Diastereofacial Selective Addition of Ethynylcerium Reagent and Barton−McCombie Reaction as the Key Steps for the Synthesis of *C*-3′-Ethynylribonucleosides and of *C*-3′-Ethynyl-2′-deoxyribonucleosides†

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We describe the preparation of 3′-alkynyluridine **4a** and -adenosine **4b** and of 3′-alkynyl-2′-deoxyuridine **16a** and -adenosine **16b** starting from the corresponding nucleosides. The desired stereochemistry of the C-3′ tertiary alcohol was obtained by reaction of an ethynylcerium−lithium reagent on a 3′-ketonucleoside with the hydroxyl group at C-5′ unprotected. The 2′-deoxygenation was performed by a Barton−McCombie reaction under appropriate conditions where the addition of tin hydride to the triple bond was suppressed. Evaluation of the anti-HIV activity of the C-3′ modified nucleosides is reported.

AIDS has stimulated the chemist's interest on the synthesis of nucleosides and analogues designed as antiretroviral drugs.[1] Numerous modified nucleosides and 2′-deoxynucleosides show marked activities as antiviral agents. For example, C-3′-methylribonucleosides and C-3′-methyl-2′-deoxyribonucleosides have shown biological activities on RNA and DNA polymerases.[2] The substitution of the hydrogen atom in the C-3′ position with preservation of the natural stereochemistry of the hydroxyl is an attractive target, since these compounds could interfere with the biosynthesis of nucleic acids. On one hand, C-3′-branched deoxynucleotides could act as slow substrates or inhibitors of HIV reverse transcriptase during viral DNA chain elongation. On the other hand, the single strand of viral DNA, where C-3′-branched deoxynucleosides have been incorporated, could show anomalous properties.[3]

The preparation of C-3′-branched nucleosides could be envisaged essentially in three different approaches. First, the C-3′ substituent is introduced on the sugar prior to the base. Starting from D-glucose, control of stereochemistry at C-1′ and at C-3′ proved to be easy.[4] However, this approach suffered some disadvantages as the preparation was multistep and the overall yield was modest. The synthetic route from 2-deoxy-D-ribose suffered from the lack of stereochemical control at the C-3′ and C-1′ positions.[3e] In the second approach, the C-nucleophile is added to the corresponding 3′-ketonucleoside or 3′-keto-2′-deoxynucleoside. However, previous studies showed a preferential nucleophilic attack from the α face giving the tertiary alcohol as the major or as the sole product with the configuration opposite of the 3′ hydroxyl group of the natural nucleoside.[5] Third, taking advantage of the preference for α attack, one may introduce the hydroxyl group last as realized by Jørgensen et al.[6] The 3′-keto-2′-deoxynucleoside was converted into a C-3′-methylidene derivative. Dihydroxylation of the double bond occurred from the α face and furnished stereospecifically the desired C-3′-branched-2′-deoxynucleoside.

Initially, we envisioned the use of 2′-deoxynucleosides as starting materials. The problems associated with this synthetic route are 2-fold:[5] the instability of intermediate ketone and the stereoselectivity of nucleophilic addition. The low basicity of the Yamamoto's reagent[7,8] and the reversal of the stereoselectivity of nucleophilic addition in its presence should circumvent these problems. However, with this reagent the desired compound was never

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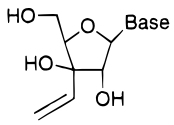
obtained. Only the α,β-unsaturated ketone resulting from the elimination of the base was observed. As an alternative, we decided to use the less sensitive 3′-ketonucleosides as starting material.

In a preliminary publication,[9] we have described the highly stereoselective addition of an alkynylcerium reagent to 3′-ketonucleosides, affording the C-3′-alkynylnucleosides with the required stereochemistry. Therefore, the key advantage of our approach is that the addition directly affords C-3′-ethynylated nucleosides in which the 3′-hydroxyl group remains in the natural configuration. Other organocerium reagents, for example, the methyl and vinylcerium reagents, were also tested on 3′-ketonucleosides, but the stereoselectivity and the yields were low.[10] Since our first publication,[9] a different route to C-3′-ethynyl nucleosides[11] and a general method for the preparation of 1,3-diols by addition of cerium reagents to sensitive β-hydroxy ketones have been described.[12] Here we present details of the preparation of C-3′-alkynylnucleosides and their transformation into the corresponding 2′-deoxyderivatives by Barton−McCombie reaction.[13]

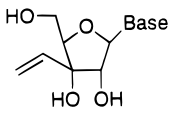
The synthesis of C-3′-alkynyluridine **4a** and -adenosine **4b** started with 2′,5′-bis-O-TBDMS-3′-ketonucleosides **1a** and **1b** prepared as reported in the literature.[14] Selective monodeprotection at O-5′ of the disilyl ethers **1a** and **1b** was done with trifluoroacetic acid−water (9:1) at 0 °C, as described for the preparation of ketone **2b.**[15]

The organolithium reagent was prepared by the reaction of 1 equiv of BuLi with (trimethylsilyl)acetylene in THF at low temperature. The ethynylcerium−lithium was prepared as described by Imamoto[16] by mixing the lithium acetylide with "dry cerium trichloride".[17] The effect of the reagent ratio (lithium acetylide/cerium chloride = 1/1, 2/1, and 3/1)[18] on the yield and the selectivity of the organocerium addition to hydroxy ketone **2a** and **2b** was investigated. The best results in respect of yield and diastereoselectivity were obtained with a 1/1 mixture of lithium acetylide and cerium chloride.[9,18] The addition with a 6-fold excess[5b] of ethynylcerium−lithium reagent to ketones **2a** and **2b** was highly stereoselective, and only a trace amount of the other diastereomer was detected by TLC. A similar control of addition of alkynylcerium−lithium reagent prepared with a large excess of a 2/1 mixture of lithium acetylide and cerium chloride on a β-hydroxy ketone has been described by Shibasaki *et al.*[19] in preparation of phorbol derivates. The reason for stereochemical control was explained by chelation effects.[19] The cerium reagent R_2CeCl reacted first with the hydroxyl group and then delivered the nucleophile syn to the alkoxy group. Since we tried a 2/1 ratio of lithium acetylide and cerium chloride and obtained poorer stereoselectivity than with a 1/1 ratio, the mechanism proposed by Shibasaki where a 2/1 ratio was best has been ruled out. However, a 6-fold excess of reagents was used under our experimental conditions. Therefore, the preparation of the cerium reagent does not exclude that a dialkynylcerium species formed in situ, especially when, as observed by Denmark et al.,[18] cerium salts remained in the precipitate resulting in its preparation. Therefore, the formulas $RCeCl_2$ and R_2CeCl according to the reagent ratio do not describe satisfactorily the structure of the reagents.

The ribofuranosyl derivatives **3a** and **3b** were isolated in 78 and 72% yields from **1a** and **1b**, respectively. The relative configuration of product **3a** was determined by X-ray crystallographic analysis.[20] The ribo configuration of product **3b** was established by chemical modification, NMR experiments,[9] and comparison with the ribo derivative **3a**. It confirmed earlier assignments based on NMR experiments of the xylo and ribo vinyl derivatives.[9] The xylo compounds **5a** and **5b** have been prepared by addition of the vinyl Grignard reagent on a appropriate 3′-keto nucleoside. The ribo compounds **6a** and **6b** have been obtained after semihydrogenation of the corresponding propargylic alcohol.



xylo **5a,b**



ribo **6a,b**

From the crystallographic structure of product **3a**, the following observations could be made. The pyrimidine ring was in an anti conformation (−ac) around the glycosidic bond. The O5′ was in a gauche$^+$ orientation (+sc). The C-3′-ethynyl uridine **3a** showed a south conformation[21] (P = 169°). The furanose ring was in a C2′ endo conformation, resulting in the pseudoequatorial orientation of the alkynyl substituent and the pyrimidine base. In this case, the conformation in the crystal corresponded to predominant conformation in solution as observed by NMR. The large coupling constant $J_{1'2'}$ of C-3′ methyl and ethynyl compounds is indicative of a C2′ endo conformation.[5c]

Removal of the silyl ethers of **3a** and **3b** using Bu_4NF in THF afforded the triols **4a** and **4b** in good yield.

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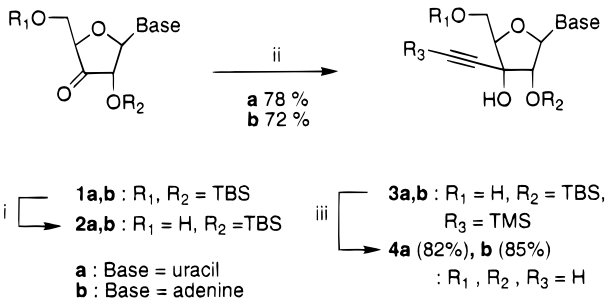
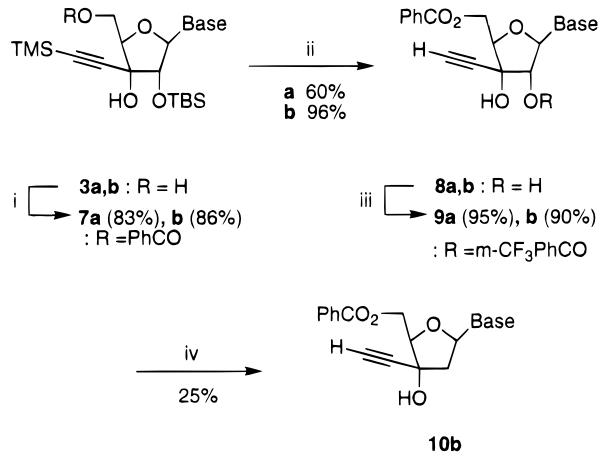
Scheme 1[a]



[a] Key: (i) $CF_3CO_2H{\cdot}H_2O$, 4 °C; (ii) $Me_3SiC{\equiv}CLi/CeCl_3$, THF, −78 °C; (iii) Bu_4NF, THF.

Scheme 2[a]



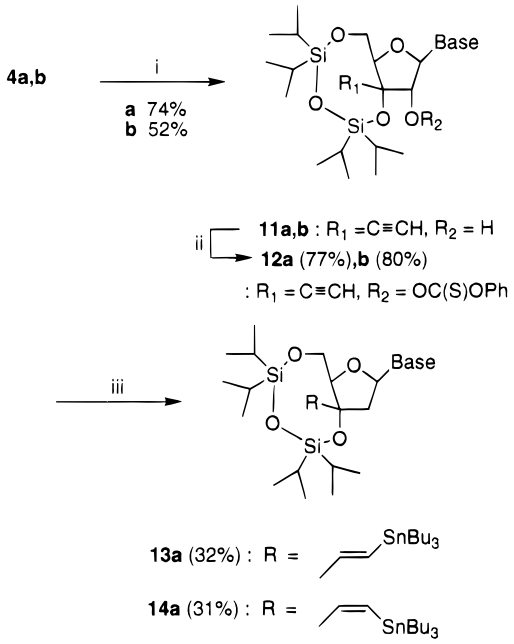
[a] Key: (i) PhCOCl, Py, −10 °C to rt; (ii) Bu_4NF, THF; (iii) *m*-$CF_3PhCOCl$, $DMAP_{cat}$, Py; (iv) *m*-methylcarbazole, *hν*, *i*-$PrOH{\cdot}H_2O$.

The next important step was the C-2′ deoxygenation of the 3′-alkynyl nucleosides **4a** and **4b** to their corresponding 2′-deoxy analogues. In an initial attempt, we tried to apply the photochemical method to the 2′-deoxygenation of products **3a** and **3b** as it has been described for the deoxygenation of nucleosides.[22]

Selective benzoylation of the primary alcohol of products **3a** and **3b** in cold pyridine by reaction with benzoyl chloride was achieved in good yield. The silyl ether group at C-2′ of products **7a** and **7b** was removed by treatment with Bu_4NF. After reaction of the benzoates **8a** and **8b** with (trifluoromethyl)benzoyl chloride in the presence of a catalytic amount of (dimethylamino)pyridine, the photoactive compounds **9a** and **9b** were obtained in overall yields of 47% and 74%, respectively. In our hands, irradiation of compounds **9a** and **9b** in the presence of *N*-methylcarbazole in a mixture of 2-propanol and water gave no deoxygenated compound and the deoxygenated compound **10b** in a low yield of 25%, respectively. Faced with the difficulties encountered during the photoreaction of the uridine derivative, we decided to explore the Barton−McCombie reaction [13] (Scheme 3) applied efficiently to the reduction of nucleosides.[23]

The reaction of **8b** with phenoxy(thiocarbonyl) chloride did not give the expected phenoxy(thiocarbonate), but instead gave the cyclic O-2′ and O-3′ thiocarbonate.

Scheme 3[a]



[a] Key: (i) TIPSCl, Py, and $NEt(iPr)_2$; (ii) PhOC(S)Cl, DMAP; (iii) Bu_3SnH, AIBN, toluene, 75 °C.

Therefore, it was necessary to protect the 3′ hydroxyl. The 3′,5′-protected nucleosides **11a** and **11b** were prepared in 74 and 52% yield, respectively, by reaction of **4a** and **4b** with 1,3-dichlorotetraisopropyldisiloxane (TIPSCl_2)[24] in pyridine in presence of Hünig's base. The reaction of compounds **11a** and **11b** with phenoxy(thiocarbonyl) chloride gave thionocarbonates **12a** and **12b** in good yield. When **12a** was treated under standard conditions (a solution of **12a**, AIBN, and Bu_3SnH in toluene was heated at 75 °C for 3 h) two major compounds **13a** and **14a** were isolated in 1/1 ratio in a 63% total yield. Their structure corresponded to the deoxygenation at the C-2′ position and to the cis and trans addition of tin hydride to the triple bond. The addition of a stannyl radical to a triple bond has been shown to be a reversible reaction[25] and the rather slow reduction of the vinylic stannylic radical to be dependent on the concentration of tin hydride.[25b] By contrast, the reduction of the thionocarbonate is apparently independent of the concentration of Bu_3SnH.[23] A low concentration of tin hydride might disfavor the addition of the stannyl hydride on to the triple bond and, therefore, might favor the formation of deoxy compounds **15a** and **15b**. Indeed, treatment of thionocarbonates**12a** and **12b** by a slow addition of tin hydride and AIBN afforded the deoxy compounds **15a** and **15b** in a 40 and 60% yield, respectively (Scheme 4). Under these conditions, none of the vinyltin adducts were produced. However, reduction of compound **12a** furnished a 1/1 mixture of the desired compound **15a** and unreacted starting material along with a complex mixture of byproducts as evidenced by ^1H NMR of the crude extract. Attempts to improve the yield of compound **15a** failed. The silyl protecting group

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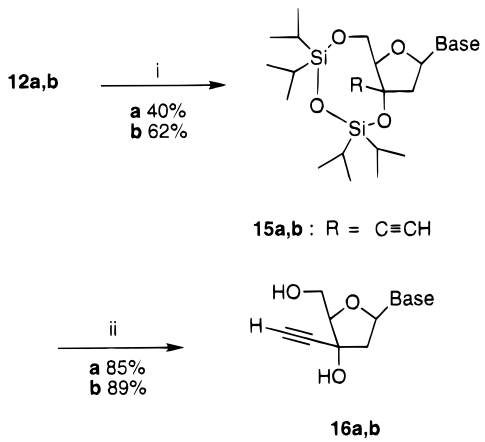
Scheme 4[a]



[a] Key: (i) slow addition of Bu_3SnH, AIBN, toluene, 75 °C; (ii) Bu_4NF, THF.

was removed with Bu_4NF to give the deoxynucleosides **16a** and **16b** in good yield.

To study the influence of the ethynyl function on the stability of oligonucleotides[26] where C-3′-ethynyluridine **16a** has been incorporated, we attempted to prepare the corresponding phosphoramidite building block. The reaction of the deoxynucleoside **16a** with dimethoxytrityl chloride gave the corresponding nucleoside protected on the 5′-position. The reaction of this compound with chloro(2-cyanoethoxy)(diisopropylamino)phosphane did not give the corresponding phosphoramidite under standard conditions.[6] Our results were in contrast to the results of others[6,27] who do not mention any problem in the preparation of the phosphoramidite building blocks with even more hindered 3′ tertiary alcohols. That this reaction did not occur was indicative of a lower reactivity of the tertiary alcohol presumably due to the electronic nature of the ethynyl group[28] at C-3′.

The anti-HIV activity of compounds **4a**,**b**, **5a**,**b**, and **16a**,**b** was evaluated on human T-cells CEM-SS infected by HIV-1 LAI. IC_{50} (μM)/CC_{50} (μM) of 0.0009/0.6 for **4a**, 0.006/0.03 for **4b**, 10/100 for **5a**, 900/500 for **5b**, 90/60 for **16a**, 70/80 for **16b**, and 0.001/>1 for AZT were determined. The most potent compound of this series, C-3′-ethynyluridine **4a**, was as active as AZT but with a lower selectivity index. However, its evaluation on human T-cells MT4 infected by HIV-1 IIIB showed no protection whereas cytoxicity was still observed, CC_{50} of 0.05 μM.[29]

Experimental Section

Material and Methods. Melting points were measured on a Reichert microscope and were uncorrected. $[\alpha]_D$ were measured on a Perkin-Elmer 241MC polarimeter. UV spectra were measured on a Hewlett-Packard 8451A. IR spectra were recorded on a Perkin-Elmer 881 or a Bruker FT IFS25. NMR spectra were recorded on a Brucker SY (200 or 400 M Hz) apparatus. For ^{1}H NMR the residual proton signal of the deuterated solvent was used as an internal reference: for $CDCl_3$ (δ = 7.26 ppm), DMSO-d_6 (δ = 2.50), MeOD-d_4 (δ = 3.30), and acetone-d_6 (δ = 2.05). For ^{13}C NMR, the ^{13}C signal of the deuterated solvent was used as an internal reference; for $CDCl_3$ (δ = 76.9 ppm, central signal), DMSO-d_6 (39.46), MeOD-d_4 (40.02). The chemical shifts are reported in ppm downfield from TMS. MS were measured on a LKB 9000S apparatus by electronic impact (EI, 70 eV), on a Trio 2000 (FISONS, UK) apparatus by chemical ionization (CI), or on a ZAB (FISONS, UK) apparatus by fast atom bombardment (FAB, matrix nitrobenzyl alcohol). Microanalyses were performed by the Strasbourg Division or by the Service Central de Microanalyses of the CNRS at Vernaison.

Unless otherwise indicated, all reagents were obtained from commercial suppliers and were used without purification. All experiments sensitive to air and/or to moisture were carried out under an argon atmosphere in oven-dried (120 °C) glassware assembled under a stream of argon. Anhydrous solvents were freshly distilled before use: tetrahydrofuran from sodium benzophenone ketyl radical, pyridine, diisopropylethylamine, and benzene from CaH_2. Analytical thin-layer chromatography was performed on silica gel precoated TLC plates (Merck, 60, F254) or on reversed phase C-18 precoated TLC plates (Merck, HPTLC RP-18, F254S). Products were isolated by flash chromatography on silica gel (Merck, 60, 230−400 mesh).

General Procedure for the Selective Deprotection of 2′,5′-*O*-Bis-TBDMS-ketonucleosides. To prepare the unstable hydroxy ketones **2a** and **2b** on 1 g scale, the solvent evaporation had to be done in a short time since longer times gave impure products of **2a** and **2b**. A solution of compound **1a** or **1b** (2.13 mmol) in a mixture of CF_3COOH (15.7 mL) and of H_2O (1.8 mL) was stirred for 30 min at 0 °C. The yellow solution was poured into a mixture of AcOEt (300 mL), cyclohexane (200 mL), and an aqueous saturated $NaHCO_3$ solution (250 mL). The phases were separated. The aqueous phase was extracted with a mixture of AcOEt (300 mL) and cyclohexane (200 mL). The combined organic phase was washed with H_2O (30 mL), dried over Na_2SO_4, and filtered. The solvents were removed in vacuo in a 500 mL flask at 0 °C. When the volume was reduced to about 250 mL, cyclohexane was added, and further evaporation gave a white solid. The unstable hydroxy ketones were used directly without further purification.

1-[2-*O*-(*tert*-Butyldimethylsilyl)-*β*-D-*erythro*-pentofuran-3-ulosyl]uracil (2a): IR (KBr) 1788 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.17 (s, 1 H), 7.48 (d, J = 8 Hz, 1 H), 5.84 (dd, J_1 = 2 Hz, J_2 = 8 Hz, 1 H), 5.72 (d, J = 8 Hz, 1 H), 4.71 (d, J = 8 Hz, 1 H), 4.26 (m, 1 H), 3.94 (m, 2 H), 0.85 (s, 9 H), 0.13 (s, 3 H), 0.04 (s, 3 H); MS (70 eV) 357 (2), 299 (45), 75 (100).

9-[2-*O*-(*tert*-Butyldimethylsilyl)-*β*-D-*erythro*-pentofuran-3-ulosyl]adenine (2b): IR (KBr) 1782 cm^{-1}; ^{1}H NMR (lit.[15c]).

1-[2-*O*-(*tert*-Butyldimethylsilyl)-3-*C*-[(trimethylsilyl)-ethynyl]-*β*-D-*ribo*-pentofuranosyl]uracil (3a). $CeCl_3 \cdot 7H_2O$ (4.76 g, 12.7 mmol) was dried at 140 °C under vacuum (1 mmHg) for 4 h. The resulting powder was cooled under argon. Dry THF (20 mL) was added, and the suspension was stirred overnight. Independently, a solution of lithium acetylide was prepared as follows: to a solution of (trimethylsilyl)acetylene (1.29 g, 13 mmol) at −78 °C in dry THF (20 mL) was added BuLi (8.24 mL, 13.2 mmol) in hexane (1.6 M). The reaction temperature was raised to −20 °C over a 1 h period. The lithium acetylide solution was cooled to −78 °C and added, via a cannula, to the dry $CeCl_3$ suspension at the same temperature (prepared above). The mixture was stirred for 1 h, and a cooled solution (−78 °C) of **2a** (0.76 g, 2.1 mmol) in THF (20 mL) was rapidly added via a cannula. After 3 h at −78 °C, glacial acetic acid (1.8 mL) was added. Over a period of 1 h, the temperature was raised to 20 °C. The mixture was poured in an aqueous phosphate buffer solution (2 M, pH 7). The aqueous phase was extracted with AcOEt (3 × 200 mL). The combined organic layers were dried over Na_2SO_4, filtered,

(26) Ikehara, M.; Ohtasaka, E.; Uesugi, S.; Tanaka, T. *Chem. Nucleosides Nucleotides* **1988**, *1*, 283−367.

(27) Tarköy, M.; Leumann, C. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1432−1434.

(28) One of the reasons we have been interested by the ethynyl group, relative to alkyl and alkenyl groups, is its high electronegativity, which is larger than a chloride atom and comparable to a cyano group. By electron withdrawing, the ethynyl group might lower the nucleophilicity of the 3′ tertiary alcohol; see: Wells, P. R. *Prog. Phys. Org. Chem.* **1966**, *6*, 111−145.

(29) Because of its important cytoxicity, compound **4a** was retained for subsequent investigations upon a panel of cultured malignant cells. Matsuda and his collaborators have described the high potent antitumor activity of compound **4a** against human tumor cells in vitro and in vivo; see ref 11 and: Weltin, D.; Jung, P. M. J.; Holl, V.; Dauvergne, J.; Burger, A.; Dufour, P.; Aubertin, A. M.; Bischoff, P.; Biellmann J. F. Submitted for publication.

and evaporated in vacuo. The residue was chromatographed (silica gel: ether−hexane 6:4) to give a white solid **3a** (0.74 g, 78% yield in two steps): mp 187−188 °C; $[\alpha]^{25}_D$ +47 (*c* 1, $CHCl_3$); UV ($CHCl_3$) λ_{max} 262 nm (ϵ 10 300); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.38 (s, 1 H), 7.76 (d, J = 8 Hz, 1 H), 5.88 (d, J = 7 Hz, 1 H), 5.79 (d, J = 8 Hz, 1H), 4.44 (d, J = 7 Hz, 1 H), 4.19 (m, 1 H), 3.95 (m, 2 H), 3.31 (s, 1 H), 2.38 (s, 1 H), 0.80 (s, 9 H), 0.14 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 162.7, 150.8, 140.6, 104.4, 102.3, 90.5, 86.8, 85.5, 79.1, 73.0, 61.4, 25.4, 17.6, −0.4, −4.3, −5.3; MS (EI) *m*/*z* 397 (100), 342 (8), 285 (34), 255 (26). Anal. Calcd for $C_{20}H_{34}O_6N_2Si_2$: C, 52.86; H, 7.49; N, 6.17. Found: C, 52.80; H, 7.68; N, 5.94.

9-[2-*O*-(*tert*-Butyldimethylsilyl)-3-*C*-[(trimethylsilyl)-ethynyl]-*β*-D-*ribo*-pentofuranosyl]adenine (3b). Preparation of **3b** from **2b** has been achieved using the method as described for **3a**. Chromatography (silica gel: ether−hexane 7:3) afforded **3b** (72% yield in two steps): mp 204 °C; $[\alpha]^{22}_D$ −32 (*c* 1.2, $CHCl_3$); UV ($CHCl_3$) λ_{max} 262 nm (ϵ 12 300); IR (KBr) 3348, 2958, 2160, 1642 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.38 (s, 1 H), 7.77 (s, 1 H), 6.48 (t, 1 H), 5.74 (d, J = 8 Hz, 1 H), 5.64 (s, 2 H), 5.16 (d, J = 8 Hz, 1 H), 4.29 (m, 1 H), 4.98 (m, 2 H), 3.23 (s, 1 H), 0.81 (s, 9 H), 0.2 (s, 9 H), 0.0 (s, 3 H), −0.48 (s, 3 H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 156.2, 152.3, 148.9, 140.3, 119.5, 104.5, 90.3, 88.0, 86.6, 78.5, 73.1, 61.9, 25.3, 17.4, −0.3, −4.5, −5.7; MS (FAB) *m*/*z* 478 (100), 462 (5), 420 (12). Anal. Calcd for $C_{21}H_{35}O_4N_5Si_2$: C, 52.83; H, 7.34; N, 14.68. Found: C, 52.56; H, 7.35; N, 14.45.

1-(3-*C*-Ethynyl-*β*-D-*ribo*-pentofuranosyl)uracil (4a). Bu_4NF (1.22 g, 3.9 mmol) was added to a solution of **3a** (0.80 g, 1.7 mmol) in THF (32 mL) at 20 °C. After 30 min of stirring, the solvent was evaporated *in vacuo*. The crude product was dissolved in a minimum of acetone and was filtered through a short column of silica gel with acetone as eluent. The residue was purified by trituration with ethanol to give pure **4a** (0.39 g, 82% yield) with identical spectral data as reported:[11] mp 224 °C (lit.[11] mp 226−228 °C); $[\alpha]^{24}_D$ +44 (*c* 1.1, MeOH); UV (MeOH) λ_{max} 262 nm (ϵ 9600); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 163.0, 150.9, 140.8, 102.0, 86.5, 85.9, 82.7, 77.7, 77.0, 72.6, 61.3. Anal. Calcd for $C_{11}H_{12}O_6N_2$: C, 49.25; H, 4.48; N, 10.45. Found: C, 49.50; H, 4.70; N, 10.23.

1-(3-*C*-Ethynyl-*β*-D-*ribo*-pentofuranosyl)adenine (4b). Preparation of **4b** from **3b** has been achieved using the method as described for **4a**. The residue was washed with ethanol to give **4b** (85% yield) with identical spectral data as reported: [11]: mp 139−140 °C (lit.[11] mp 149−152 °C); $[\alpha]^{24}_D$ −31 (*c* 0.6, H_2O); UV(MeOH) λ_{max} 262 nm (ϵ 16 300); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 156.1, 152.3, 149.1, 140.3, 119.3, 87.8, 86.7, 82.7, 77.5, 76.9, 72.8, 61.9. Anal. Calcd for $C_{12}H_{13}O_4N_5 \cdot H_2O$: C, 46.60; H, 4.85; N, 22.65. Found: C, 46.97; H, 4.57; N, 22.72.

9-[5-*O*-Benzoyl-2-*O*-(*tert*-butyldimethylsilyl)-3-[(trimethylsilyl)ethynyl]-*β*-D-*ribo*-pentofuranosyl]adenine (7b). Benzoyl chloride (0.24 g, 1.7 mmol) was added to a solution of **3b** (0.75 g, 1.57 mmol) in dry pyridine (14 mL) at −10 °C. The temperature was allowed to raise to rt, and the solution was stirred further for 2 h. Water (10 mL) was then added and the aqueous phase extracted with chloroform (2 × 20 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. Chromatography (silica gel: ether−hexane 7:3) afforded **7b** (0.79 g, 86% yield): mp 176−178 °C; IR (KBr) 2960, 2176, 1723, 1651 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.17 (s, 1 H), 8.14 (m, 3 H), 7.53 (m, 3 H), 5.97 (d, J = 7 Hz, 1 H), 5.51 (s, 2 H), 5.30 (d, J = 7 Hz, 1 H), 5.73 (m, 2 H), 4.55 (m, 1 H), 3.37 (s, 1 H), 0.78 (s, 9 H), 0.06 (s, 12 H), −0.34 (s, 3 H); MS (70 eV) 581 (10), 566 (45), 524 (100).

9-(5-*O*-Benzoyl-3-ethynyl-*β*-D-*ribo*-pentofuranosyl)adenine (8b). Bu_4NF (0.933 g, 2.9 mmol) was added to a solution of compound **7b** (0.72 g, 1.23 mmol) in THF (29 mL). The solution was stirred at rt for 30 min, and then the solvent was evaporated *in vacuo*. The residue was dissolved in a minimum of acetone and chromatographed (silica gel: ethyl acetate−acetone 7:3) to give a white solid (0.46 g, 96% yield): mp 147−150 °C; $[\alpha]^{24}_D$ −28 (*c* 1.5, DMSO); UV (MeOH) λ_{max} 234, 262 nm (ϵ 14 900, 15 700); IR (KBr) 2100, 1724, 1664, 1604 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.31 (s, 1 H), 8.07 (s, 1 H), 7.99 (m, 2 H), 7.60 (m, 3 H), 7.30 (s, 2 H), 6.33 (s, 1 H); 6.01 (d, J = 8 Hz, 1 H), 5.90 (d, J = 8 Hz, 1 H), 5.10 (t, J = 8 Hz, 1 H), 4.61 (m, 2 H), 4.33 (m, 1 H), 3.70 (s, 1 H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 165.0, 156.0, 152.6, 149.5, 139.9, 133.3, 129.1, 129.4, 128.7, 119.1, 85.8, 83.7, 82.0, 77.5, 76.8, 72.3, 64.9. Anal. Calcd for $C_{19}H_{17}O_5N_5$: C, 57.72; H, 4.33; N, 17.71. Found: C, 57.60; H, 4.41; N, 17.67.

9-(5-*O*-Benzoyl-3-ethynyl-2-*O*-[*m*-(trifluoromethyl)benzoyl]-*β*-D-*ribo*-pentofuranosyl)adenine (9b). Product **8b** (0.20 g, 0.51 mmol) and DMAP (2.5 mg, 0.02 mmol) were dissolved in dry pyridine (10 mL). The solution was cooled to 0 °C, and *m*-(trifluoromethyl)benzoyl chloride (90 μL, 0.61 mmol) was added. The solution was stirred at rt for 3 h. Water (4 mL) was then added and the aqueous phase extracted with ether (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was chromatographed (silica gel: ethyl acetate−acetone 99:1) to afford a white solid **9b** (0.25 g, 90% yield): mp 212 °C dec; IR (KBr) 2097, 1733, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.29 (m, 3 H), 8.01 (m, 3 H), 7.70 (m, 4 H), 7.34 (s, 2 H), 7.17 (s, 1 H), 6.44 (d, J = 7 Hz, 1 H), 6.36 (d, J = 7 Hz, 1 H), 4.76 (m, 2 H), 4.56 (m, 1 H), 3.89 (s, 1 H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 165.5, 163.4, 156.0, 152.7, 149.3, 139.3, 133.8, 130.1, 129.2, 128.7, 126.3, 119.0, 84.5, 84.0, 80.2, 78.9, 78.2, 71.8, 64.9. Anal. Calcd for $C_{27}H_{20}O_6N_5F_3$: C, 57.15; H, 3.55; N, 12.34. Found: C, 57.01; H, 3.67; N, 12.30.

9-(5-*O*-Benzoyl-3-ethynyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)adenine (10b). To a solution of **9b** (0.10 g, 0.17 mmol) under argon in a 1:10 mixture of water and 2-propanol (152 mL) was added *N*-methylcarbazol (0.04 g, 0.19 mmol). The resulting solution was irradiated with a UV lamp (125 W) for 13 h. The solvents were evaporated *in vacuo*, and the residue was purified by preparative TLC (silica gel). Elution with a solution of chloroform and methanol (96:4) afforded the desired compound **10b** (0.016 g, 25% yield): mp 98 °C; IR (KBr) 2927, 1719, 1642 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.35 (s, 1 H), 8.08 (s, 1 H), 8.00 (m, 2 H), 7.57 (m, 1 H), 7.45 (m, 2 H), 6.57 (dd, J_1 = 7.5 Hz, J_2 = 6 Hz, 1 H), 5, 70 (s, 2 H), 4.73 (m, 2 H), 4.50 (m, 1 H), 2.98 (m, 1 H), 2.76 (s, 1 H); MS (70 eV) 379 (100), 361 (7), 279 (100).

1-[3-*C*-Ethynyl-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1, 3-diyl)-*β*-D-*ribo*-pentofuranosyl]uracil (11a). To a solution of **4a** (0.20 g, 0.75 mmol) in dry pyridine (12 mL) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (0.25 mL, 0.82 mmol). The solution was stirred overnight, and dry $NEt(^iPr)_2$ (0.74 mL, 7.5 mmol) was added. The solution was stirred further for 2 h, and the solvents were evaporated in vacuo. The residue was filtered quickly over a short column of silica gel (silica gel:ether). Evaporation of the solvent gave a slightly yellow compound (0.28 g, 74% yield). The unstable compound **11a** showed a single spot on TLC and was used without further purification: mp 98−99 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.4 (s, 1 H), 7.46 (d, J = 8 Hz, 1 H), 5.81 (d, J = 2 Hz, 1 H), 5.71 (d, J = 8 Hz, 1 H), 4.37 (m, 1 H), 4.17 (m, 3 H), 3.21 (s, 1 H), 2.86 (s, 1 H), 1.08 (m, 28 H); MS (70 eV) 511 (100), 467 (10).

9-(3-*C*-Ethynyl-3, 5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-*β*-D-*ribo*-pentofuranosyl)adenine (11b). Preparation of **11b** from **4b** has been achieved using the method as described for **11a.** The residue was dissolved in a small volume of ethyl acetate and precipitated by addition of hexane to give **11b** (52% yield). The unstable product was sufficiently pure to be used directly in the next step: mp 275−279 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.40 (s, 1 H), 8.04 (s, 1 H), 6.08 (d, J = 2 Hz, 1 H), 5.57 (s, 2 H), 4.52 (t, J = 2 Hz, 1 H), 4.42 (m, 1 H), 4.19 (m, 2 H), 3.37 (d, J = 2 Hz, 1 H), 2.81 (s, 1 H), 1.08 (m, 28 H); MS (CI) 534 (2), 410 (100).

1-[3-*C*-Ethynyl-2-*O*-[phenoxy(thiocarbonyl)]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1, 3-diyl)-*β*-D-*ribo*-pentofuranosyl]uracil (12a). Phenyl thionocarbonate chloride (98 μL, 0.7 mmol) was added to a solution of **11a** (0.31 g, 0.6 mmol) and DMAP (0.16 g, 1.3 mmol) in dry acetonitrile (12 mL) under argon. The solution was stirred for 2 h, and the solvent was evaporated in vacuo. The residue was partitioned between AcOEt (44 mL) and H_2O (15 mL). The organic phase and the aqueous phase were separated, and the aqueous phase was extracted with AcOEt (3 × 40 mL). The combined organic phases were dried over Na_2SO_4 and evaporated in vacuo. The

residue was dissolved in the minimum amount of $CHCl_3$ and chromatographed on silica gel (ether−hexane 4:6) to afford **12a** (0.3 g, 77% yield). The unstable product was sufficiently pure to be used directly in the next step: mp 73−80 °C; IR (KBr) 2949, 2100, 1691, 1288 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.0 (s, 1 H), 7.42 (m, 5 H), 7.13 (m, 1 H), 6.07 (d, J = 2 Hz, 1 H), 6.04 (d, J = 2 Hz, 1 H), 5.75 (d, J = 8 Hz, 1 H), 4.44 (m, 1 H), 4.19 (m, 3 H), 2.92 (s, 1 H), 1.07 (m, 28 H); MS (CI, NH_3) 603 (0.5), 573 (0.6).

9-[3-*C*-Ethynyl-2-*O*-[phenoxy(thiocarbonyl)]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1, 3-diyl)-β-D-*ribo*-pentofuranosyl]adenine (12b). Phenyl thionocarbonate chloride (22 μL, 0.16 mmol) was added to a solution of **11b** (0.08 g, 0.15 mmol) and DMAP (0.04 g, 0.32 mmol) in dry dichloromethane (3 mL). The solution was stirred for 2 h, and water (30 mL) was added. The aqueous phase was extracted with dichloromethane (2 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was dissolved in dichloromethane and applied on preparative TLC plates (silica gel: ether−hexane 6:4) to give **12b** (0.08 g, 80% yield). The unstable product was sufficiently pure to be used directly in the next step: mp 218−220 °C; IR (KBr) 2950, 2109, 1678, 1221 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.39 (s, 1 H), 8.16 (s, 1 H), 7.37 (m, 3 H), 7.13 (m, 2 H), 6.39 (d, J = 2 Hz, 1 H), 6.38 (d, J = 2 Hz, 1 H), 5.61 (s, 2 H), 4.49 (m, 1 H), 4.23 (m, 2 H), 2.91 (s, 1 H), 1.13 (m, 28 H); MS (CI, CH_4) 698.7 (0.7), 670.4 (9), 136 (4%), 94 (100).

(*E*)- and (*Z*)-1-[3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-3-[(tributylstannyl)vinyl]-2-deoxy-β-D-*erythro*-pentofuranosyl]uracil (13a) and (14a). A degassed solution of **12a** (0.12 g, 0.18 mmol), Bu_3SnH (0.1 mL, 0.39 mmol), and AIBN (0.01 g, 0.05 mmol) in toluene (5 mL) under argon was heated for 3 h. After evaporation of the solvent, the crude product was chromatographed on analytical TLC plates (silica gel: chloroform−ethanol 99:1) to afford **13a** (32% yield) and **14a** (31% yield).

(*E*)-Olefinic derivative 13a: oil; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.63 (s, 1 H), 7.31 (d, J = 8 Hz, 1 H), 6.36 (d, J = 19 Hz, 1 H), 6.07 (m, 2 H), 5.70 (bd, J = 8 Hz, 1 H), 4.16 (m, 2 H), 3.83 (m, 1 H), 2.55 (m, 2 H), 1.36−1.03 (m, 55 H); MS (FAB) 809 (17), 787 (18), 729 (100).

(*Z*)-Olefinic derivative 14a: mp 145−185 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.49 (s, 1 H), 7.43 (d, J = 8 Hz, 1 H), 6.00 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1 H), 5.75 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 1 H), 5.62 (d, J = 11 Hz, 1 H), 5.29 (d, J = 11 Hz, 1 H), 4.00 (m, 3 H), 2.81 (m, 1 H), 2.21 (m, 1 H), 1.03 (m, 55 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.1, 150.1, 140.1, 138.9, 126.9, 102.2, 86.3, 82.7, 79.9, 60.9, 48.9, 25.7, 29.9, 17.2, 16.6, 13.6, 13.1, 12.3; MS (FAB) 809 (20), 729 (100).

1-[3-*C*-Ethynyl-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2-deoxy-β-D-*erythro*-pentofuranosyl]uracil (15a). A degassed solution of Bu_3SnH (83 μL, 0.31 mmol) and AIBN (0.01 g, 0.08 mmol) in toluene (1 mL) under argon was added with a syringe pump over a 4 h period to a degassed solution of **12a** (0.18 g, 0.28 mmol) in toluene (6 mL) under argon. After evaporation of the solvent, the residue was filtered through a short column of silica gel (ether). The resulting mixture of products was further purified by C-18 HPLC (acetonitrile−water 9:1) to give **15a** (0.06 g, 40% yield). Alternatively, the mixture of products was treated with Bu_4NF in THF, and the resulting crude product was chromatographed on analytical TLC plates (silica gel: acetone−ethyl acetate 1:9) to furnish the final compound **16a** in a comparable yield: mp 163 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.23 (s, 1 H), 7.54 (d, J = 4 Hz, 1 H), 6.13 (dd, J_1 = 8 Hz, J_2 = 3 Hz, 1 H), 5.71 (d, J = 4 Hz, 1 H), 4.36 (m, 1 H), 4.00 (m, 2 H), 2.82 (s, 1 H), 2.77 (m, 2 H), 1.08 (m, 28 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.3, 150.3, 139.8, 101.8, 86.8, 83.9, 81.9, 78.9, 73.81, 62.12, 50.6, 17.5, 17.4, 17.3, 17.26, 14.4, 13.4, 12.8; MS (ID) 451 (13), 339 (15), 105 (100).

9-[3-*C*-Ethynyl-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2-deoxy-β-D-*erythro*-pentofuranosyl]adenine (15b). Preparation of **15b** from **12b** has been achieved using the method as described for **15a**. Chromatography (silica gel: chloroform−ethyl acetate 3:7) afforded **15b** (60% yield): mp 241−244 °C; IR (KBr) 2940, 2107 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.36 (s, 1 H), 8.15 (s, 1 H), 6.39 (dd, J_1 = 6 Hz, J_2 = 5.5 Hz,1 H), 5.61 (s, 2 H), 4.39 (m, 1 H), 4.11 (m, 2 H), 3.02 (m, 2 H), 2.79 (s, 1 H), 1.05 (m, 28 H); MS (FAB^+) 518 (100), 474 (50).

1-(3-*C*-Ethynyl-2-deoxy-β-D-*erythro*-pentofuranosyl)uracil (16a). Bu_4NF (0.04 g, 0.13 mmol) was added to a solution of **15a** (0.03 g, 0.06 mmol) in THF (3 mL). The solution was stirred for 2 h, and the solvent was evaporated in vacuo. The crude product, dissolved in a minimum of acetone, was filtered through a short column of silica gel (acetone). After evaporation of the solvent, the residue was purified by trituration with acetone to give **16a** (0.01 g, 85% yield): mp 205−207 °C; IR (KBr) 2940, 2113, 1653 cm^{-1}; $[\alpha]^{24}_D$ +79 (*c* 0.7, MeOH); UV (MeOH) λ_{max} 262 nm (ϵ 9600); ^1H NMR (acetone-d_6, 200 MHz) δ 9.95 (s, 1 H), 8.15 (d, J = 8 Hz, 1 H), 6.35 (dd, J_1 = 8 Hz, J_2 = 6 Hz, 1 H), 5.61 (d, J = 8 Hz, 1 H), 5.24 (s, 1 H), 4.20 (dd, J_1 = J_2 = 5 Hz,1 H), 4.06 (m, 1 H), 3.91 (m, 2 H), 3.20 (s, 1 H), 2.52 (m, 2 H); ^1H NMR (MeOD-d_4, 200 MHz) δ 9.89 (s, 1 H), 8.10 (d, J = 8 Hz, 1 H), 6.26 (dd, J_1 = 8 Hz, J_2 = 6 Hz,1 H), 5.70 (d, J = 8 Hz, 1 H), 3.98 (m, 1 H), 3.87 (m, 2 H), 3.12 (s, 1 H), 2.45 (m, 2 H); ^{13}C NMR (MeOD-d_4, 100 MHz) δ 166.2, 152.2, 142.6, 102.6, 90.0, 85.8, 76.8, 73.4, 63.4, 47.5; MS (FAB) 505.1 (15), 275.1 (35), 253 (100). Anal. Calcd for $C_{11}H_{12}N_2O_5 \cdot 1/3H_2O$: C, 51.16; H, 4.90; N, 10.85. Found: C, 51.37; H, 4.90; N, 10.92.

9-(3-*C*-Ethynyl-2-deoxy-β-D-*erythro*-pentofuranosyl)adenine (16b). Preparation of **16b** from **15b** has been achieved using the method as described for **16a**. The residue was washed with chloroform to give **16b** (89% yield): mp 131−133 °C; IR (KBr) 2095, 1645 cm^{-1}; $[\alpha]^{24}_D$ −8 (*c* 1.3, MeOH); UV (MeOH) λ_{max} 262 nm (ϵ 15 400); ^1H NMR (acetone-$_{d6}$, 200 MHz) δ 8.25 (s, 1 H), 8.18 (s, 1 H), 6.71 (s, 2 H), 6.44 (dd, J_1 = 9.5 Hz, J_2 = 5 Hz, 1 H), 5.66 (dd, J_1 = 8.5 Hz, J_2 = 4 Hz, 1 H), 5.26 (s, 1 H), 4.13 (m, 1 H), 3.90 (m, 2 H), 3.18 (dd, J_1 = 12.5 Hz, J_2 = 9.5 Hz, 1 H), 3.17 (s, 1 H), 2.59 (dd, J_1 = 12.5 Hz, J_2 = 5 Hz, 1 H). Anal. Calcd for $C_{12}H_{13}O_3N_5 \cdot 1/2H_2O$: C, 50.70; H, 4.60; N, 24.65. Found: C, 50.41; H, 4.66; N, 24.48.

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Supporting Information Available: Ortep plot of one molecule of **3a** with the labeling scheme used. Experimental details and spectroscopic characteristics of **5a**, **5b**, **6a**, **6b** and of the intermediates for their preparation and of **7a**, **8a**, and **9a** (7 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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