added at $-20\,^\circ$C to a solution of diisopropylamine (20 mL, 150 mmol) in dry THF (200 mL). After 15 min the temperature was brought to $-65\,^\circ$C and a solution of 2′,3′,5′-tri-*O*-(*t*butyldimethylsilyl)uridine (**5a**) (30 g, 50 mmol) in dry THF (100 mL) was added dropwise, while the internal temperature was maintained below $-60\,^\circ$C. The resulting yellowish solution was stirred at $-70\,^\circ$C for 3 h. Within 5 min a solution of ethyl formate (10 mL, 125 mmol) in dry THF (20 mL) was added dropwise to the resulting clear orange solution, while the internal temperature was maintained below $-50\,^\circ$C. The resulting clear reddish solution was stirred at $-60\,^\circ$C for 2 h and then quenched at $-50\,^\circ$C with acetic acid (10 mL), and then at $0\,^\circ$C with water (50 mL). The solvent was evaporated under reduced pressure and the residue was partitioned between diethyl ether (200 mL) and aqueous HCl (1%, 100 mL). The organic phase was separated, washed sequentially with H_2O (100 mL), saturated aqueous $NaHCO_3$ (100 mL), and brine (100 mL), dried over Na_2SO_4, and evaporated under reduced pressure to give the crude product (36 g) as a colored foam. Part of the foam (3.25 g) was dissolved in methanol (50 mL) and treated with small portions of $NaBH_4$ (400 mg, 10 mmol). After 40 min at RT the reaction mixture was acidified with 1N HCl (10 mL); the solution was concentrated under reduced pressure to 20 mL, then diluted with diethyl ether (50 mL). The separated organic phase was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4, and evaporated under reduced pressure to give the crude product (3.1 g) as a colored foam. Flash column chromatography (20–40% ethyl acetate in hexanes) gave the recovered starting material (2.0 g, 89%) and **6a** (418 mg) contaminated with diisopropyl(hydroxymethyl)amine which was readily removed by heating the product at $90\,^\circ$C under vacuum (0.2 mm Hg) to yield 285.3 mg (68% based on recovered starting material). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = -0.05$, 0.04 (s, each 3H, SiMe), 0.06 (s, 6H, 2 × SiMe), 0.09, 0.11 (s, each 3H, SiMe), 0.85, 0.89, 0.91 (s, each 9H, Si*t*Bu), 3.11 (t, 1H, $J = 6.6$ Hz, 7-OH), 3.64–3.85 (m, 2H, 5′-Hs), 3.96 (ddd, 1H, $J = 6.1$, 5.0, 1.8 Hz, 4′-H), 4.22 (dd, 1H, $J = 4.4$, 1.8 Hz, 3′-H), 4.48 (d, 2H, $J = 6.6$ Hz, 7-H), 5.09 (dd, 1H, $J = 6.6$, 4.4 Hz, 2′-H), 5.49 (d, 1H, $J = 6.6$ Hz, 1′-H), 5.88 (t, 1H, $J = 2.0$ Hz, 5-H), 8.76 (brs, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = -5.5$, −5.4, −5.0, −4.6 (each CH_3), −4.5 (2 × CH_3), 25.7, 25.8, 25.9 (each 3 × CH_3), 29.3 (C), 29.6 (2 × C), 60.6, 62.9 (each CH_2), 70.5, 72.5, 85.8, 89.8, 101.3 (each CH), 150.2, 156.5, 163.2 (each C).

5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-isopropylidene-6-(hydroxymethyl)uridine (6b): Following the procedure described for the preparation of **6a**, compound **5b** was transformed into **6b** in 94% yield based on recovered starting material. ^{1}H NMR (200 MHz, $CDCl_3/D_2O$ 10:1): $\delta = 0.05$, 0.06 (s, each 3H, SiMe), 0.87 (s, 9H, Si*t*Bu), 1.32, 1.53 (s, each 3H, CMe_2), 3.80–3.90 (m, 2H, 5′-H), 4.05–4.18 (m, 1H, 4′-H), 4.51 (brs, 2H, 7-Hs), 4.79 (dd, 1H, $J = 6.4$, 4.6 Hz, 3′-H), 5.18 (dd, 1H, $J = 4.6$, 1.0 Hz, 2′-H), 5.79 (brs, 2H, 1′, 1′-H, 5-H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = -5.4$ (2 × CH_3), 18.2 (C), 25.2 (CH_3), 25.8 (3 × CH_3), 27.0 (CH_3), 60.2, 64.0 (each CH_2), 81.7, 84.1, 89.3, 91.0, 100.9 (each CH), 113.6, 150.5, 155.7, 164.0 (each C); anal. calcd $C_{19}H_{32}N_2O_7Si$: C 53.25, H 7.53, N 6.54; found: C 53.20, H 7.55, N 6.70.

6-[[[*tert*-Butyldimethylsilyl]oxy]methyl]-3,4-[[*tert*-butyldimethylsilyl]oxy]-[2*aR*,3*a*,4*a*,5*b*]-spiro[furan-2[3*H*],3′-[3*H*]oxazolo[3,4-*c*]pyrimidine]-5′,7′(1′H,6′H)-dione (7a): A solution of **6a** (413 mg, 0.67 mmol) and $PhI(OAc)_2$ (636 mg, 1.97 mmol) in cyclohexane (20 mL), deoxygenated by successive freeze-pump-thaw cycles with nitrogen, was treated with iodine (188 mg, 0.74 mmol) and then irradiated at 25–30 °C with a 450 W tungsten-filament lamp equipped with a borosilicate glass filter for 6 h. The organic phase was then washed with 10% aqueous $Na_2S_2O_3$ (10 mL), H_2O (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), and dried over Na_2SO_4. The organic phase was evaporated under reduced pressure and column chromatography of the residue (25% ethyl acetate in hexanes) gave **7a** (143 mg, 0.23 mmol, 36%) as a white solid. M.p. 244–245 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = -0.06$, 0.04, 0.06, 0.07, 0.08, 0.10 (s, each 3H, SiMe), 0.86, 0.90, 0.91 (s, each 9H, Si*t*Bu), 3.68 (dd, 1H, $J = 10.7$, 5.8 Hz, 5′α-H), 3.76 (dd, 1H, $J = 10.7$, 8.0 Hz, 5′β-H), 4.13 (ddd, 1H, $J = 8.0$, 5.8, 1.1 Hz, 4′-H), 4.23 (dd, 1H, $J = 5.2$, 1.1 Hz, 3′-H), 4.84 (dd, 1H, $J = 14.8$, 1.4 Hz, 7α-H), 5.00 (dd, 1H, $J = 14.8$, 1.5 Hz, 7β-H), 5.00 (d, 1H, $J = 5.2$ Hz, 2′-H), 5.56 (dd, 1H, $J = 1.5$, 1.4 Hz, 5-H), 8.23 (brs, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = -5.48$, −5.41, −5.18, −4.77, −4.59, −4.49 (CH_3), 17.9, 18.0, 18.3 (C), 25.7, 25.8, 25.9 (each 3 × CH_3), 62.5, 67.5 (each CH_2), 70.8, 71.6, 86.6, 92.8 (each CH), 119.4, 146.8, 153.3, 164.0 (each C); IR (KBr): 2929, 1721, 1698, 1259, 1127, 837, 778 cm^{-1}; anal. calcd $C_{28}H_{54}N_2O_7Si_3$: C 54.68, H 8.85, N 4.56; found: C 55.50, H 8.80, N 4.68.

6-[[[*tert*-Butyldimethylsilyl]oxy]methyl]-6,6*a*-dihydro-2,2-dimethyl-[3*aR*,4*b*,6*a*]-spiro-[furo[3,4-*d*]-1,3-dioxole-4(3*aH*),3′-[3*H*]oxazolo[3,4-*c*]pyrimidine]-5′,7′(1′H,6′H)-dione (7b): Following the procedure described for the preparation of **7a**, compound **6b** was transformed into **7b** in 49% yield (0.39 mmol) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.06$ (s, 6H, SiMe), 0.89 (s, 9H, Si*t*Bu), 1.38, 1.60 (s, each 3H, CMe_2), 3.78 (d, 2H, $J = 6.3$ Hz, 5′-H), 4.27 (td, 1H, $J = 6.3$, 2.9 Hz, 4′-H), 4.80 (dd, 1H, $J = 6.5$, 2.9 Hz, 3′-H), 5.01 (AB_q, 2H, $J = 14.6$ Hz, 7-Hs), 5.46 (d, 1H, $J = 6.4$ Hz, 2′-H), 5.58 (brs, 1H, 5-H), 8.75 (brs, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = -5.4$ (2 × CH_3), 18.3 (C), 25.6 (CH_3), 25.8 (3 × CH_3), 26.1 (CH_3), 63.1, 67.6 (each CH_2), 79.7, 80.6, 84.2, 93.3 (each CH), 115.0 118.8, 147.0, 152.2, 164.2 (each C); anal. calcd $C_{19}H_{30}N_2O_7Si$: C 53.50, H 7.09, N 6.57; found: C 53.45, H 7.11, N 6.60.

3,4-Dihydroxy-5-(hydroxymethyl)-[2*aR*,3*a*,4*a*,5*b*]-spiro[furan-2[3*H*],3′-[3*H*]oxazolo[3,4-*c*]pyrimidine]-5′,7′(1′H,6′H)-dione (8): TBAF · SiO_2 (1.16 mol F^- per g silica gel, 5.53 g, 6.42 mmol) was added to a solution of spironucleoside **7a** (877 mg, 1.43 mmol) in dry THF (20 mL). The resulting suspension was stirred for 48 h at RT, then filtered through celite and the precipitate washed with a solution of 10% MeOH in CH_2Cl_2 (30 mL). After the solvent was evaporated under reduced pressure, the residue was purified by flash column chromatography (10% MeOH in

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CH_2Cl_2) to yield **8** (350 mg, 1.28 mmol, 90%) as a white solid. M.p. 171–172 °C; ^{1}H NMR (200 MHz, CD_3OD): $\delta = 3.65$ (dd, 1H, $J = 12.3$, 4.1 Hz, 5′α-H), 3.75 (dd, 1H, $J = 12.3$, 3.7 Hz, 5′β-H), 4.16–4.22 (m, 2H, 4′-H, 3′-H) 4.93 (d, 1H, $J = 5.9$ Hz, 2′-H), 5.00 (dd, 1H, $J = 15.0$, 1.5 Hz, 7α-H), 5.09 (dd, 1H, $J = 15.0$, 1.5 Hz, 7β-H), 5.68 (t, 1H, $J = 1.5$ Hz, 5-H); ^{13}C NMR (50 MHz, CD_3OD): $\delta = 63.6$, 68.9 (each CH_2), 71.2, 72.0, 88.4, 94.3 (each CH), 120.8, 149.5, 155.1, 166.6 (each C).

7-Hydroxy-6,6*a*,9,9*a*-tetrahydro-2,2,4,4-tetrakis(1-methylethyl)-[6*aR*,7*a*,8*a*,9*ab*]-spiro[8*H*-furo[3,2-*f*]-1,3,5,2,4-trioxadisilocin-8,3′-[3*H*]oxazolo[3,4-*c*]-pyrimidine]-5′,7′(1′H,6′H)-dione (9): 1,2-Dichloro-1,1,3,3-tetraisopropyldisiloxane (122 mL, 0.38 mmol) was added to a solution of spironucleoside **8** (102 mg, 0.37 mmol) in dry pyridine (5 mL). The resulting mixture was stirred overnight at RT. The solution was then partitioned between ethyl acetate (20 mL) and H_2O (20 mL) and the separated organic phase was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The remaining pyridine was evaporated azeotropically by codistillation with toluene to give a crude foam (331 mg) which was purified by flash column chromatography (ethyl acetate) to afford **9** (117 mg, 0.23 mmol, 61%) as a white foam. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.05$–1.08 (m, 28H, 4 × Si*i*Pr), 3.16 (d, 1H, $J = 8.2$ Hz, 2′-OH), 5.00 (m, 3H, 7-H, 2′-H), 3.86 (dd, 1H, $J = 11.4$, 8.8 Hz, 5′α-H), 4.03 (dd, 1H, $J = 11.4$, 3.7 Hz, 5′β-H), 4.10 (m, 1H, 4′-H), 4.64 (dd, 1H, $J = 7.5$, 4.3 Hz, 3′-H), 5.58 (t, 1H, $J = 1.4$ Hz, 5-H), 8.38 (brs, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 12.5$, 12.9, 13.2, 13.3 (each CH), 16.7 (CH_3), 16.8 (3 × CH_3), 16.9 (CH_3), 17.2 (2 × CH_3), 17.3 (CH_3), 63.4, 67.4 (each CH_2), 69.4, 70.2, 84.3, 93.3 (each CH), 118.2, 146.7, 152.4, 163.8 (each C).

7-(Phenylthionoformyloxy)-6,6*a*,9,9*a*-tetrahydro-2,2,4,4-tetrakis(1-methylethyl)-[6*aR*,7*a*,8*a*,9*ab*]-spiro[8*H*-furo[3,2-*f*]-1,3,5,2,4-trioxadisilocin-8,3′-[3*H*]oxazolo[3,4-*c*]pyrimidine]-5′,7′(1′H,6′H)-dione (10): Phenyl chlorothionoformate (40 mL, 0.22 mmol) was added to a solution of compound **9** (101 mg, 0.20 mmol) and DMAP (50 mg, 0.40 mmol) in dry CH_2Cl_2 (2 mL). The resulting mixture was stirred at RT for 1 h. The solution was then diluted with ethyl acetate (15 mL) and washed successively with 1% aqueous HCl (10 mL), $NaHCO_3$ (10 mL), and H_2O (10 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue (129 mg) was purified by flash column chromatography (ethyl acetate) to yield **10** (120 mg) as a white foam. ^{1}H NMR (200 MHz, [D$_6$]acetone): $\delta = 1.08$–1.12 (m, 28H, 4 × Si*i*Pr), 3.99–4.09 (m, 3H, 5′-H, 4′-H), 5.06 (dd, 1H, $J = 15.1$, 1.4 Hz, 7α-H), 5.17 (dd, 1H, $J = 15.1$, 1.6 Hz, 7β-H), 5.21 (dd, 1H, $J = 7.9$, 6.5 Hz, 3′-H), 5.64 (dd, 1H, $J = 1.6$, 1.4 Hz, 5-H), 6.37 (d, 1H, $J = 6.5$ Hz, 2′-H), 7.16 (m, 2H, *o*-Ph), 7.35 (m, 1H, *p*-Ph), 7.48 (m, 2H, *m*-Ph), 8.33 (brs, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 12.6$ (2 × CH), 13.0, 13.2 (each CH), 16.8, 16.9, 17.0 (each CH_3), 17.1 (3 × CH_3), 17.2, 17.3 (each CH_3), 61.0, 67.9 (each CH_2), 80.4, 68.6, 82.3, 93.3 (each CH), 116.2 (C), 121.5 (2 × CH), 126.5 (CH), 129.4 (2 × CH), 146.4, 151.5, 153.4, 163.6, 194.6 (C).

6,6*a*,9,9*a*-Tetrahydro-2,2,4,4-tetrakis(1-methylethyl)-[6*aR*,8a,9*ab*]-spiro-[8*H*-furo[3,2-*f*]-1,3,5,2,4-trioxadisilocin-8,3′-[3*H*]oxazolo[3,4-*c*]pyrimidine]-5′,7′(1′H,6′H)-dione (11): $(TMS)_3SiH$ (36 mL, 0.12 mmol) and AIBN (1 mg) were added to a solution of thionocarbonate **10** (38 mg, 0.06 mmol) in toluene (0.5 mL, deoxygenated by successive freeze-pump-thaw cycles with nitrogen). The resulting mixture was stirred at 80 °C for 4.5 h. Evaporation of the solvent under reduced pressure and flash column chromatography of the residue (40% ethyl acetate in hexanes) gave **11** (28 mg, 94%) as a white solid. M.p. 112–115 °C; ^{1}H NMR (200 MHz, C_6D_6): $\delta = 1.12$–1.24 (m, 28H, 4 × Si*i*Pr), 2.56 (dd, 1H, $J = 14.1$, 8.3 Hz, 2′α-H), 3.20 (dd, 1H, $J = 14.1$, 8.4 Hz, 2′β-H), 3.76 (dd, 1H, $J = 14.6$, 1.2 Hz, 7α-H), 4.08 (dd, 1H, $J = 14.6$, 1.6 Hz, 7β-H), 4.14 (m, 3H, 5′-H, 4′-H), 5.22 (ddd, 1H, $J = 8.4$, 8.3, 3.1 Hz, 3′-H), 4.91 (dd, 1H, $J = 1.6$, 1.2 Hz, 5-H), 8.85 (brs, 1H, NH); ^{13}C NMR (50 MHz, C_6D_6): $\delta = 13.1$ (2 × CH), 13.5, 13.6 (each CH) ,17.3 (2 × CH_3), 17.4, 17.5 (each CH_3), 17.6 (3 × CH_3), 17.7 (CH_3), 42.9, 63.7, 66.2 (each CH_2), 72.6, 85.0, 93.1 (each CH), 118.6, 147.0, 151.7, 164.0 (each C); IR (KBr): 2952, 1719, 1679, 1463, 1036 cm^{-1}; MS (70 eV, EI): *m/z* (%) 499 (1) $[M]^+$, 455 (32) $[M - i\text{Pr}]^+$, 359 (67), 341 (100), 153 (45); anal. calcd $C_{22}H_{38}N_2O_7Si_2$: C 52.98, H 7.68, N 5.62; found: C 52.09, H 7.51, N 5.49.

4-Hydroxy-5-(hydroxymethyl)-[2*aR*,4*a*,5*b*]-spiro[furan-2[3*H*],3′-[3*H*]oxazolo[3,4-*c*]pyrimidine]-5′,7′(1′H,6′H)-dione (12): TBAF · SiO_2 (1.16 mol F^- per g silica gel, 150 mg, 0.17 mmol) was added to a solution of **11** (33 mg, 0.07 mmol) in dry THF (1.5 mL). The resulting suspension was stirred for 2 h at room temperature, then filtered through celite, and the filter washed with a solution of 10% MeOH in CH_2Cl_2 (30 mL). After the solvent was evaporated under reduced pressure, the residue was purified by flash column chromatography (10% MeOH in CH_2Cl_2) to yield **12** (16 mg, 0.06 mmol, 90%) as a white solid. ^{1}H NMR (200 MHz, CD_3OD): $\delta = 2.28$ (dd, 1H, $J = 14.4$, 5.7 Hz, 2′α-H), 3.28 (dd, 1H, $J = 14.4$, 7.9 Hz, 2′β-H), 3.63 (dd, 1H, $J = 12.1$, 6.1 Hz, 5′α-H), 3.76 (dd, 1H, $J = 12.1$, 3.2 Hz, 5′β-H), 4.01 (ddd, 1H, $J = 6.1$, 6.1, 3.2 Hz, 4′-H), 4.46 (ddd, 1H, $J = 7.9$, 6.1, 5.7 Hz, 3′-H), 4.96 (d, 2H, $J = 1.4$ Hz, 7-H), 5.62 (t, 1H, $J = 1.4$ Hz, 5-H); ^{13}C NMR (50 MHz, CD_3OD): $\delta = 43.3$, 63.5, 67.9 (each CH_2), 71.3, 89.1, 93.9 (each CH), 121.6, 149.3, 155.0, 166.9 (each C).

6,6*a*,9,9*a*-Tetrahydro-2,2,4,4-tetrakis(1-methylethyl)-[6*aR*,8*bS,9*ab*]-spiro-[8*H*-furo[3,2-*f*]-1,3,5,2,4-trioxadisilocin-8,3′-[3*H*]oxazolo[3,4-*c*]pyrimidine]-5′,7′(1′H,6′H)-dione (14)**: Following the procedure described for the preparation of **7a**, compound **13**[14] was transformed into **11** and **14** in 71% combined yield). M.p. 185–187 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.02$–1.10 (m, 28H, 4 × *i*Pr), 2.42 (dd, 1H, $J = 12.4$, 7.1 Hz, 2′α-H), 3.42 (dd, 1H, $J = 12.4$, 10.9 Hz, 2′β-H), 3.90 (dd, 1H, $J = 12.5$, 3.9 Hz, 5′α-H), 3.98 (dd, 1H, $J = 12.5$, 3.0 Hz, 5′β-H), 4.21 (ddd, 1H, $J = 7.7$, 3.9, 3.0 Hz, 4′-H), 4.65 (ddd, 1H, $J = 10.9$, 7.7, 7.1 Hz, 3′-H), 4.80 (dd, 1H, $J = 14.8$, 1.2 Hz, 7α-H), 4.98 (dd, 1H, $J = 14.8$, 1.5 Hz, 7β-H), 5.56 (brs, 1H, 5-H), 8.46 (brs, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 12.6$ (2 × CH), 13.0, 13.3 (each CH), 16.9 (2 × CH_3), 17.2 (6 × CH_3), 40.9, 61.4, 66.7 (each CH_2), 69.6, 84.9, 93.1 (each CH), 118.5, 147.2, 152.4, 164.1 (each C); IR (KBr): 2945, 1722, 1680, 1469, 1040, 892 cm^{-1}; anal. calcd $C_{22}H_{38}N_2O_7Si_2$: C 52.98, H 7.68, N 5.62; found: C 51.55, H 7.62, N 5.70.

2-Deoxy-3,5-*O*-[1,1,3,3-tetrakis(1-methylethyl)-1,3-di-siloxanediyl]-D-*erythro*-pentonic acid, γ-lactone (19): TMSBr (33 mL, 0.25 mmol) was added to a solution of **11** (50 mg, 0.1 mmol) in toluene (5 mL). The resulting mixture was stirred at RT for 4 h, then diluted with ethyl acetate (15 mL). The organic phase was washed with $NaHCO_3$ (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and evaporated. Column chromatography (1% ethyl acetate in cyclohexane) yielded **19** (24 mg, 0.065 mmol, 65%) as an oil. R_f (ethyl acetate/cyclohexane 1:99) = 0.62; b.p. 175 °C (2.1 mm Hg); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.01$–1.08 (m, 28H, 4 × Si*i*Pr), 2.69 (dd, 1H, $J = 17.3$, 9.2 Hz, 2-H), 2.86 (dd, 1H, $J = 17.3$, 8.0 Hz, 2-H), 3.93 (dd, 1H, $J = 12.0$, 6.4 Hz, 5-H), 4.12 (dd, 1H, $J = 12.0$, 3.6 Hz, 5-H), 4.21 (ddd, 1H, $J = 6.8$, 6.4, 3.6 Hz, 4-H), 4.62 (ddd, 1H, $J = 9.2$, 8.0, 6.8 Hz, 3-H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 12.6$, 12.7, 12.9, 13.2 (each C), 17.0, 17.2, 17.3, 17.4 (each 2 × CH_3), 37.8, 62.6 (each CH_2), 69.9, 84.9 (each CH), 172.7 (C); IR (NaCl): 2945, 1797, 1466, 1128, 1036, 885 cm^{-1}; MS (70 eV, EI): *m/z* (%): 331 (100) $[M - i\text{Pr}]^+$, 303 (8), 259 (10), 135 (20); anal. calcd $C_{17}H_{34}O_5Si_2$: C 54.50, H 9.15; found: C 54.45, H 9.11.

6-(2,2-Dibromovinyl)-3′,5′-*O*-(tetraisopropyldisilox-ane-1,3-diyl)-2′-deoxyuridine (21): Triphenylphosphane (1.31 g, 5 mmol) followed by tetrabromomethane (1.66 g, 5 mmol) were added under a nitrogen atmosphere to a stirred suspension of zinc powder (326 mg, 5 mmol) in dry dichloromethane (15 mL). The light-protected, bromine-colored solution was stirred overnight at room temperature until most of the zinc had dissolved and had been replaced by a white precipitate. A solution of 1-[3,5-bis-*O*-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)-2-deoxy-β-D-*erythro*-furanosyl]uracil-6-carboxaldehyde (**20**) (633 mg, 1.27 mmol)[14b] in dry CH_2Cl_2 (10 mL) cooled at 0 °C was added to this suspension, followed by dry DMF (5 mL). The clear, dark red-brown solution was stirred for 2 h at room temperature, and then diluted with dichloromethane (50 mL) and quenched with saturated aqueous $Na_2S_2O_3$ (50 mL). The phases were separated and the organic phase was washed with H_2O (2 × 50 mL) and dried over Na_2SO_4. The solvent was evaporated and the colored residue was filtered and washed with CH_2Cl_2 through a short pad of silica gel in order to remove the more polar colored components and most of the Ph_3PO. The combined fractions were concentrated and triturated with pentane in order to precipitate the remaining Ph_3PO. The precipitate was filtered off and this process was repeated twice until no more precipitate formed. The resulting foam (460 mg) was subjected to column chromatography (ethyl acetate/hexanes 4:1) to yield pure **21** (345 mg, 42%) as a white foam. M.p. 120–122 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.0$–1.2 (m, 28H, 4 × Si*i*Pr), 2.36 (ddd, 1H, $J = 15.3$, 9.0, 6.4 Hz, 2′α-H), 2.74 (ddd, 1H, $J = 15.3$, 9.0, 4.4 Hz, 2′β-H), 3.78 (ddd, 1H, $J = 6.4$, 6.3, 4.0 Hz, 4′-H), 3.96 (dAB$_q$, 2H, $J = 14.1$ Hz, the lower field doublet is further split to a doublet, $J = 4.0$ Hz, 5′-H), 4.80 (ddd, 1H, $J = 9.0$, 6.4, 6.4 Hz, 3′-H), 5.74 (brs, 1H, 5-H), 6.00 (dd, 1H, $J = 9.0$, 4.4 Hz, 1′-H), 7.22 (d, 1H, $J = 1.2$ Hz, 7-H), 9.24 (brs, 1H, NH); ^{13}C NMR (50 MHz, C_6D_6): $\delta = 33.1$, 33.2 (each CH), 33.6 (2 × CH), 37.4 (2 × CH_3),

37.5 (CH_3), 37.7 ($4 \times CH_3$), 37.9 (CH_3), 60.1, 85.2 (each CH_2), 94.7, 105.4, 105.9 (each CH), 118.7 (C), 124.9, 150.2 (each CH), 169.6, 170.2, 182.9 (each C); IR (KBr): 2937, 2863, 1700, 1096, 1032 cm^{-1}; MS (70 eV, EI): *m/z* (%): 609 (11) $[M - i\mathrm{Pr}]^+$, 529 (26), 315 (16), 81 (100); anal. calcd $C_{23}H_{38}Br_2N_2O_6Si_2$: C 42.21, H 5.85, N 4.28; found: C 42.39, H 5.74, N 4.37.

Reaction of compound 21 with $(Bu_3Sn)_2$: A solution of **21** (65.5 mg, 0.1 mmol) and hexabutylditin (150 mL, 0.3 mmol) in dry benzene (2 mL, deoxygenated by successive freeze-pump-thaw cycles with nitrogen), was irradiated under reflux with a 300 W tungsten-filament lamp equipped with a borosilicate glass filter for 12 h at which time no starting material remained by TLC (ethyl acetate/hexanes 1:1) analysis. The concentrated crude reaction product was purified with PLC (ethyl acetate/hexanes 3:7) to give **22** (25.7 mg; 52%) and **23** (12.9 mg, 26%).

3′,5′-*O*-(Tetraisopropyldisiloxane-1,3-diyl)-2′-deoxy-6,1′-etheno-β-uridine (22): R_f (40% ethyl acetate in hexanes) = 0.14; m.p. 201–202 °C; ^{1}H NMR (200 MHz, C_6D_6): δ = 1.2–1.3 (m, 28H, $4 \times$ Si*i*Pr), 2.16 (dd, 1H, J = 13.9, 7.8 Hz, 2β′-H), 2.59 (dd, 1H, J = 13.9, 8.3 Hz, 2α′-H), 4.14 (ddd, 1H, J = 9.3, 6.4, 3.4 Hz, 4′-H), 4.25 (dd, 1H, J = 10.9, 3.4 Hz, 5α′-H), 4.47 (dd, 1H, J = 10.9, 9.3 Hz, 5β′-H), 5.15 (d, 1H, J = 1.7 Hz, 5-H), 5.20 (d, 1H, J = 5.9 Hz, 7-H), 5.49 (ddd, 1H, J = 8.3, 7.8, 6.4 Hz, 3′-H), 5.59 (d, 1H, J = 5.9 Hz, 8-H), 8.87 (brs, 1H, NH); ^{13}C NMR (50 MHz, C_6D_6): δ = 13.2, 13.3 (each CH), 13.8 ($2 \times$ CH), 17.4 ($2 \times CH_3$), 17.6 (CH_3), 17.7 ($3 \times CH_3$), 17.8, 17.9 (each CH_3), 42.8, 65.4 (each CH_2), 75.7, 87.3, 96.9 (each CH), 102.0 (C), 122.6, 143.5 (each CH), 147.7, 153.4, 163.6 (each C); IR (KBr): 2945, 2866, 1700, 1684, 1460, 1052 cm^{-1}; MS (70 eV, EI): *m/z* (%): 451 (100) $[M - i\mathrm{Pr}]^+$, 421 (21), 217 (14); anal. calcd $C_{23}H_{38}N_2O_6Si_2$: C 55.84, H 7.74, N 5.66; found: C 55.65, H 7.69, N 5.63.

3′,5′-*O*-(Tetraisopropyldisiloxane-1,3-diyl)-2′-deoxy-6,1′-etheno-α-uridine (23): R_f (40% ethyl acetate in hexanes) = 0.20; m.p. 243–244 °C; ^{1}H NMR (200 MHz, C_6D_6): δ = 1.1–1.2 (m, 28H, $4 \times$ Si*i*Pr), 1.93 (dd, 1H, J = 12.3, 7.2 Hz, 2β′-H), 3.42 (dd, 1H, J = 12.3, 11.0 Hz, 2α′-H), 3.85 (dd, 1H, J = 13.2, 2.7 Hz, 5β′-H), 3.99 (dd, 1H, J = 13.2, 1.7 Hz, 5α′-H), 4.54 (ddd, 1H, J = 11.0, 8.6, 7.2 Hz, 3′-H) 4.81 (ddd, 1H, J = 8.6, 2.7, 1.7 Hz, 4′-H), 5.23 (d, 1H, J = 1.5 Hz, 5-H), 5.24 (d, 1H, J = 5.9 Hz, 7-H), 5.78 (d, 1H, J = 5.9 Hz, 8-H), 8.82 (brs, 1H, NH); ^{13}C NMR (50 MHz, C_6D_6): δ = 13.2 ($2 \times$ CH), 13.4, 14.0 (each CH), 17.1, 17.2, 17.3, 17.4, 17.5 (each CH_3), 17.6 ($3 \times CH_3$), 38.0, 60.8 (each CH_2), 70.5, 84.6, 97.0 (each CH), 101.0 (C), 122.3, 143.0 (each CH), 148.1, 153.4, 163.5 (each C); IR (KBr): 2947, 2868, 1714, 1681, 1125, 1041 cm^{-1}; MS (70 eV, EI): *m/z* (%): 451 (100) $[M - i\mathrm{Pr}]^+$, 381 (17); anal. calcd $C_{23}H_{38}N_2O_6Si_2$: C 55.84, H 7.74, N 5.66; found: C 55.70, H 7.72, N 5.61.

2′-Deoxy-6,1′-ethenouridine (24): Bu_4NF in THF (1M, 133 mL, 0.133 mmol) and glacial acetic acid (9 μL, 0.162 mmol) were added to a solution of **22** (32 mg, 0.055 mmol) in THF (1.5 mL). The resulting clear solution was stirred for 24 h at room temperature. The solvent was evaporated and the residue was purified by a short column chromatography (5% methanol in dichloromethane) to afford **24** (16 mg, 90%); the ^{1}H NMR spectrum was in complete agreement with the reported one.[7a]

3′,5′-*O*-(Tetraisopropyldisiloxane-1,3-diyl)-2′-deoxy-6,1′-ethano-β-uridine (25): Following the procedure described for the preparation of **26**, compound **22** was transformed into the corresponding **25**. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.95–1.15 (m, 28H, $4 \times$ Si*i*Pr), 2.04–2.34 (m, 3H, 8-Hs, 2′β-H), 2.70–3.06 (m, 2H, 7-Hs), 3.24 (dd, 1H, J = 13.6, 8.2 Hz, 2′α-H), 3.67–3.75 (m, 1H, 4′-H), 3.92–3.96 (m, 2H, 5′-Hs), 5.07 (ddd, J = 8.2, 8.2, 8.2 Hz, 3′H), 5.52 (s, 1H, 5-H), 7.94 (brs, 1H, NH).

3′,5′-*O*-(Tetraisopropyldisiloxane-1,3-diyl)-2′-deoxy-6,1′-ethano-α-uridine (26): A solution of **23** (27 mg, 0.05 mmol), Et_3N (7 μL, 0.05 mmol), and 5% Rh-Al (9 mg) in MeOH (4 mL) was stirred under an atmosphere of hydrogen for 5 h at RT. Filtration through celite and evaporation of the filtrate under reduced pressure gave the crude product, which was purified by PLC (20% ethyl acetate in *n*-hexanes) to give **26** as a white solid (16.9 mg, 68%). M.p. 182–184 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.97–1.24 (m, 28H, $4 \times$ Si*i*Pr), 2.07–2.41 (m, 3H, 8-Hs, 2′β-H), 2.73 (ddd, 1H, J = 16.2, 8.0, 8.0 Hz, 7α-H), 2.96 (ddd, 1H, J = 16.1, 7.6, 7.6 Hz, 7β-H), 3.34 (dd, 1H, J = 10.9, 10.9 Hz, 2′α-H), 3.94 (s, 2H, 5′-Hs), 4.30–4.55 (m, 2H, 3′-H, 4′-H), 5.52 (s, 1H, 5-H), 8.47(brs, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.6, 12.7, 13.1, 13.5 (each CH), 16.9, 17.0, 17.1, 17.2 (each CH_3), 17.27, 17.34 (each $2 \times CH_3$), 27.0, 38.2, 41.1, 60.1 (each CH_2) 69.1, 84.2, 96.1 (each CH), 100.8, 148.8, 157.9, 163.9 (each C); anal. calcd $C_{23}H_{40}N_2O_6Si_2$: C 55.61, H 8.12, N 5.64; found C 54.96, H 8.15, N, 5.59.

2′,3′,5′-Tri-*O*-(*tert*-butyldimethylsilyl)-6-(2,2-dibromovinyl)uridine (28): A solution of PPh_3 (855 mg, 3.26 mmol) in dry CH_2Cl_2 (15 mL) was added at −20 °C under nitrogen to a solution of CBr_4 (1.08 g, 3.26 mmol) in dry CH_2Cl_2 (15 mL). After 15 min at this temperature, a solution of 2′,3′,5′-tri-*O*-(*t*butyldimethylsilyl)uridine-6-carboxaldehyde (1.0 g, 1.63 mmol)[25] and Et_3N (0.24 mL, 1.63 mmol) in dry CH_2Cl_2 (15 mL) was added at −60 °C. The cold bath was then removed and the resulting mixture was stirred at RT for 3 h. It was then diluted with pentane (50 mL), filtered, evaporated, and the residue was purified by flash column chromatography (15% ethyl acetate in hexanes) to yield **28** (879 mg, 1.14 mmol, 70%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = −0.03 (s, 3H, SiMe), −0.05 (s, 9H, $3 \times$ SiMe), 0.09, 0.11 (s, each 3H, SiMe), 0.86, 0.88, 0.92 (s, each 9H, Si*t*Bu), 3.66 (dd, 1H, J = 10.7, 4.7 Hz, 5′α-H), 3.81 (dd, 1H, J = 10.7, 6.8 Hz, 5′β-H), 3.87 (m, 1H, 4′-H), 4.25 (dd, 1H, J = 4.6, 3.4 Hz, 3′-H), 4.97 (dd, 1H, J = 5.6, 4.6 Hz, 2′-H), 5.47 (d, 1H, J = 5.6 Hz, 1′-H), 5.83 (dd, 1H, J = 2.0, 1.0 Hz, 5-H), 7.17 (d, 1H, J = 2.0 Hz, 7-H), 9.56 (brs, 1H, NH); ^{13}C NMR (50 MHz, C_6D_6): δ = −5.43, −5.33, −4.85, −4.56, −4.55, −4.51 (each CH_3), 17.87, 17.92, 18.29 (each C), 25.78, 25.81, 25.87 (each $3 \times CH_3$), 62.5 (CH_2), 70.9, 71.8, 84.8, 92.0 (each CH), 99.6 (C), 104.8, 128.9 (each CH), 149.8, 150.8, 163.0 (each C); anal. calcd $C_{29}H_{54}Br_2N_2O_6Si_3$: C 45.19, H 7.06, N 3.63; found: C 44.97, H 7.15, N 3.71.

2′,3′,5′-Tri-*O*-(*tert*-butyldimethylsilyl)-6,1′-ethenouridine (29): A solution of 2′,3′,5′-tri-*O*-(*t*butyldimethylsilyl)-6-(2,2-dibromovinyl)uridine (77 mg, 0.1 mmol) and hexabutylditin (150 mL, 0.3 mmol) in dry toluene (1 mL, deoxygenated by successive freeze-pump-thaw cycles with nitrogen), was irradiated at 90 °C with a 450 W tungsten-filament lamp equipped with a borosilicate glass filter for 32 h at which time no starting material remained by TLC (ethyl acetate/hexanes 1:1) analysis. The concentrated crude reaction product was purified with PLC (ethyl acetate/hexanes 2:8) to give **29** (22.6 mg, 37%) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = −0.06, 0.01, 0.07, 0.09, 0.11, 0.14 (s, 3H, SiMe), 0.79 (s, 9H, Si*t*Bu), 0.91 (s, 18H, $2 \times$ Si*t*Bu), 3.70 (dd, 1H, J = 10.5, 4.8 Hz, 5′α-H), 3.92 (t, 1H, J = 4.8 Hz, 4′-H), 4.09 (dd, 1H, J = 10.1, 4.8 Hz, 5′β-H), 4.26 (d, 1H, J = 4.6 Hz, 3′-H), 5.43 (d, 1H, J = 4.6 Hz, 2′-H), 5.64 (dd, 1H, J = 1.8 Hz, 5-H), 6.27 (d, 1H, J = 6.1 Hz, 7-H), 6.97 (d, 1H, J = 6.0 Hz, 8-H), 8.20 (brs, 1H, NH); ^{13}C NMR (50 MHz, C_6D_6): δ = −5.50, −5.48, −5.34, −4.91, −4.72, −4.62 (each CH_3), 17.3, 17.8, 18.0 (each C), 25.6, 25.8, 25.9 (each $3 \times CH_3$), 62.8 (CH_2), 70.5, 74.1, 87.2, 96.3 (each CH), 105.7 (C), 122.4, 145.3 (each CH), 147.7, 155.5, 164.2 (each C); anal. calcd $C_{29}H_{54}N_2O_6Si_3$: C 57.01, H 8.91, N 4.58; found: C 57.20, H 8.89, N 4.50.

General procedure for the reaction of compound 21 with different reducing agents: The metal hydride or deuteride (see Table 1 for equivalent amounts) was added to a solution of **21** (65.5 mg, 0.1 mmol) in dry benzene (2 mL). The mixture was deoxygenated by successive freeze-pump-thaw cycles with nitrogen. AIBN (1.6 mg, 10 mol%) was then added and the reaction mixture was heated at 80 °C. Another portion of AIBN (1.6 mg, 10 mol%) was added after 1.5 h. When TLC (ethyl acetate/hexanes 1:1) indicated the disappearance of the starting material (see Table 1) the solvent was evaporated under reduced pressure and the residue was purified with PLC; see Table 1 for yields of individual experiments.

Reaction of compound 21 with Bu_3SnH (syringe-pump addition): A solution of Bu_3SnH (59 mL, 0.22 mmol) in dry toluene (1 mL) was added through a syringe pump (Precidor Type 5003, INFORS AG, Basel) within 3 h to a solution of **21** (65.5 mg, 0.1 mmol) and AIBN (1.6 mg, 10 mol%) in dry toluene (2 mL, deoxygenated by successive freeze-pump-thaw cycles with nitrogen), and after 1.5 h another portion of AIBN (1.6 mg, 10 mol%) was added to the reaction mixture. After the addition was completed the reaction mixture was refluxed for 1 h, then concentrated under reduced pressure, and purified by PLC to give (*E*)-**31** (5 mg, 8.5%), (*Z*)-**31** (10 mg, 17.5%), **22** (19.6 mg, 34%), and **23** (8.9 mg, 18%) in order of elution.

6-(*trans*-2-Bromovinyl)-2′-deoxy-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-uridine [(*E*)-31]: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.9–1.1 (m, 28H, $4 \times$ Si*i*Pr), 2.33 (ddd, 1H, J = 13.7, 9.1, 7.0 Hz, 2α′-H), 2.80 (ddd, 1H, J = 13.7, 8.9, 4.4 Hz, 2β′-H) 3.78 (ddd, 1H, J = 6.8, 6.8, 4.2 Hz, 4′-H), 3.99 (m, 2H, 5′-H), 4.88 (ddd, 1H, J = 8.9, 7.0, 6.8 Hz, 3′-H), 5.63 (d, 1H, J = 2.0 Hz, 5-H), 5.92 (dd, 1H, J = 9.1, 4.4 Hz, 1′-H), 6.99 (AB_q, 2H, J = 13.9 Hz, 7-H, 8-H), 7.97 (brs, 1H, NH); IR (KBr): 2964, 2867, 1692, 1466, 1262, 1094, 1031, 802 cm^{-1}; MS (70 eV, EI): *m/z* (%): 315 (7), 81 (100).

6-(*cis*-2-Bromovinyl)-2′-deoxy-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-uridine [(*Z*)-31]: ^{1}H NMR (200 MHz, C_6D_6): δ = 1.1–1.3 (m, 28H, $4 \times$

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Si*i*Pr), 2.04 (ddd, 1H, $J = 13.7$, 9.5, 7.0 Hz, 2α'-H), 2.62 (ddd, 1H, $J = 13.7$, 8.8, 3.2 Hz, 2β'-H) 3.90 (ddd, 1H, $J = 6.6$, 6.6, 4.4 Hz, 4′-H), 4,24 (m, 2H, 5′-H), 5.14 (ddd, 1H, $J = 8.8$, 7.0, 6.6 Hz, 3′-H), 5.42 (dd, 1H, $J = 9.5$, 3.2 Hz, 1′-H), 5.52 (s, 1H, 5-H), 5.93 (AB_q, 2H, $J = 8.2$ Hz, the lower field doublet is further split to a doublet, $J = 1.0$ Hz, 7-H, 8-H), 9.34 (brs, 1H, NH); NOE irradiation of H-1′ results in positive NOEs on H-7 (13%), H-4′ (3%), and H-2a′ (7%); irradiation of H-7 results in positive NOE on H-1′ (11%); ^{13}C NMR (50 MHz; C_6D_6): $\delta = 13.1$, 13.2, 13.6, 13.7 (each CH), 17.3 ($2 \times CH_3$), 17.4 (CH_3), 17.5, 17.6 (each $2 \times CH_3$), 17.7 (CH_3), 39.8, 64.9 (each CH_2), 74.3, 85.8, 86.5, 104.2, 115.0, 126.3 (each CH), 149.1, 149.9, 161.5 (each C); IR (KBr): 2945, 2868, 1718, 1684, 1463, 1094, 1084, 886 cm^{-1}; MS (70 eV, EI): *m/z* (%): 315 (10), 81 (100); anal. calcd $C_{23}H_{39}BrN_2O_6Si_2$: C 47.99, H 6.83, N 4.87; found: C 47.15, H 6.79, N 4.93.

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