A Short, Flexible Route toward 2′-*C*-Branched Ribonucleosides

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A five-step synthesis of 2′-*C*-branched ribonucleosides from commercially obtained 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (**4**) is described. The free hydroxyl group of **4** was oxidized in high yield with Dess−Martin periodane reagent. The resultant 2-ketosugar was treated with MeMgBr/$TiCl_4$, CH_2═CHMgBr/$CeCl_3$, or TMSC≡CLi/$CeCl_3$, and in each case addition to the ketone proceeded stereoselectively to provide 2-alkylated ribofuranosides. After conversion to the corresponding tetrabenzoyl derivatives, the 2-alkylribofuranosides were coupled to nucleobases under Vorbrüggen persilylation conditions, giving the β-nucleosides with high stereoselectivity. Deprotection with methanolic ammonia provided the title compounds in 17−49% overall yields from **4**.

In the past ten years, a number of 2′-*C*-branched nucleosides have displayed promising anticancer[1] and antiviral[2] activities as well as interesting biochemical properties, such as DNA cleavage[3] and ribonucleotide reductase inactivation.[4] We have recently initiated a program aimed toward developing new 2′-*C*-branched ribonucleosides and ribonucleotides as bioorganic tools and as potential chemotherapeutic agents. Within this framework, 2′-*C*-vinyl- and 2′-*C*-ethynylribonucleotides have been designed as potential mechanism-based inactivators of ribonucleotide reductases. While there are numerous examples of 2′-*C*-branched 2′-*deoxyribo*nucleosides in the literature, there are surprisingly few 2′-*C*-branched *ribo*nucleosides and no 2′-*C*-vinyl- or 2′-*C*-ethynylribonucleosides. Our initial goal was to develop a short, flexible synthetic route toward 2′-*C*-branched ribonucleosides in general and 2′-*C*-vinyl- or 2′-*C*-ethynylribonucleosides in particular.

Several synthetic methodologies have been reported toward 2′β-*C*-branched nucleosides, and these can be divided into two general strategic types: (1) a convergent approach, where the nucleobase is glycosylated with the appropriately modified sugar,[5] and (2) a linear approach starting from the unmodified nucleoside.[1a−g,6] The linear approach offers a relatively rapid route to 2′β-*C*-branched nucleosides; however, while this approach has provided access to a variety of 2′β-alkyl-2′-deoxyribonucleosides with high stereoselectivity, it has not offered the corresponding 2′-alkylribonucleosides stereoselectively. Where 2′-alkylribonucleosides have been accessible using the linear approach (specifically, via reaction of 2′-ketonucleoside derivatives with organometallics), the diastereomeric 2′-alkylarabinonucleosides are usually the major (and, in some cases, the exclusive) products.[1a−e,6]

Compared with the linear approach, the convergent approach is potentially more flexible since a variety of nucleobases can be coupled to the modified sugar. However, the stereoselectivity of the nucleobase coupling may be compromised by the presence of the alkyl substituent on the β face of the sugar.[5e] Reported routes to 2′-*C*-branched ribonucleosides using the convergent approach[5] are relatively lengthy, low yielding, or not easily amenable to the incorporation of alkyl groups other than methyl and were therefore considered suboptimal for our purposes.

A recent report[7] describing the synthesis of 2-ketoribofuranose **1** inspired the formulation of a short, general, convergent approach toward 2′-*C*-branched ribonucleosides (Scheme 1). This route necessitates the choice of organometallic reagents which selectively add to ketone functionalities in the presence of esters. Organotitanium[8] and organocerium[9] reagents are known to provide such selectivity. Given this selectivity, the stereochemical arrangement of the adjacent substituents should favor the addition of alkyl groups to the β face of the ketone to provide 2-alkylsugars **2**. After conversion of the free 2-hydroxyl group to its benzoate ester, the

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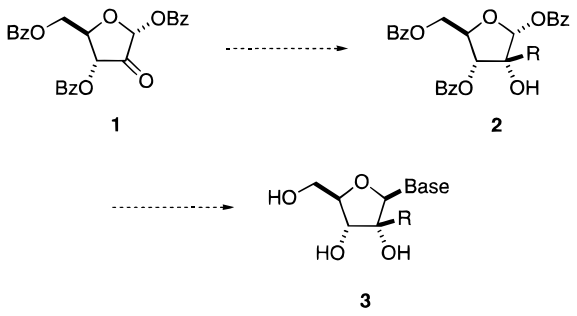
Scheme 1



sugars can then be coupled to a variety of nucleobases using Vorbrüggen-type persilylation conditions.[10] The steric bulkiness of the 2-benzoate group in addition to its well-known propensity to facilitate trans approach of the incoming nucleobase by stabilizing the sugar oxonium intermediate[11] made this the protecting group of choice. Ammonolysis of the benzoate protecting groups would then provide the modified nucleoside analogues **3**. This route was attractive to us because of its brevity and the potential to install a variety of 2′ alkyl substituents as well as a range of natural and unnatural nucleobases.

In a preliminary communication, we have reported the synthesis of 2′-*C*-methylribonucleosides, using MeMgBr/$TiCl_4$ to form the new C−C bond.[12] In this full account, we provide a detailed description and discussion of this work. In addition, we demonstrate that organocerium chemistry is suitable for installing different R groups into the sugar and illustrate the flexibility of this route by obtaining 2′-*C*-vinyl- and 2′-*C*-ethynylribonucleosides.

Results and Discussion

Formation of 2′-*C*-Methylribonucleosides Using $MeTiCl_3$. Ketone **1** was formed in high yield by the oxidation of commercially available[13] 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (**4**, Scheme 2) with Dess−Martin periodane reagent as previously described.[7] Using this procedure, a considerable portion of the corresponding hydrate of **1** is also formed upon aqueous workup. In our hands, the ratio of ketone to hydrate is generally about 10:3. The presence of this hydrate would be potentially detrimental to subsequent reactions with organometallic reagents. While high-vacuum drying and codistillation with toluene were both unsuccessful in converting the hydrate to the ketone, stirring a CH_2Cl_2 solution of the ketone/hydrate mixture with a large amount of $MgSO_4$ overnight gave essentially pure ketone after filtration and concentration.

Ketone **1** was then treated with MeMgBr/$TiCl_4$.[14] Three products were isolated from this reaction: the anticipated product **5** as well as its transesterified isomers **8** as a mixture of anomers. The chromatographic and spectral properties of these isomers matched those in a previous report where **5** and **8** had been formed by another route.[5a,b] The ratio of **5** to transesterification products **8** was about 5:3, with an overall yield of 66%. Despite the formation of three products, the methyl group had added with complete stereoselectivity to the β face of the sugar; no products resulting from approach from the α face were isolated. The organotitanium reagent also appeared to be quite chemoselective as expected, since no products resulting from ester cleavage were detected either.

All three products were useful for our purposes and converged to the tetrabenzoylated **11** upon treatment with benzoyl chloride and DMAP in the presence of Et_3N. Regardless of whether the starting material was purified **5** or the anomeric mixture of **8**, the product **11** was isolated in about 70% yield with a β/α ratio of 4:1. Again, the two anomers of **11** were spectroscopically identical with previous reports.[5a,b] The mechanism of this reaction involves transesterification of **5** to α-**8** followed by anomerization of α-**8** to β-**8**. Although these two steps are likely reversible, β-**8** is apparently the least sterically hindered and is most rapidly benzoylated.[15] This conversion of **5** to β-**11** has been observed before under similar conditions (heating with benzoyl chloride in pyridine).[5b]

Purified β-**11** was coupled with several nucleobases under persilylation conditions.[10] For the pyrimidine bases, coupling was accomplished using $SnCl_4$ as the Lewis acid and refluxing in acetonitrile for 3 h. Glycosylation yields were 57% and 77% for uracil and 6-azauracil, respectively. Despite the presence of the 2β-methyl substituent, only one anomer, identified as β (vide infra), of protected nucleosides **14a** and **14b** was observed in each case. A sample of **11** enriched in the α anomer was coupled to uracil under identical conditions to give the same product observed with purified β-**11** in the same yield and with the same stereoselectivity (i.e., the reaction works through a 1,2-acyloxonium intermediate[11]). Apparently, the choice of benzoyl ester protecting groups is critical for this selectivity, since the peracetyl counterpart of **11** is reported to give a 7:3 mixture of β/α nucleoside anomers when coupled to thymine under similar conditions.[5e] Coupling of β-**11** with purine bases (N^6-benzoyladenine and 6-(methylthio)purine) was carried out using TMSOTf as Lewis acid, refluxing for over 12 h in acetonitrile to ensure conversion of the initially formed N-7 regioisomers to the thermodynamically favored N-9 glycosylation products.[16] Again, the coupling appeared to be completely stereoselective, forming the protected β-nucleosides (vide infra) **14c** and **14d** in 86% and 47% yields, respectively.

Compounds **14a**−**d** were each treated with methanolic ammonia to provide the deprotected nucleosides **17a**−**d**. 2′-*C*-Methyluridine (**17a**) and 2′-*C*-methyladenosine (**17c**) were physically and spectroscopically identical with previously reported data of these compounds,[5] providing unambiguous proof of their regio- and stereochemical assignments. Evidence for the regio- and stereochemical identity of **17b** and **17d** was provided by a comparison of ^{13}C NMR data of these two nucleosides with their unmethylated counterparts 6-azauridine and 6-methylthiopurine riboside (Table 1) and with methylnucleo-

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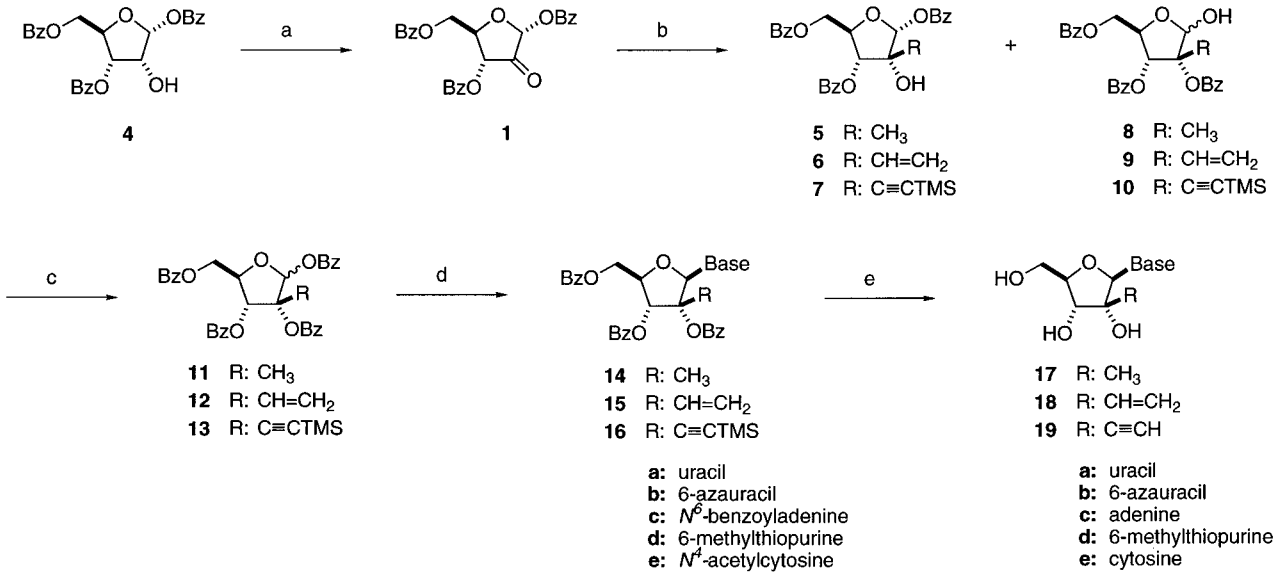
Scheme 2[a]



(a) Dess-Martin periodane (see ref. 7); (b) $MeTiCl_3$ or $RCeCl_2$; (c) BzCl, DMAP, Et_3N; (d) bis(trimethylsilyl)acetamide, pyrimidine (purine), $SnCl_4$ (TMSOTf); (e) NH_3/MeOH

Table 1. ^{13}C NMR Chemical Shifts for Nucleoside Analogues[a]

	nucleobase						ribose					
compound	C4	C2	C6	C5	C8	Me	C1′	C4′	C2′	C3′	C5′	substit
uridine[b]	166.5	152.0	142.2	102.6			89.8	84.6	74.1	69.8	61.1	
17a	166.5	152.0	141.9	102.6			92.1	82.2	79.5	72.8	60.0	19.4
18a	166.2	151.5	141.8	102.5			91.9	82.0	82.0	71.4	59.8	134.6, 119.0
19a	165.5	152.0	141.7	102.4			91.4	82.2	79.3	74.5	59.8	78.1, 76.2
6-azauridine[b]	158.5	149.5		137.3			90.2	84.2	73.2	70.5	61.8	
17b	158.2	149.7		137.4			92.0	83.4	79.9	74.4	62.5	18.6
adenosine[c,d]	149.2	152.6	156.3	119.5	140.2		88.2	86.1	73.7	70.9	61.9	
17c	149.9	153.4	156.9	119.6	139.6		91.7	83.5	79.4	72.6	60.4	20.7
6-MTPR[b,d]	148.8	152.4	161.2	132.1	144.0	12.1	88.7	86.6	74.7	71.1	62.1	
17d	146.4	151.8	162.6	130.2	142.4	11.8	91.7	82.7	79.6	72.5	60.2	19.3
cytidine[b]	158.0	166.5	142.0	96.5			90.7	84.1	74.3	69.6	61.1	
18e	157.7	166.4	141.6	96.5			92.3	82.2	81.8	71.3	60.0	134.9, 118.4
19e	157.9	166.5	141.5	96.5			92.0	81.9	79.9	74.5	59.8	77.8, 76.3

[a] All spectra obtained in D_2O except where noted. [b] Sigma Chemical Co.; MTPR (6-(methylthio)purine riboside). [c] Data from ref 17. [d] Spectrum obtained in DMSO-d_6.

sides **17a** and **17c**. The nucleobase peaks of **17b** and **17d** were virtually identical to those of their respective unmethylated counterparts, indicating that these new compounds were N-1 (**17b**) and N-9 (**17d**) substituted.[17] Also, the peaks belonging to the methylribose portions of **17b** and **17d** were essentially identical to the methylribose moieties of the known **17a** and **17c**, consistent with the stereoassignments for the methyl and nucleobase substituents.

Formation of 2′-*C*-Vinyl- and 2′-*C*-Ethynylribonucleosides Using Organocerium Chemistry. The experiments described above toward 2′-*C*-methylribonucleosides provided a convenient illustration of the potential of our general synthetic route outlined in Scheme 1. Several of the synthetic intermediates and final nucleosides had been previously reported and served to unambiguously identify the products. However, our primary goal was to obtain previously unreported 2′-*C*-vinyl- and 2′-*C*-ethynylribonucleosides. Although organotitanium reagents are useful for adding methyl and other alkyl groups to ketones and aldehydes, they cannot be employed for adding vinyl and ethynyl groups (vinyltitanium compounds, for instance, readily undergo oxidative homocoupling of the alkyl ligands in lieu of addition to carbonyl groups[8]). We therefore explored the utility of organocerium chemistry for this purpose. Organocerium(III) reagents have also been reported to be chemoselective, undergoing efficient addition to aldehydes and ketones in the presence of esters, even with substrates that are susceptible to enolization.[9] Reagents of this type can be formed in situ using Grignard reagents or alkyllithiums in the presence of cerium chloride,[9] and 2′-deoxy-3′-ketonucleosides have been treated with such reagents to form 3′-vinyl- and 3′-ethynyl-substituted nucleosides with complete (α) diastereoselectivity.[18]

Treatment of ketosugar **1** with organocerium reagents derived from vinylmagnesium bromide or lithium (tri-

(17) (a) For ^{13}C NMR correlation studies on N^7- versus N^9-substituted purines, see: Chenon, M.-T.; Pugmire, R. J.; Grant, D. M.; Panzica, R. P.; Townsend, L. B. *J. Am. Chem. Soc.* **1975**, *97*, 4627. (b) For ^{13}C NMR spectra of N^1- versus N^3-methyluracil derivatives, see: Still, I. W.; Plavac, N.; McKinnon, D. M.; Chauhan, M. S. *Can. J. Chem.* **1978**, *56*, 725. (c) N^3-β-D-Pyrimidineribofuranosides also display a characteristic downfield shift of the H-1′ proton of up to 1 ppm compared to that of the N^1- nucleosides (Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1974**, *39*, 3660). All the ^{1}H NMR spectra of 2′-*C*-alkylated pyrimidines **17**−**19** showed H-1′ between 5.9 and 6.1 ppm, consistent with N^1-substitution.

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methylsilyl)acetylide gave a mixture of alkylated products, similar to that observed when $MeMgBr/TiCl_4$ was employed (Scheme 2).[19] Partial chromatographic separation allowed for the tentative assignments of the 1,2-addition products (**6** or **7**) as well as the transesterified anomers (**9** or **10**). In these cases, however, several isomers of partially debenzoylated adducts were also detected. This was unexpected given the reported chemoselectivity of organocerium reagents.[9] While the presence of so many products might be considered scatological, all of these materials converged on the tetrabenzoylated 2-alkylated sugar (**12** or **13**) upon benzoyl chloride/DMAP/Et_3N treatment. Furthermore, the chromatographic cleanup of these various products is not necessary: the two-step procedure of alkylation and benzoylation is accomplished more easily and in good yield (84% and 75% for **12** and **13**, respectively) when the crude intermediate alkylation products were directly benzoylated. The ^1H NMR spectra of the resultant perbenzoylated anomers were compared with the corresponding methyl-substituted sugars α-**11** and β-**11**, and in both cases the β-anomer was tentatively assigned as the major product after benzoylation. For all three perbenzoylated sugars **11**−**13**, the H-3 peak for the major anomer was a doublet of $J \approx 7-8$ Hz, while the corresponding peak for the minor anomer appeared ca. 0.3 ppm upfield as a doublet with $J \approx 2-3$ Hz.

Prior to performing nucleobase couplings (uracil and N^4-acetylcytosine) with **12** and **13**, we suspected that the larger vinyl and ethynyl substituents might compromise the high preference for forming the β-nucleoside observed with the 2-*C*-methyl sugar **11**. This anticipated problem did not occur, however, and the protected β-nucleosides **15a,e** and **16a,e** were obtained in good yields (62−73%). Deprotection provided the desired 2′-*C*-vinyl- and 2′-*C*-ethynyluridines and cytidines **18a,e** and **19a,e**. Again, cross-comparative analysis of the ^{13}C NMR (Table 1)[17b] and ^1H NMR data[17c] of these new compounds with uridine and cytidine and with methyl-substituted **17a**−**d** were consistent with our assigned regio- and stereochemistry.

In conclusion, the methodology described here allows rapid access to 2′-*C*-alkylated ribonucleosides in good overall yields. The incorporation of the unsaturated substituents should provide useful functional handles for obtaining other 2′-*C*-substituted ribonucleosides not readily accessible by direct organometallic addition.[20] We are currently exploring this avenue as well as the conversion of nucleosides **18** and **19** to their respective nucleotide 5′-diphosphates for *in vitro* testing on ribonucleotide reductases.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra (300 and 74.5 MHz, respectively) were recorded on a Bruker ARX-300 instrument. ^{13}C NMR data for compounds **17**−**19** are listed in Table 1. Mass spectra were obtained on an AutoSpecQ hybrid (E_1BE_2qQ) mass spectrometer (VG Fisons, Altrincham, U.K.) using 3-nitrobenzyl alcohol as matrix. Thin-layer chromatography was run on Whatman 250 μm AL SIL G/UV aluminum-backed plates. Flash chromatography was carried out with 70−230 mesh silica gel 60 (EM Science). Starting material 1,3,5-tri-*O*-benzoyl-α-D-ribofuranoside was purchased from Pfanstiel Laboratories, Inc. All other chemicals/reagents were purchased from Aldrich Chemical Co.

1,3,5-Tri-*O*-benzoyl-2-*C*-methyl-α-D-ribofuranose (5) and 2,3,5-Tri-*O*-benzoyl-2-*C*-methyl-α/β-D-ribofuranose (8). $TiCl_4$ (1.91 mL, 3.30 g, 17.4 mmol) was added dropwise to 55 mL of anhydrous ether cooled to −78 °C. To the resultant yellow etherate was slowly added 3.0 M methylmagnesium bromide in ether (5.78 mL, 17.4 mmol); the reaction mixture was then allowed to warm to −30 °C, whereupon a solution of 1,3,5-tri-*O*-benzoyl-2-keto-α-D-ribofuranose (**1**)[21] (2.00 g, 4.35 mmol) in 5 mL of ether was added via syringe. After 4 h at −30 to −10 °C, TLC analysis showed no **1** present, and the reaction mixture was poured into 60 mL of water. The organic phase was separated and the aqueous phase extracted with 3 × 50 mL of ether. The combined organic layer was washed (water), dried ($MgSO_4$), filtered, and concentrated to a syrup, which was passed through silica gel (hexanes/ethyl acetate 5:2) to give two main fractions: 0.85 g of **5** ($R_f = 0.65$) and 0.51 g of an anomeric mixture of **8** ($R_f = 0.45$) for a 66% overall yield. The spectral and/or chromatographic properties of **5** and **8** matched that of previous reports.[5a,b] Further purification was not carried out, and the materials were directly benzoylated to **11** as described below.

1,2,3,5-tetra-*O*-benzoyl-2-*C*-methyl-α-(and β)D-ribofuranose (11). To a solution of 4-(dimethylamino)pyridine (232 mg, 1.89 mmol) in 20 mL of dry CH_2Cl_2 and 3 mL of dry Et_3N was added benzoyl chloride (0.44 mL, 532 mg, 3.78 mmol) followed by a solution of methylsugars **5** (0.39 g, 0.82 mmol) and **8** (0.51 g, 1.07 mmol) in 5 mL of CH_2Cl_2. After 3 h at ambient temperature, the reaction mixture was poured into 150 mL of ether and washed with 3 × 75 mL of 1 N HCl, 75 mL of saturated $NaHCO_3$, and 75 mL of brine. The organic phase was dried (Na_2SO_4), filtered, concentrated to a syrup, and recrystallized from hexanes and ethyl acetate to give 541 mg of pure β-**11**. The mother liquor was concentrated and passed through silica gel (hexane/ethyl acetate 4:1) to afford 254 mg of **11** as a mixture of anomers (α/β ratio ca 2:1 according to ^1H NMR). Overall yield: 795 mg (72%) and α/β ratio ca. 1:4. **β-11:** mp 155−156 °C (lit.[5b] mp 155−156 °C). ^1H NMR ($CDCl_3$): δ 7.15−8.15 (m, 20H), 7.09 (s, 1H), 5.97 (d, J = 8.1 Hz, 1H), 4.80 (m, 1H), 4.70 (dd, J = 4.0, 12.1, 1H), 4.56 (dd, J = 4.7, 12.1, 1H), 1.97 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 16.8, 63.5, 76.1, 78.5, 86.7, 97.8, 128.1, 128.5, 128.6, 129.5, 129.7, 129.9, 132.9, 133.4, 133.6, 133.8, 164.5, 164.7, 165.6, 166.0. MS (FAB): *m/e* 459 (M^+ − OBz). $[\alpha]_D = +69.7°$ (c = 2.925, $CHCl_3$) (lit.[5a] +68°, c = 1, $CHCl_3$). Anal. Calcd for $C_{34}H_{28}O_9 \cdot {}^1/_4H_2O$: C, 69.80; H, 4.91. Found: C, 69.71; H, 4.68. **α-11:** ^1H NMR ($CDCl_3$, diagnostic peaks only): δ 6.85 (s, 1H), 5.70 (d, J = 2 Hz, 1H), 2.00 (s, 3H).

Preparation of Anhydrous Cerium(III) Chloride. A THF slurry of anhydrous $CeCl_3$ was prepared using a slight modification of a procedure described by Bender et al.[18] $CeCl_3 \cdot 7H_2O$ (99.999%) was ground to a fine powder, transferred to 3-necked flask, and heated with an oil bath to 140−160 °C under vaccuum (0.1 mmHg) for at least 2 h. The vessel was purged with N_2 and the oil bath replaced with an ice bath. After the $CeCl_3$ had cooled,[9] the appropriate volume of THF (freshly distilled from benzophenone−ketyl) was slowly added and the resultant slurry stirred overnight.

1,2,3,5-Tetra-*O*-benzoyl-2-*C*-vinyl-α-(and β)D-ribofuranose (12). To a −78 °C suspension of $CeCl_3$ (17.2 g of heptahydrate, 46.2 mmol, dried as described above) in THF (200 mL) was added vinylmagnesium bromide (1 M in THF, 42.6 mL, 42.6 mmol) over 20 min. The mixture was stirred for 1.5 h, whereupon a solution of dried **1**[21] (4.87 g, 10.6 mmol) in 100 mL of THF was transferred in via cannula over 15−20 min. After an additional 30 min, TLC showed no detectable **1**, whereupon the dry ice/acetone bath was removed and 100 mL of saturated NH_4Cl was poured into the reaction mixture. After being allowed to warm to ambient temperature, the

(19) Ketosugar **1** was also treated with $MeMgBr/CeCl_3$ to give results similar to those when $MeMgBr/TiCl_4$ was added to this ketone: a mixture of **5** (major product) and the anomers **8** (minor products).

(20) Functionalized 2′-*C*α-branched 2′-deoxyuridines have recently been reported via the corresponding 2′-*C*α-allylic uridine: Lawrence, A. J.; Pavey, J. B. J.; Cosstick, R.; O'Neil, I. A. *J. Org. Chem.* **1996**, *61*, 9213.

(21) Obtained according to ref 7 and dried with $MgSO_4$ in CH_2Cl_2 overnight.

mixture was filtered through Celite, washing the filtered solid with 3 × 100 mL of ether and 100 mL of saturated NH_4Cl. The organic layer of the filtrate was further extracted with 3 × 100 mL of saturated NH_4Cl, and the combined aqueous phase was washed with 200 mL of ether. The combined organic phases were then dried (Na_2SO_4) and concentrated to provide 5.7 g of a viscous yellow oil. This material was taken up in 250 mL of dry CH_2Cl_2, whereupon 2.50 g (20.5 mmol) of (dimethylamino)pyridine, 4.60 mL (39.6 mmol) of benzoyl chloride, and 25 mL of distilled Et_3N were added. After 4 h, the reaction mixture was worked up as described for **11** to yield 5.27 g of **12** (84% overall from **1**) as a mixture of anomers (α/β ratio ca. 1:4). ^{1}H NMR ($CDCl_3$): δ 4.58 (dd, J = 12.1, 4.7 Hz, 1H, β), 4.70−4.95 (m, 3H, α and β), 5.42 (d, J = 11.3 Hz, 1H, β), 5.48 (d, J = 17.7, 1H, β), 5.54 (d, J = 11.0 Hz, 0.2H, α), 5.80 (d, J = 17.6 Hz, 0.2H, α), 5.87 (d, J = 3.0 Hz, 0.2H, α), 6.29 (d, J = 8.2 Hz, 1H, β), 6.40 (dd, J = 17.6, 11.2, 0.2 H, α), 6.49 (dd, J = 17.7, 11.3 Hz, 1H, β), 7.15−8.30 (m, 27H, α and β). ^{13}C NMR ($CDCl_3$; β peaks only): δ 63.8, 73.8, 78.5, 87.2, 97.2, 119.2, 128.1, 128.6, 129.6, 129.8, 129.9, 130.0, 132.6, 133.6, 133.6, 133.7, 164.2, 164.4, 165.3, 166.0. MS (FAB): *m/e* 471 (M^+ − OBz). Anal. Calcd for $C_{35}H_{28}O_9$: C, 70.94; H, 4.76. Found: C, 70.65; H, 4.96.

1,3,5-Tri-*O*-benzoyl-2-*C*-[(trimethylsilyl)ethynyl]-α-D-ribofuranose (7). To a −78 °C solution of (trimethylsilyl)-acetylene (0.72 mL, 0.50 g, 5.1 mmol) in 25 mL of THF was added *n*-butyllithium (1.6 M in hexanes, 3.12 mL, 5.0 mmol) dropwise over 5 min. After 30 min, the solution was transferred via cannula to a −78 °C suspension of $CeCl_3$ (2.04 g of heptahydrate, 5.48 mmol, dried as described above) in 10 mL of THF dropwise over 10−15 min. After 1.5 h, a solution of **1**[21] (530 mg, 1.15 mmol) in 6 mL of THF was added over 5 min. After another 2 h, there was no detectable **1** by TLC (hexane:EtOAc 7:1). The reaction mixture was quenched and worked up as described for above for **12**. The crude residue was then passed through silica gel (hexane:EtOAc 85:15, then 75:25, then 65:35). The first material off the column was **7** (377 mg, 59%), which crystallized from hexane:EtOAc:CH_2Cl_2. Other fractions from the column were determined by ^{1}H NMR to contain mixtures of other alkylated products (154 mg total): that is, trimethylsilyl protons, sugar ring protons, and benzoyl protons were all present. These other products were combined and benzoylated as described below. **7**: mp 136−138 °C. ^{1}H NMR ($CDCl_3$): δ 0.26 (s, 9H), 3.34 (br s, 1H), 4.70 (m, 2H), 4.88 (m, 1H), 5.58 (d, J = 2.3 Hz, 1H), 6.67 (s, 1H), 7.48 (m, 6H), 7.60 (m, 3H), 8.12 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 0.5, 64.9, 74.0, 76.6, 82.9, 94.5, 99.0, 101.8, 128.3, 129.3, 129.8, 129.9, 133.1, 133.6, 133.7, 164.9, 165.4, 166.0. $[\alpha]_D$ = +23° (*c* 0.665, $CHCl_3$). MS (FAB): *m/e* 559 (M + 1). Anal. Calcd for $C_{31}H_{30}O_8Si$: C, 66.65; H, 5.41. Found: C, 66.57; H, 5.49.

1,2,3,5-Tetra-*O*-benzoyl-2-*C*-trimethylsilyethynyl-α/β-D-ribofuranose (13). Method A. To a solution of **7** (286 mg, 0.51 mmol) in 6 mL of dry CH_2Cl_2 was added 61 mg of 4-(dimethyamino)pyridine (0.50 mmol), 0.115 mL of benzoyl chloride (140 mg, 1.0 mmol), and 0.60 mL of Et_3N. After 3 h, the reaction mixture was worked up as described above for **11** and the residue passed through silica gel (hexane:CH_2Cl_2:EtOAc 19:1:1, then 12:1:1, then 8:1:1). Using this chromatographic procedure, α-**13** and β-**13** were partially separated for analysis. β-**13** was recrystallized from hexane:EtOAc:CH_2Cl_2 to give white needles. Total yield after chromatography: 339 mg (100%). Ratio of α to β: 1:4.

The mixture of other products isolated during the formation of **7** (154 mg) was likewise benzoylated using the same amounts of reagents. After workup and chromatography (hexane:EtOAc:CH_2Cl_2), 170 mg of **13** was isolated as a mixture of anomers (α/β 1:4). Since the starting material for this benzoylation reaction was a mixture of compounds that were not all characterized, a yield for this process could not be calculated; however, the overall yield from **1** was 82%.

Method B. After the organocerium reaction (from 5.3 g, 11.5 mmol of **3**), the crude alkylation products were benzoylated together directly as in method A, except 4 equiv of benzoyl chloride was used. After chromatography, 5.70 g of **13** (75% overall yield from **3**) was isolated. Ratio of α to β: 1:4. **α-13.** ^{1}H NMR ($CDCl_3$): δ 0.26 (s, 9H), 4.75−4.95 (m, 3H), 6.01 (d, J = 2.0 Hz), 7.14 (s, 1H), 7.20−7.65 (m, 12H), 7.45−8.20 (m, 8H). ^{13}C NMR ($CDCl_3$): δ −0.4, 65.0, 75.9, 76.2, 83.1, 96.0, 98.6, 98.8, 128.3, 128.3, 128.4, 128.4, 128.8, 129.0, 129.4, 129.6, 129.8, 129.9, 129.9, 133.1, 133.4, 133.5, 133.6, 163.5, 164.1, 165.0, 166.1. MS (FAB): *m/e* 663 (M + 1), 541 (M^+ − OBz). $[\alpha]_D$ = +18° (*c* 21.75, $CHCl_3$). Anal. Calcd for $C_{38}H_{34}O_9Si$: C, 68.87; H, 5.17. Found: C, 68.82; H, 5.31. ***β*-13:** mp 122−123 °C. ^{1}H NMR ($CDCl_3$): δ 0.11 (s, 9H), 4.65 (m, 1H), 4.81 (m, 2H), 6.42 (d, J = 7.3 Hz, 1H), 7.04 (s, 1H), 7.16 (m, 2H), 7.35−7.70 (m, 10H), 7.97 (m, 2H), 8.17 (m, 6H). ^{13}C NMR ($CDCl_3$): δ −0.6, 63.5, 75.8, 79.1, 79.5, 96.0, 96.2, 97.3, 128.0, 128.4, 128.5, 128.5, 128.8, 129.1, 129.2, 129.4, 129.5, 129.8, 129.8, 130.0, 132.8, 133.5, 133.5, 133.6, 163.5, 164.2, 164.9, 165.9. MS (FAB): *m/e* 663 (M + 1), 459 (M^+ − OBz). $[\alpha]_D$ = +6.4° (*c* 5.365, $CHCl_3$). Anal. Calcd for $C_{38}H_{34}O_9Si$: C, 68.87; H, 5.17. Found: C, 68.63; H, 5.20.

2′,3′,5′-Tri-*O*-benzoyl-2′-*C*-methyluridine (14a). To a suspension of uracil (176 mg, 1.57 mmol) in 5 mL of distilled acetonitrile was added *N*,*O*-bis(trimethylsilyl)acetamide (0.775 mL, 638 mg, 3.14 mmol), and the resultant solution was brought to reflux for 30 min. The solution was allowed to cool to ambient temperature, whereupon a solution of β-**11** (430 mg, 0.74 mmol) in 5 mL of acetonitrile was added. $SnCl_4$ (0.300 mL, 668 mg, 2.56 mmol) was added slowly dropwise, and the reaction mixture was brought to reflux for 3 h. The cooled reaction mixture was then taken up into 200 mL of ethyl acetate and washed with 3 × 125 mL of saturated $NaHCO_3$ and 125 mL of brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated, and the resultant syrup was passed through silica gel (ethyl acetate/hexanes 1:1) to afford 239 mg (57%) of **14a** as a white foam. A small amount was recrystallized from ethyl acetate and hexanes for analytical purposes: mp 201−202 °C (lit.[5c] mp 200−201 °C). ^{1}H NMR ($CDCl_3$): δ 9.12 (br s, 1H), 8.09 (m, 4H), 7.90 (m, 2H), 7.38−7.66 (m, 8H), 7.22−7.36 (m, 2H), 6.55 (s, 1H), 5.79 (d, J = 5.3 Hz, 1H), 5.74 (d, J = 8.2 Hz, 1H), 4.77−4.97 (m, 2H), 4.60−4.71 (m, 1H), 1.78 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 18.0, 63.4, 75.5, 80.4, 84.1, 89.4, 102.4, 128.4, 128.6, 129.5, 129.7, 129.8, 130.0, 133.5, 133.6, 133.7, 140.8, 149.9, 162.8, 165.2, 165.3, 166.2. MS (FAB): *m/e* 571 (M + 1). $[\alpha]_D$ = −23° (*c* 0.315, $CHCl_3$) (lit.[5c] −23°, *c* 1, $CHCl_3$). Anal. Calcd for $C_{31}H_{26}N_2O_9$: C, 65.26; H, 4.59; N, 4.91. Found: C, 65.01; H, 4.47; N, 4.81.

2′,3′,5′-Tri-*O*-benzoyl-2′-*C*-vinyluridine (15a) was prepared according to the procedure described above for the synthesis of **14a** with (a) 110 mg of uracil (0.912 mmol), 0.460 mL of *N*,*O*-bis(trimethylsilyl)acetamide (379 mg, 1.86 mmol) in 4 mL of acetonitrile; (b) 270 mg of **12** (0.456 mmol) in 6 mL of acetonitrile; and (c) 0.170 mL of $SnCl_4$ (378 mg, 1.45 mmol). The reaction mixture was heated to reflux for 3 h, cooled, diluted with 50 mL of EtOAc, and poured into 80 mL of saturated $NaHCO_3$. The mixture was stirred until effervescence ceased and then filtered through Celite, washing the filter cake with 3 × 50 mL of ethyl acetate. The organic layer was separated and the aqueous phase extracted with 2 × 30 mL of ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated, and the residue was passed through silica gel (hexanes/EtOAc 1:1) to provide 164 mg (62%) of **15a**: mp 115−118 °C. ^{1}H NMR ($CDCl_3$): δ 9.6 (br s, 1H), 8.11 (m, 4H), 7.86 (m, 2H), 7.20−7.70 (m, 10H), 6.66 (s, 1H), 6.13 (dd, J = 17.5, 11.1 Hz, 1H), 6.06 (d, J = 5.2, 1H), 5.64 (dd, J = 8.2, 2.0 Hz, 1H), 5.45 (two d, J = 17.6, 11.1 Hz, 2H), 4.95 (dd, J = 12.3, 3.2 Hz, 1H), 4.82 (dd, J = 12.3, 5.7 Hz, 1H), 4.66 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 63.5, 73.8, 81.2, 85.8, 89.6, 102.3, 120.9, 128.8, 128.9, 129.0, 129.1, 130.1, 130.2, 130.5, 131.0, 133.9, 134.0, 134.1, 141.4, 150.1, 162.7, 164.9, 165.5, 166.6. MS (FAB): *m/e* 583 (M + 1). $[\alpha]_D$ = −21° (*c* 0.230, $CHCl_3$). Anal. Calcd for $C_{32}H_{26}N_2O_9$: C, 65.98; H, 4.50; N, 4.81. Found: C, 65.98; H, 4.45; N, 4.79.

***N*⁴-Acetyl-2′,3′,5′-tri-*O*-benzoyl-2′-*C*-vinylcytidine (15e)** was prepared according to the procedure described above for the synthesis of **14a** with (a) 260 mg of N^4-acetylcytosine (1.70 mmol), 0.83 mL of *N*,*O*-bis(trimethylsilyl)acetamide (683 mg, 3.36 mmol) in 4 mL of acetonitrile; (b) 440 mg of **12** (0.743 mmol) in 6 mL of acetonitrile; and (c) 0.400 mL of $SnCl_4$ (890 mg, 3.42 mmol). The reaction mixture was heated to reflux

for 15 min and then cooled to ambient temperature. After 3 h, the mixture was worked up as described above for **15a**, and the resulting residue was passed through silica gel (hexanes/EtOAc/EtOH 5:4:1) to provide 300 mg (65%) of **15e**: mp 128−129 °C. ^{1}H NMR ($CDCl_3$): δ 10.63 (br s, 1H), 8.10 (m, 4H), 7.82 (m, 3H), 7.10−7.65 (m, 10H), 6.85 (br s, 1H), 6.06 (m, 2H), 5.33 (two d, J = 17.4, 11.4 Hz, 2H), 4.90 (m, 2H), 4.73 (m, 1H), 2.30 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 25.3, 63.6, 74.1, 81.4, 86.1, 90.0 (br), 96.9, 120.4, 128.7, 128.8, 128.9, 129.0, 130.1, 130.2, 130.5, 133.9, 134.0, 134.1, 146.1, 155.1, 163.8, 164.9, 165.4, 166.6, 171.8. MS (FAB): *m/e* 624 (M + 1). $[\alpha]_D = -35°$ (*c* 1.05, $CHCl_3$). Anal. Calcd for $C_{34}H_{29}N_3O_9$: C, 65.48; H, 4.69; N, 6.74. Found: C, 65.50; H, 4.77; N, 6.86.

2′,3′,5′-Tri-*O*-benzoyl-2′-*C*-[(trimethylsilyl)ethynyl]uridine (16a) was prepared according to the procedure described above for the synthesis of **14a** with (a) 319 mg of uracil (2.85 mmol), 1.40 mL of *N*,*O*-bis(trimethylsilyl)acetamide (1.15 g, 5.66 mmol) in 5 mL of acetonitrile; (b) 925 g of **13** (1.39 mmol) in 5 mL of acetonitrile; and (c) 0.700 mL of $SnCl_4$ (1.56 g, 5.98 mmol). The reaction mixture was quenched and extracted as described above for **15a**. The combined organic layers were further washed with 3 × 50 mL of saturated $NaHCO_3$ and 50 mL of brine, dried (Na_2SO_4), filtered, and concentrated, and the residue was passed through silica gel (hexanes/EtOAc 3:2 followed by 1:1) to provide 562 mg (62%) of **16a**: mp 160−161 °C. ^{1}H NMR ($CDCl_3$): δ 8.70 (br s, 1H), 8.13 (m, 4H), 7.92 (d, J = 8.3 Hz, 1H), 7.85 (m, 2H), 7.40−7.65 (m, 8H), 7.27 (m, 2H), 6.73 (s, 1H), 5.99 (d, J = 2.1 Hz, 1H), 5.80 (d, J = 8.2 Hz, 1H), 5.15 (dd, J = 11.6, 8.7 Hz, 1H), 4.75 (dd, J = 11.6, 4.0 Hz, 1H), 4.67 (m, 1H), 0.23 (s, 9H). ^{13}C NMR ($CDCl_3$): δ −0.3, 64.3, 76.3, 77.9, 82.6, 87.6, 96.8, 100.7, 101.7, 128.7, 128.8, 128.9, 129.0, 130.0, 130.2, 130.3, 130.6, 133.7, 134.1, 141.5, 150.4, 163.1, 164.1, 165.1, 166.5. MS (FAB): *m/e* 653 (M + 1). $[\alpha]_D$ = +11° (*c* 0.96, $CHCl_3$). Anal. Calcd for $C_{35}H_{32}N_2O_9Si$: C, 64.40; H, 4.94; N, 4.29. Found: C, 64.29; H, 4.98; N, 4.35.

***N*^{4}-Acetyl-2′,3′,5′-tri-*O*-benzoyl-2′-*C*-[(trimethylsilyl)ethynyl]cytidine (16e)** was prepared according to the procedure described above for the synthesis of **14a** with (a) 933 mg of *N*^{4}-acetylcytosine (6.10 mmol), 3.00 mL of *N*,*O*-bis(trimethylsilyl)acetamide (2.47 g, 12.1 mmol) in 6 mL of acetonitrile; (b) 1.88 g of **13** (2.84 mmol) in 10 mL of acetonitrile; and (c) 1.43 mL of $SnCl_4$ (3.18 g, 12.1 mmol). The reaction mixture was heated to reflux for 3.5 h, whereupon the mixture was worked up as described above for **16a** and the residue passed through silica gel (hexanes/EtOAc 3:2 followed by 1:1) to provide 1.43 g (73%) of **16e**: mp 130−131 °C. ^{1}H NMR ($CDCl_3$): δ 8.77 (br s, 1H), 8.26 (d, J = 7.6 Hz, 1H), 8.13 (m, 4H), 7.85 (m, 2H), 7.65−7.38 (m, 9H), 7.24 (d, J = 7.6 Hz, 1H), 7.00 (s, 1H), 6.01 (d, J = 1.7 Hz, 1H), 5.21 (dd, J = 11.4, 8.7 Hz, 1H), 4.80−4.64 (m, 2H), 2.27 (s, 3H), 0.23 (s, 9H). ^{13}C NMR ($CDCl_3$): δ −0.3, 25.4, 64.4, 76.5, 78.7, 82.8, 87.9, 96.6, 96.9, 100.9, 128.8, 128.9, 129.0, 130.0, 130.2, 130.3, 130.7, 133.7, 134.0, 134.1, 146.4, 155.2, 163.8, 164.3, 165.2, 166.5, 171.6. MS (FAB): *m/e* 694 (M + 1). $[\alpha]_D = -12.1°$ (*c* 0.54, $CHCl_3$). Anal. Calcd for $C_{37}H_{35}N_3O_9Si$: C, 64.06; H, 5.08; N, 6.06. Found: C, 63.75; H, 4.97; N, 5.70.

2′-*C*-Methyluridine (17a). An ice-cold solution of 199 mg (0.349 mmol) of **14a** in 40 mL of methanol was saturated with ammonia gas and the vessel stoppered. After 2 days, the solvent was removed and the residue was taken up in 15 mL of water and washed with 3 × 15 mL of CH_2Cl_2 and 15 mL of ether. The aqueous phase was concentrated, residual water being removed via ethanol azeotrope, and the resulting material was passed through silica gel (ethyl acetate/methanol 9:1 followed by 4:1) to afford 78 mg (87%) of **17a** as a white solid: mp 101−103 °C (lit.[5d] softened at 101 °C). ^{1}H NMR ($CDCl_3$): δ 7.82 (d, J = 8.0 Hz, 1H), 5.92 (s, 1H), 5.81 (d, J = 8.1 Hz, 1H), 3.93 (m, 2H), 3.76 (m, 2H), 1.11 (s, 3H). MS (FAB): *m/e* 259 (M + 1). $[\alpha]_D = +84.9°$ (*c* 0.695, H_2O) (lit.[5d] +82°, *c* 0.7, H_2O). Anal. Calcd for $C_{10}H_{14}N_2O_6 \cdot {}^2/_3H_2O$: C, 44.45; H, 5.72; N, 10.37. Found: C, 44.74; H, 5.84; N, 10.10.

2′-*C*-Vinyluridine (18a). Deprotection of 164 mg of **15a** (0.28 mmol) in methanolic ammonia for 24 h was followed by removal of solvent in vacuo. The residue was redissolved in water (20 mL) and washed with 3 × 20 mL of CCl_4. The aqueous layer was concentrated and the residue passed through silica gel (EtOAc/MeOH 9:1 followed by 4:1) to give 70 mg (90%) of **18a**: mp 173−174 °C. ^{1}H NMR (D_2O): δ 7.88 (d, J = 8.1 Hz, 1H), 5.90 (s, 1H), 5.81 (d, J = 8.1 Hz, 1H), 5.64 (dd, J = 17.3, 10.8 Hz, 1H), 5.32 (two d, J = 17.3, 10.6 Hz, 2H), 4.15 (d, J = 9.4 Hz, 1H), 4.00 (m, 2H), 3.83 (dd, J = 13.1, 3.7 Hz, 1H). MS (FAB): *m/e* 271 (M + 1). $[\alpha]_D = +82°$ (*c* 0.505, MeOH). Anal. Calcd for $C_{11}H_{14}N_2O_6$: C, 48.89; H, 5.22; N, 10.37. Found: C, 48.73; H, 5.22; N, 10.28.

2′-*C*-Vinylcytidine (18e). Deprotection of 577 mg of **15e** (0.93 mmol) and workup was as described above for **18a**. The resultant residue was passed through silica gel (EtOAc/MeOH 4:1 followed by 2:1) to give 243 mg (83%) of **18e**: mp 202−204 °C. ^{1}H NMR (D_2O): δ 7.80 (d, J = 7.6 Hz, 1H), 5.95 (m, 2H), 5.53 (dd, J = 17.3, 10.8 Hz, 1H), 5.28 (d, J = 16.7, 1H), 5.18 (d, J = 10.9 Hz, 1H), 4.11 (d, J = 9.4 Hz, 1H), 4.00 (m, 2H), 3.80 (dd, J = 13.0, 3.7 Hz, 1H). ^{13}C NMR (D_2O): δ 60.0, 71.4, 81.8, 82.2, 92.3, 96.5, 118.5, 134.9, 141.6, 157.7, 166.3. MS (FAB): *m/e* 270 (M + 1). $[\alpha]_D = +94°$ (*c* 0.48, MeOH). Anal. Calcd for $C_{11}H_{15}N_3O_5 \cdot H_2O$ C, 45.99; H, 5.96; N, 14.63. Found: C, 46.28; H, 5.86; N, 14.49.

2′-*C*-Ethynyluridine (19a). Deprotection of 511 mg of **16a** (0.78 mmol) and workup was as described above for **18a**, except the reaction ran for 2 days. The resultant residue was passed through silica gel (EtOAc followed by EtOAc/MeOH 9:1) to give 210 mg (91%) of **19a**: mp 161−162 °C. ^{1}H NMR (D_2O): δ 7.95 (d, J = 8.1 Hz, 1H), 6.04 (s, 1H), 5.89 (d, J = 8.1 Hz, 1H), 4.22 (d, J = 9.1 Hz, 1H), 4.02 (m, 2H), 3.83 (dd, J = 13.4, 4.4 Hz, 1H), 3.03 (s, 1H, slowly exchanges). MS (FAB): *m/e* 269 (M + 1). $[\alpha]_D$ = +124° (*c* 0.505, MeOH). Anal. Calcd for $C_{11}H_{12}N_2O_6$: C, 49.26; H, 4.51; N, 10.44. Found: C, 49.56; H, 4.52; N, 10.35.

2′-*C*-Ethynylcytidine (19e). Deprotection of 670 mg of **16e** (0.97 mmol) and workup was as described above for **18a**, except the reaction ran for 2 days. The resultant residue was passed through silica gel (EtOAc/MeOH 5:2) to give 234 mg (91%) of **19e**. Recrystallization from EtOH provided an analytically pure sample: mp 233−234 °C dec. ^{1}H NMR (D_2O): δ 2.85 (s, 1H, slowly exchanges), 3.75 (dd, J = 3.9, 13.0 Hz, 1H), 3.95 (m, 2H), 4.11 (d, J = 9.2 Hz, 1H), 5.96 (d, J = 7.6 Hz, 1H), 6.01 (s, 1H), 7.78 (d, J = 7.6 Hz, 1H). MS (FAB): *m/e* 268 (M + 1). $[\alpha]_D$ = +162° (*c* 0.25, MeOH). Anal. Calcd for $C_{11}H_{13}N_3O_5$: C, 49.44; H, 4.90; N, 15.72. Found: C, 49.17; H, 4.81; N, 15.36.

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Supporting Information Available: Full spectral and analytical data for compounds **14b**−**d** and **17b**−**d** (3 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.

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