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Simon M. N. Efange^a; Yung-Chi Cheng^b; Thomas J. Bardos^a

^a Department of Medicinal Chemistry, State University of New York at Buffalo, Amherst, N.Y. ^b Department of Pharmacology, University of North Carolina, North Carolina Chapel Hill

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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF 2-PYRIMIDINONE NUCLEOSIDES.

III.^{1,2} 5-ALKYNYL-2-PYRIMIDINONE 2'-DEOXYRIBOSIDES.

Simon M.N. Efang^a, Yung-Chi Cheng^b and Thomas J. Bardos^{*a}

^aDepartment of Medicinal Chemistry, State University of New York at Buffalo, Amherst, N.Y. 14260, ^bDepartment of Pharmacology, University of North Carolina, Chapel Hill, North Carolina, 27514.

Abstract: The syntheses of 5-ethynyl-, 5-phenylethynyl- and 5-propynyl-2(1H)-pyrimidinone 2'-deoxyribosides are described. Two of the new nucleosides, 14 a and 14 c, showed significant antiviral activities against HSV-1 and HSV-2 in tissue culture.

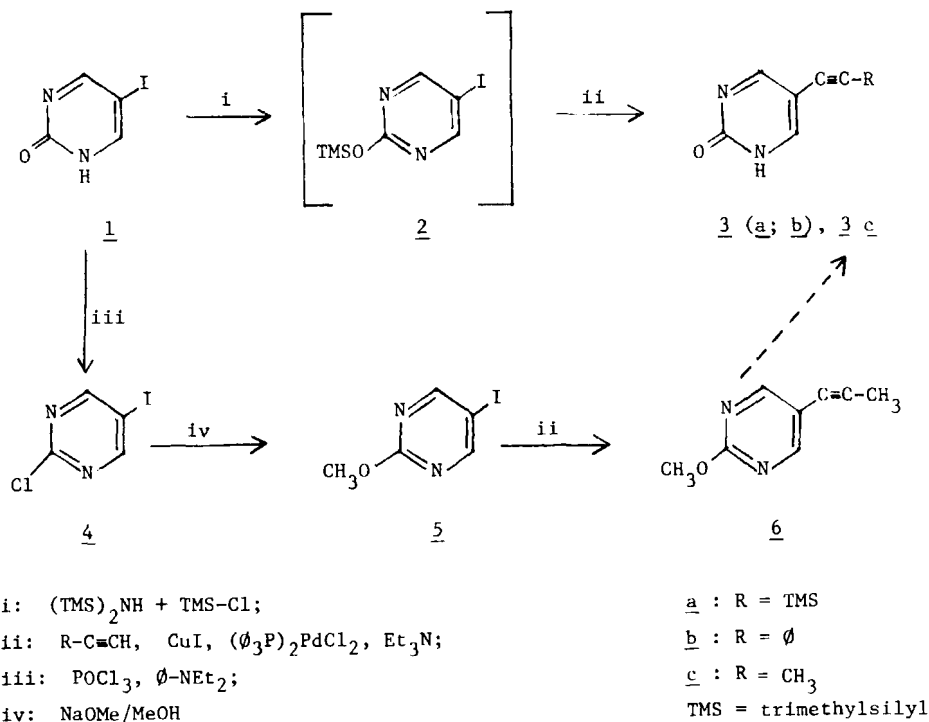
Previous work in our laboratory led to the discovery of the selective inhibitory activities of certain 5-substituted-2-pyrimidinone 2'-deoxyribosides (notably the 5-methylmercapto-, 5-iodo-, and 5-bromo- derivatives) against the Herpes simplex virus type 1 and type 2, at concentrations which are non-toxic to human cells.^{1,2} These 2-pyrimidinone nucleosides appear to have the advantage over the corresponding 5-substituted 2'-deoxyuridines and 2'-deoxycytidines in that they are resistant to degradation by either thymidine phosphorylase³ or cytidine deaminase. For this reason, the synthesis of the 2-pyrimidinone analogues of other uracil and cytosine nucleosides known to have antiherpes activity has been undertaken. The present paper deals with the synthesis and properties of the 2'-deoxyribosides of several 5-alkynyl-2-pyrimidinones.

Although 5-iodopyrimidine nucleosides have been coupled with terminal alkynes to give the corresponding 5-(1-alkynyl)nucleosides in good to excellent yields,⁴⁻⁶ the relatively poor stability and yields obtained in the synthesis of 1-[3,5-di-O-(p-chlorobenzoyl)-2-deoxy-β-D-ribofuranosyl]-5-iodo-2-pyrimidinone,² (12), advised against the use of the latter as the starting material in the early experiments aimed at the synthesis of the title compounds. The pyrimidine bases 3a, 3b, and 6 were therefore synthesized to be used as the corresponding 2-O-alkyl or-silyl derivatives for coupling in Hilbert-Johnson type reactions with the protected halogenose.

Compound 3a, 5-(2-trimethylsilylethynyl)-2(1H)-pyrimidinone, was obtained in 77% yield, by stirring 5-iodo-2-trimethylsilyloxy pyrimidine, 2, with CuI, (Ø₃P)₂PdCl₂ and trimethylsilylacetylene, in dry triethylamine

In an analogous manner, 5-(2-phenylethynyl)-2(1H)-pyrimidinone, 3b, was obtained in 36% yield. Attempts to synthesize 5-(1-propynyl)-2(1H)-pyrimidinone, 3c, in a similar manner were unsuccessful, presumably because the cold liquid propyne (obtained by cooling gaseous propyne with Dry ice acetone), when introduced into the mixture, caused a drastic lowering of the reaction temperature thereby impeding the progress of the reaction. An alternative scheme was therefore used. The stable 2-O-methyl intermediate 5 was synthesized in 56% overall yield, from 5-iodo-2(1H)-pyrimidinone, 1, via the known 2-chloro derivative 4.⁷ 2-Methoxy-5-(1-propynyl)-pyrimidine, 6, was obtained in 77% yield, by shaking a mixture of 5, CuI and $(\phi_3P)_2PdCl_2$ in dry triethylamine under 20-30 psi of propyne (Scheme 1).

Silylation of 3a in the usual manner gave 5-(2-trimethylsilylethynyl)-2-trimethylsilyloxy pyrimidine, 7a, which was condensed, in the presence of a catalytic amount of $SnCl_4$, with 3,5-di-O-(p-chlorobenzoyl)-2-deoxy- α -D-ribofuranosyl chloride,⁸ 8, to yield the α and β anomers of the blocked nucleoside, 9a (14%) and 10a (12%), respectively. The assignment of anomeric configuration of these and subsequent structures is based on NMR data. Treatment of the α anomer, 9a, with fluoride anion, in an attempt to remove the trimethylsilyl



SCHEME 1

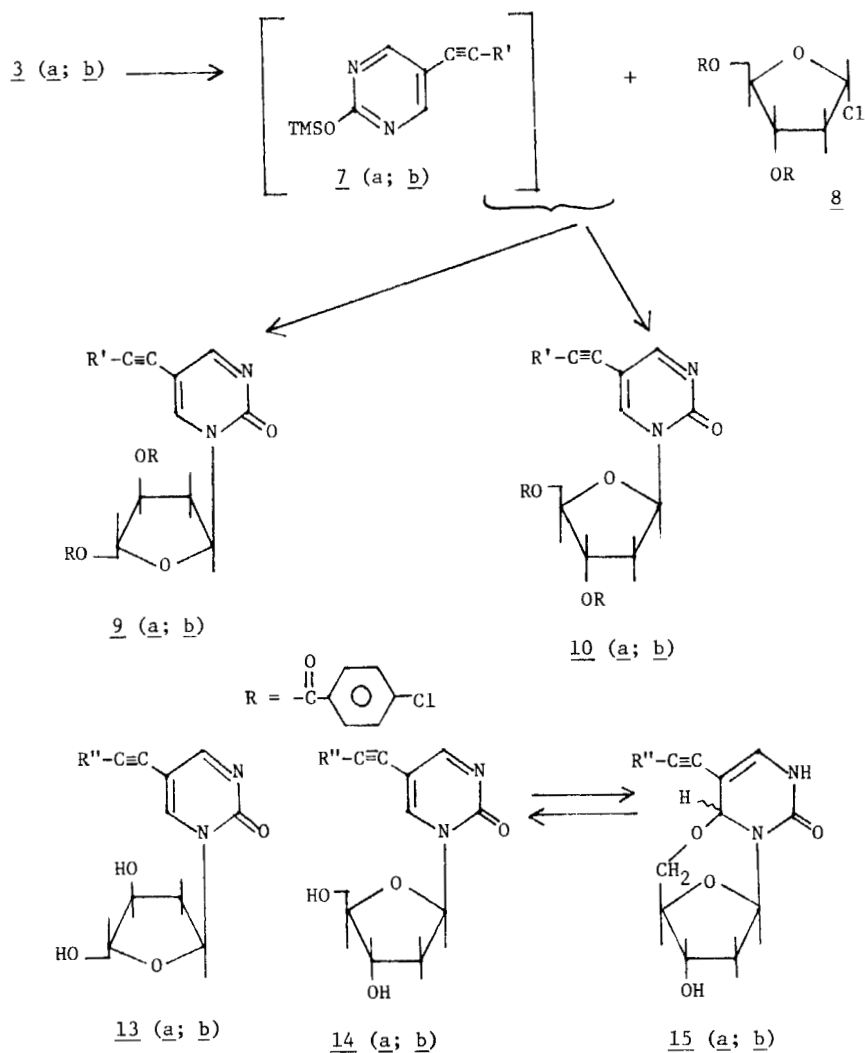
group of the alkynyl substituent, resulted in the destruction of the pyrimidine ring; similar results have been obtained by other investigators.⁹ The target nucleoside, 1-(2-deoxy- β -D-ribofuranosyl)-5-ethynyl-2-pyrimidinone, 14a, was obtained by the treatment of the blocked β -anomer, 10a, with cold dry methanolic ammonia. The NMR spectrum of this compound (in DMSO- d_6 + D_2O) shows a triplet at δ 6.03 (for the anomeric proton) and two doublets at δ 8.63 and 8.73 (for H-6 and H-4, respectively); these data are consistent with the structure 14a. In addition, there are the following signals: a) a singlet at δ 5.04 (for H-6), b) a doublet of doublets at δ 5.82 (for the anomeric proton), and c) a singlet at δ 6.65 (for H-4). This second set of signals is consistent with the cyclonucleoside structure 15a. Such adduct formation was also seen in the case of the β -anomers of 5-halo-2-pyrimidinone-2'-deoxyribosides.² Calculations from the NMR spectrum indicate that the 5-ethynyl-2-pyrimidinone- β -2'-deoxyriboside has been obtained as a mixture of the "open" form 14a and the cycloadduct 15a in approximately a 1:1 ratio. Additional evidence could be obtained from the NMR spectrum of the α anomer, 13a.

5-(2-Phenylethynyl)-2-trimethylsilyloxypyrimidine, 7b, prepared by silylation of 3b, was condensed with halogenose 8 (using $SnCl_4$ as a catalyst) in a similar manner as described above, to yield the anomeric blocked nucleosides 10b (49%) and 9b (40%). The β anomer, 10b, was subsequently deblocked with methanolic ammonia. The NMR spectrum of the product obtained after deblocking indicates a singlet at δ 5.52 (for H-6), a doublet of doublets at δ 5.85 (for the anomeric proton), a doublet at δ 6.75 (for H-4) which becomes a singlet on the addition of D_2O , and a doublet (exchangeable) at δ 9.50 (for N^3-H). This pattern is indicative of the cyclonucleoside structure 15b. There is no evidence of the presence of the "open" form 14b.

Although the predominance of the cycloadduct 15b may reflect the increased electron withdrawing capacity of the C^5 -substituent, as seen in the case of the 5-bromo vs. 5-iodo derivative,² the increased exposure to methanolic ammonia may also be implicated because the deblocking reaction for 10b was run over a much longer period than was for the deprotection of 10a (Scheme 2).

Many more difficulties were encountered in the synthesis of the 5-(1-propynyl)-2-pyrimidinone nucleosides, 13c and 14c (see Scheme 3). Although 6 was synthesized as a stable "Hilbert-Johnson intermediate", attempts to condense the latter with the halogenose 8 (with the aid of either $SnCl_4$ or $HgBr_2-HgO$) were unsuccessful. In order to increase the reactivity of the intermediate, attempts were made to deblock 6 to yield 5-(1-propynyl)-2(1H)-pyrimidinone, 3c; the latter would then be silylated and subsequently employed in the condensation reaction.

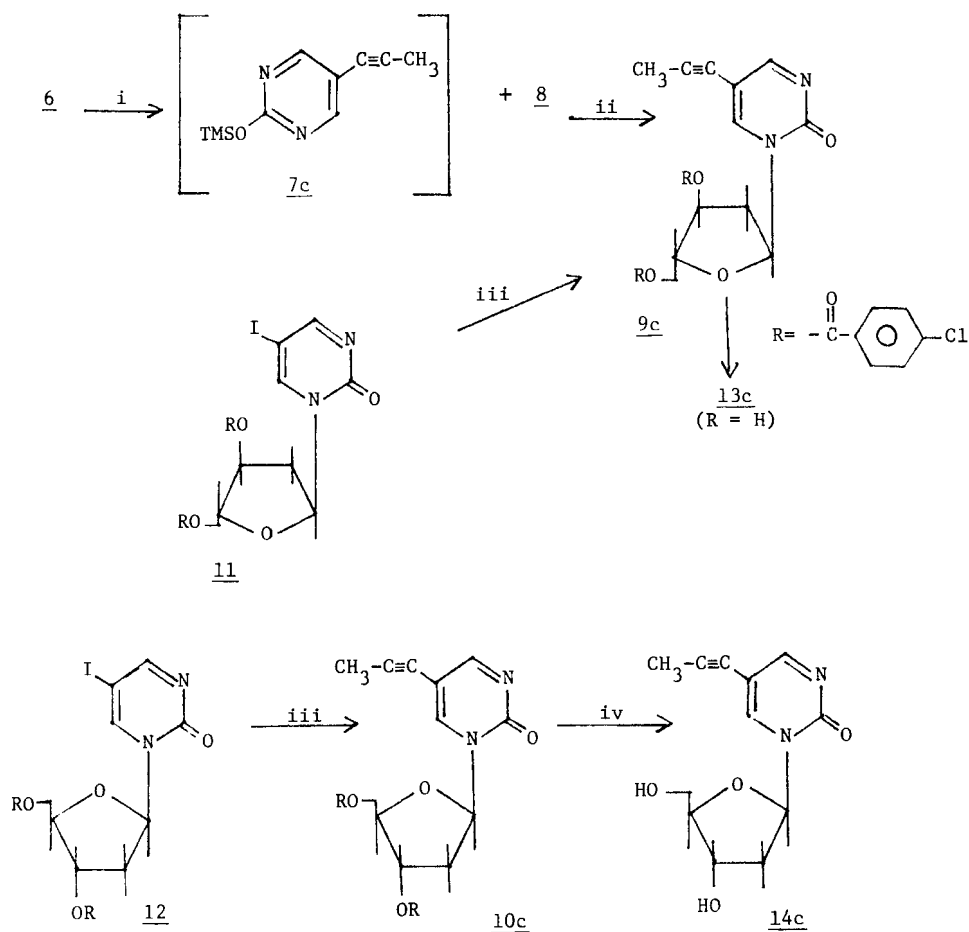
When 6 was refluxed in 3N HCl for 1½ hours, extensive decomposition occurred. Prolonged heating of 6 in 90% trifluoroacetic acid failed to de-



a series : $\text{R}' = \text{TMS}$; $\text{R}'' = \text{H}$

b series : $\text{R}' = \text{R}'' = \emptyset$

SCHEME 2



i: TMS-Cl + NaI/CH₃CN; **ii**: TMS-triflate/Cl₂C₂H₄;

iii: (PPh₃)₂PdCl₂-CuI, H-C≡C-CH₃; **iv**: MeOH/NH₃, 4°C;

R = $\text{Cl}-\text{C}_6\text{H}_4-\text{C}(=\text{O})-$; TMS: trimethylsilyl

SCHEME 3

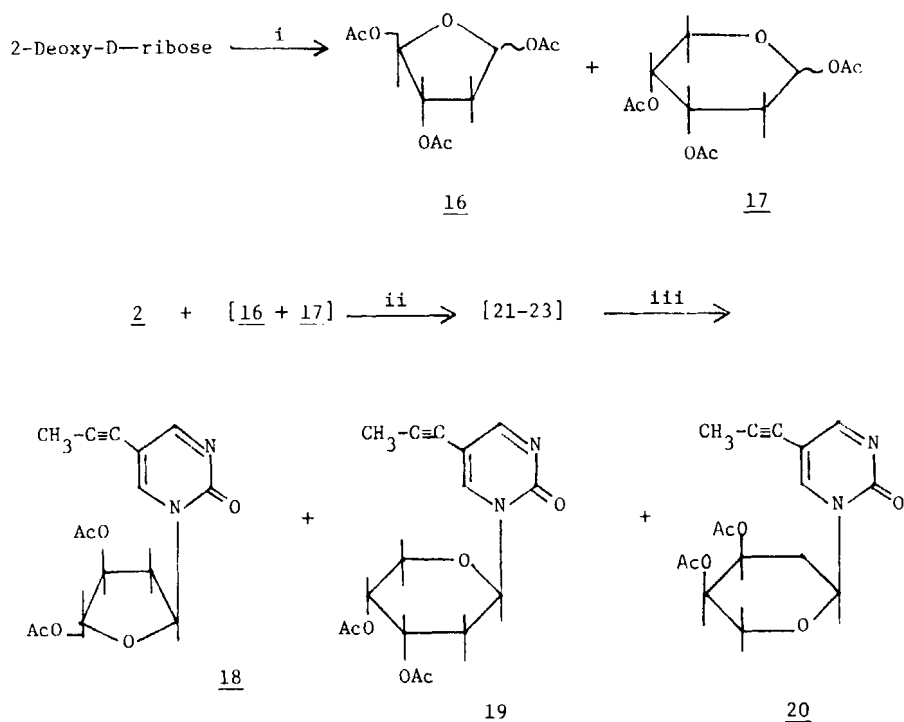
block the pyrimidine, and the use of iodotrimethylsilane in 1,2-dichloroethane (at 50°C) yielded three products (as determined by tlc). When acetonitrile was substituted for 1,2-dichloroethane under the same reaction conditions, 6 was deblocked cleanly; the product could be seen on tlc as a fluorescent material. However, attempts to isolate 3c from the reaction mixture were fruitless; subsequent to work-up, the intense fluorescence which is characteristic of the 5-(1-alkynyl)-2(1H)-pyrimidinones disappeared, indicating loss of the integrity of the chromophore. The procedure was therefore modified.

In light of the fact that the deblocking of 6 with iodotrimethylsilane produces, prior to quenching, 5-(1-propynyl)-2-trimethylsilyloxypyrimidine, 7c, the intermediate which is employed in the subsequent Hilbert-Johnson reaction, and that the other reactive species in the mixture, iodotrimethylsilane, is a Lewis acid which could catalyze the desired condensation reaction, a "one-pot" deblocking-condensation sequence was adopted. Earlier studies by Vorbrüggen¹⁰ had demonstrated that the condensation of a silylated pyrimidine and a halogenose at room temperature, promoted by trimethylsilyl triflate, produced a favorable (i.e., low) α/β ratio of the blocked nucleosides. Therefore, 6 was deblocked with iodotrimethylsilane and subsequent to completion of the demethylation, the halogenose 8 and trimethylsilyltriflate were added; disappointingly, this procedure yielded almost exclusively the α anomer 9c. The same results were obtained when the catalyst was changed to SnCl_4 and the condensation reaction was performed at 0°C. These results could be attributed to, among other factors, the influence of solvent polarity, possibly resulting in increased transannular participation¹¹ by the C⁵-acyloxy group of the sugar, and in a substantially greater rate of formation of the α anomer relative to the β anomer, in contrast to the results of Vorbrüggen,¹⁰ but in line with the earlier studies of Šorm¹¹ and coworkers who used HgBr_2 as the catalyst. At this point we decided to study an alternative pathway, using the blocked 5-iodonucleosides 11 and 12.²

When propyne gas was bubbled through a mixture of the α anomer 11, CuI and $(\text{O}_3\text{P})_2\text{PdCl}_2$, in triethylamine, the blocked 5-propynyl α -nucleoside 9c was obtained in 47% yield. Under similar conditions, the desired blocked β nucleoside 10c was obtained from 12 in 24% yield. The lower yield is attributed to the relative instability of the β -anomer of the blocked 5-iodonucleoside.² Compound 10c was only characterized by spectroscopic methods. In both of these carbon-carbon bond forming reactions, some epimerization at C-1' was observed in the reaction mixture (this was visible on tlc as a closely migrating minor component which would co-chromatograph with the corresponding anomer).

The deblocked nucleosides 13c (50%) and 14c (58%) were obtained by the methanolic ammonia treatment of 9c and 10c, respectively. The NMR spectra are consistent with the "open" nucleoside structures. The spectrum of the β anomer, however, reveals, in addition to 14c, also the presence of the cyclonucleoside 15c (about 25%): a singlet at δ 5.41 (for H-6), a doublet of doublets at δ 5.85 (for the anomeric proton) and a singlet at δ 6.53 (for H-4) are clearly visible. This pattern is consistent with that obtained for other O⁵, 6-cyclic 2-pyrimidinone β -nucleosides (see 15a and b, above) (Scheme 3).

An earlier attempt to synthesize the target compound 14c utilized the peracetylated 2-deoxy-D-ribose (which in effect was a mixture of the isomeric sugar triacetates, *i.e.*, furanose and pyranose forms, 16 and 17, respectively).¹²⁻¹⁴ This approach was in part a reinvestigation of some previous results obtained in our initial attempts to synthesize the corresponding 5-halonucleosides.² In addition, since it had been shown that 5-(2-bromovinyl)-2'-deoxyuridine 3',5'-diacetate was almost as active as the parent compound BVDU,¹⁵ by analogy, it was reasoned that the synthesis of 1-(2-deoxy-3,5-di-O-acetyl- β -D-ribofuranosyl)-5-(1-propynyl)-2-pyrimidinone could conceivably provide a prodrug, and deblocking might be unnecessary. Since the iodine substituent has been shown to be the most reactive in the Pd-catalyzed coupling reactions with alkynes,¹⁶ and since, presumably, no other halides would be present following the work-up procedure of the Hilbert-Johnson reaction between 5-iodo-2-trimethylsilyloxypyrimidine, 2, and the triacetates of 2-deoxyribose, the separation of isomers could therefore be carried out after the Pd-catalyzed "propynylation" reaction. 5-Iodo-2-trimethylsilyloxypyrimidine 2 was reacted with a mixture of the triacetates (16 + 17), using SnCl₄ as catalyst. After work-up, the crude product, *i.e.*, a mixture of isomeric blocked 5-iodo nucleosides,² [21-23], was reacted with propyne in the presence of the catalyst (ϕ_3P)₂PdCl₂-CuI (Scheme 4). Upon completion of the latter reaction, tlc (ethyl acetate) showed only two closely migrating fluorescent spots. The less mobile component, subsequent to initial chromatographic separation, was determined by spectroscopic methods to be the α anomer of the furanoside 18. However, the other component gave a very complex NMR spectrum; on tlc, using a different solvent system, (30% acetone/CHCl₃), this component was found to comprise two very closely migrating fluorescent products. These were subsequently separated by chromatography on silica gel, and their NMR spectra were examined. The more mobile of these two compounds shows a signal for the anomeric proton at δ 6.05 ($J_{1,2}$ =10 Hz); this large coupling constant is uncharacteristic of the furanoside ring¹⁷ but is consistent with the deoxy-ribopyranoside structure.¹⁸ This component has, therefore, been assigned the structure 19. The NMR spectrum of the less mobile component (which



i : $\text{Ac}_2\text{O}/\text{pyridine}, 0^\circ \longrightarrow 25^\circ\text{C};$

ii : $\text{SnCl}_4/\text{Cl}_2\text{C}_2\text{H}_4;$

iii : $\text{CH}_3\text{-C}\equiv\text{CH}, (\text{C}_6\text{H}_5)_2\text{PdCl}_2, \text{CuI}, \text{Et}_3\text{N}.$

SCHEME 4

is also the least mobile of all three products obtained from the propynylation reaction) shows the anomeric proton at δ 5.82 ($J_{1,2}=10$ Hz); this too, is consistent with a pyranoside structure. Early studies of acetylated deoxyribo- and ribopyranosyl nucleosides conducted by Samek and Farkas revealed that the anomeric proton of the β anomer is shifted downfield (relative to that of the α anomer) by a value of approximately 0.28 ppm.¹⁹ This shift was attributed to the diamagnetic anisotropy of the acetoxyl group, and the value of the shift was presumed to depend on the spatial orientation of the acetoxyl group relative to the anomeric proton.¹⁹ Furthermore, studies of cyclohexyl systems have shown that an axial C-3 substituent is more effective than an equatorial substituent at the same position in deshielding a C-1 proton, and this shift has been observed to

vary between 0.2 and 0.4 ppm.²⁰ This deshielding effect has also been reported by Wittenberg in his synthesis of the anomeric 2'-deoxyribopyranosyl-thymines.¹⁸ Based on the assumption that the most stable conformations of 19 and 20 are those in which the bulky pyrimidine would occupy the equatorial position, and in light of the corroborative evidence cited above, the less mobile component obtained from subsequent chromatography has been assigned the structure 20.

In view of the fact that the mixture of 2-deoxy-D-ribose triacetates utilized in the synthesis of the 5-iodo nucleosides contained a substantial quantity of the pyranose form, and in the absence of any information suggesting that the Lewis acid-catalyzed isomerization of pyrimidine nucleosides (N^3 to N^1 , or α to β)¹⁰ could result in attendant isomerization of furanoside to pyranoside, it would be reasonable to conclude that the three isomeric blocked nucleosides 18-20 obtained in the last reaction step had been formed directly from the corresponding 5-iodo compounds. Consequently, the products [21 - 23] of the coupling reaction between 2 and the triacetates of 2-deoxy-D-ribose, although not isolated in the present work but previously described,² are now confirmed to include the α furanoside and the α and β pyranoside isomers of the acetylated 5-iodo-2-pyrimidinone-2'-deoxyriboside. The apparent lack of formation of the desired β -furanoside isomer in this reaction has been discussed.²

The 5-ethynyl and 5-propynyl-2-pyrimidinone β -deoxyribosides EPdR (14a) and PPdR (14c), respectively, were tested for antiherpes activity *in vitro*, as previously described.^{2,21} At 100 mg/ml concentration, EPdR was found to be equally, or more active than its 5-iodo analog IPdR² against HSV-1 (KOS), HSV-1 (CL101) and HSV-2 (333), with average PFU values of 0.26, 0.14 and 1.6, respectively, expressed as % of the control. PPdR showed somewhat lower activity than EPdR against HSV-1 (KOS) and HSV-2 (333), with average PFU values of 2.0 and 2.25, respectively (% of control). Only EPdR was tested against the various drug-resistant strains of HSV-1; it gave similar or better results than the previously described IPdR.²

Detailed *in vitro* and *in vivo* results relating to the structure-activity relationships and mode of action of 2-pyrimidinone nucleosides as antiviral agents will be reported upon completion of our studies with this series of compounds.

EXPERIMENTAL SECTION

Melting points were taken on a Mel-temp apparatus and are uncorrected. IR spectra were obtained with a Perkin-Elmer 197 spectrophotometer.²² NMR spectra were taken on a Varian T-60 with tetramethylsilane as the internal reference. Elemental analyses were performed by Atlantic Microlab, Inc.,

Atlanta, GA, or Galbraith Labs., Knoxville, Tenn. Optical rotations were obtained on a Perkin-Elmer 141 polarimeter at 589 nm (Na lamp). Thin-layer chromatography was performed on Analtech GHLF tlc plates and visualization was done in a UV and/or iodine chamber. Preparative thin-layer chromatography was carried out on 20 x 20 silica gel plates prepared from Macherey-Nagel MN-Kieselgel P/UV₂₅₄. Flash chromatography was performed with Baker silica gel. UV spectra were taken on a Beckman Model 25 spectrophotometer. Column chromatography with gradient elution was performed with the Glenco medium pressure linear gradient system (with VWR silica gel of particle size 60-200 microns). The column was connected to two solvent chambers (in series) positioned high above the column and the flow rate was maintained at 12-15 ml per minute.

5-(2-Trimethylsilyl)ethynyl-2(1H)-pyrimidinone (3a)

A suspension of 15.06 g (67.83 mmol) of 5-iodo-2(1H)-pyrimidinone, 1, was refluxed in 40 ml of hexamethyldisilazane and 2 ml of chlorotrimethylsilane for 1 hour. The excess reagent was removed in vacuo to yield a yellow oil (2) which was dissolved with 30 ml of dry degassed triethylamine. To this solution was added 11.5 ml (81.37 mmol) of trimethylsilylacetylene, 0.32 g (2.5 mol %) of CuI and 0.48 g (1 mol %) of $(\text{O}_3\text{P})_2\text{PdCl}_2$. The reaction mixture was stirred under nitrogen, at room temperature, for 3 days and diluted with 100 ml of dry THF. The mixture was filtered under dry nitrogen; the precipitate was washed several times with dry THF and the filtrate was concentrated to a residue. The latter was treated with methanol to give the white crystalline, chromatographically homogeneous material (9.99 g, 76 %). Analytically pure material could be obtained by recrystallization from methanol; mp 203-206°C. NMR (DMSO- d_6) δ 0.22 (s, 9, $\text{Si}(\text{CH}_3)_3$), 8.4 (s, 2, 4-H and 6-H); IR (KBr) ν_{max} 3000 (broad), 2160, 1675 (shoulder), 1650, 1540, 1465, 1390, 1340, 1250, 1210 (shoulder), 845 cm^{-1} . Anal. Calcd. for $\text{C}_9\text{H}_{12}\text{N}_2\text{OSi}$: C, 56.22; H, 6.29; N, 14.57. Found: C, 56.39; H, 6.29; N, 14.57.

5-(2-Phenylethynyl)-2(1H)-pyrimidinone (3b)

A suspension of 3.98 g (17.9 mmol) of 1 in 25 ml of hexamethyldisilazane and 1 ml of chlorotrimethylsilane was refluxed for one hour, cooled and concentrated to a yellow oil. The latter was dissolved in 20 ml of anhydrous degassed triethylamine and introduced into a stainless steel bomb previously flushed with nitrogen. To this were added 82 mg of CuI, 60 mg of $(\text{O}_3\text{P})_2\text{PdCl}_2$ and phenylacetylene (4ml). The bomb was flushed with dry nitrogen, sealed and heated in an oil bath (temp. 75-80°C) for 15 hours. The reaction mixture was cooled, diluted with 70 ml of methanol and concentrated to a dark oil. On tlc, this mixture showed one major (fluorescent)

product (15% ethyl acetate in methylene chloride). The residue was chromatographed on 50 g of silica gel (eluted with a gradient of 0 to 20% ethyl acetate in methylene chloride and then 20% methanol in methylene chloride). After concentration of the fractions containing the fluorescent product, the solid was recrystallized from acetone, filtered, washed with cold acetone and dried at 50°C to provide 1.27 g (36%) of the yellow material; mp 217-221°C; NMR (DMSO- d_6) δ 7.45 (br s, 5, phenyl), 8.5 (s, 2, 4-H and 6-H); IR (KBr) ν_{\max} 3430 (broad), 3332 (shoulder), 3030 (shoulder), 2600 (broad), 1625, 1540, 1460, 1350, 1240 cm^{-1} . Anal. Calcd. for $\text{C}_{12}\text{H}_8\text{N}_2\text{O} \cdot \frac{1}{2}\text{H}_2\text{O}$: C, 70.23; H, 4.42; N, 13.65. Found: C, 70.18; H, 4.50; N, 13.64.

2-Chloro-5-iodopyrimidine (4)

A suspension of 9.51 g (42.83 mmol) 5-iodo-2(1H)-pyrimidinone, 1, in 80 ml of phosphorus oxychloride and 3 ml of distilled N,N-diethylaniline was refluxed, with exclusion of moisture, for 40 minutes (oil bath temperature 130-140°C). The reaction mixture was cooled, poured slowly into a vigorously stirred ice-water slurry and the resulting mixture was extracted with dichloromethane (5 x 200 ml). The organic extract was washed with a saturated bicarbonate solution (2 x 150 ml), dried over magnesium sulfate and concentrated to a solid residue. Further purification was accomplished by sublimation at 0.2 mm Hg (maximum bath temperature, 80°C) to give 6.11 g (70 %) of an off-white, chromatographically pure material; mp 133-135°C (lit.⁷ mp 129-130°C); NMR (CDCl_3 and Acetone- d_6) δ 8.9 (s, 2, aromatic); IR (CHCl_3) ν_{\max} 3025, 1520, 1385, 1355 (shoulder), 1200, 1165, 1005 cm^{-1} . Anal. Calcd. for $\text{C}_4\text{H}_2\text{ClIN}_2\text{O}$: C, 19.98; H, 0.84; Cl, 14.75; I, 52.78; N, 11.65. Found: C, 19.96; H, 0.84; Cl, 14.65; I, 52.58; N, 11.65.

5-Iodo-2-methoxypyrimidine (5)

To a suspension of 8.84 g (36.8 mmol) of 4 in 40 ml of anhydrous methanol was added, dropwise, a solution of sodium methoxide (prepared from 1 g, 43.5 mmol), of Na and 50 ml of anhydrous methanol). The mixture was stirred, with exclusion of moisture, and monitored by tlc. After 90 min, the mixture was concentrated to remove the bulk of the methanol, the residue was diluted with water (65 ml) and extracted with methylene chloride (3 x 100 ml). The organic extract was dried over anhydrous magnesium sulfate and concentrated to a minimum volume with concomitant precipitation of the product. The mixture was cooled in an ice bath, the product collected by filtration, washed with pet. ether and dried to provide 6.94 g (80%) of the chromatographically homogeneous, analytically pure, white crystalline material; mp 121.5-123.5°C; NMR (CDCl_3 and Acetone- d_6) δ 3.95 (s, 3, OCH_3), 8.73 (s, 2, aromatic); IR (CHCl_3) ν_{\max} 3015, 1555, 1465, 1395, 1325, 1195, 1030 cm^{-1} . Anal. Calcd for $\text{C}_5\text{H}_5\text{IN}_2\text{O}$: C, 25.45; H, 2.14; I, 53.77; N, 11.87. Found: C, 25.32; H, 2.25; I, 53.71; N, 11.89.

2-Methoxy-5-(1-propynyl)pyrimidine (6)

In a Parr pressure bottle 31.67 g (0.13 mol) of 5, 0.73 g (2.9 mol %) of CuI and 1.02 g (1.1 mol %) of bis(triphenylphosphine)PdCl₂ were suspended in 200 ml of anhydrous triethylamine (distilled over BaO). The bottle was evacuated and filled with 85% propyne. The bottle was repeatedly shaken and filled with propyne until the pressure had stabilized at 20 psi, and then the mixture was shaken, in a Parr hydrogenator, for 24 hours. More propyne was added at this time and shaking was continued for an additional 48 hours. On tlc (methylene chloride), there was only one major product; no starting material was observed. The mixture was diluted with methylene chloride (300 ml), washed with saturated bicarbonate solution (2 x 60 ml), dried over magnesium sulfate and concentrated to a minimum volume with attendant precipitation. Petroleum ether was added to the mixture and after cooling, the first crop was obtained by filtration. The filtrate was concentrated to give a second crop. Both crops were dried and sublimed at 0.3 mm Hg (max. oil bath temp 100°C) to yield 15.26 g (77 %) of analytically pure, white crystalline material; mp 88-89.5°C. NMR (Acetone-d₆) δ 2.07 (s, 3, C \equiv C-CH₃), 3.97 (s, 3, OCH₃), 8.53 (s, 2, aromatic); IR (CHCl₃) ν_{\max} 3015, 2940, (shoulder), 2880, 2290, 2250, 1590, 1530, 1470, 1410, 1330, 1280, 1200, 1050, 1030, 940 cm⁻¹. Anal. Calcd. for C₈H₈N₂O: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.76; H, 5.44; N, 18.87.

1-[3,5-Di-O-(p-chlorobenzoyl)-2-deoxy- α -D-ribofuranosyl]-5-(2-trimethylsilyl)ethynyl-2-pyrimidinone (9a) and 1-[3,5-di-O-(p-chlorobenzoyl)-2-deoxy- β -D-ribofuranosyl]-5-(2-trimethylsilyl)ethynyl-2-pyrimidinone (10a)

5-(2-Trimethylsilylethynyl)-2(1H)-pyrimidinone, 3a (1.41 g, 7.32 mmol), was refluxed in 14 ml of hexamethyldisilazane and 0.3 ml of chlorotrimethylsilane for 3 hours, and the resulting solution was concentrated to an oily residue. The residual solvent was removed by co-evaporation with 1,2-dichloroethane (2 x 20 ml). The residue was dissolved in 30 ml of anhydrous dichloroethane and the solution was added to a cooled solution of 2.5 g (5.82 mmol) of the halogenose 8 in 25 ml of dry 1,2-dichloroethane. The cooled mixture was then treated, dropwise, with a solution of 0.17 ml of SnCl₄ in 25 ml of anhydrous 1,2-dichloroethane. The mixture was stirred at 0°C for 2 hours and periodically monitored by tlc (15% ethyl acetate in methylene chloride; Macherey-Nagel silica gel G). The mixture was diluted with dichloroethane (100 ml) and saturated bicarbonate solution (50 ml), and filtered over Celite, the residue being washed several times with dichloroethane. The organic layer was subsequently washed with water (50 ml), dried over MgSO₄, and concentrated to a residue which was chromatographed on 100 g silica gel (eluted with a gradient of 0 to 12% ethyl acetate in methylene chloride). The fractions containing the slower moving anomer, 9a, were pooled, concentrated to

a white residue and the latter was recrystallized from ethanol to provide, after drying, 0.48 g (14%); mp 150–152°C; $[\alpha]_D^{35} = -49.8^\circ$ (CHCl₃, c 0.11M). NMR (CDCl₃) δ 2.85 (m, 2, 2'-H), 4.55 (d, 2, 5'-H, $J_{1',2'} = 5$ Hz), 5.02 (t, 1, 4'-H), 5.65 (d, 1, 3'-H), 6.30 (d, 1, 1'-H, $J_{1',2'} = 6$ Hz), 7.28–8.22 (m, 9, 6-H and phenyl), 8.65 (d, 1, 4-H, $J_{4,6} = 3$ Hz); IR (CHCl₃) ν_{\max} 3000, 2960, 2160, 1725, 1665, 1595, 1500, 1395, 1265, 1090, 1015, 845 cm⁻¹; UV (CHCl₃) λ_{\max} 342 nm (ϵ 4200). Anal. Calcd for C₂₈H₂₆Cl₂N₂O₆Si: C, 57.44; H, 4.48; Cl, 12.11; N, 4.78; Si, 4.80. Found: C, 57.03; H, 4.57; Cl, 13.70; N, 4.78; Si, 4.61.

The faster moving anomer 10a was obtained in a manner similar to that described for the α anomer. After recrystallization from ethanol and drying, 0.42 g (12%) of the white powder was obtained; mp 183–185°C; $[\alpha]_D^{35} = 103.6^\circ$ (CHCl₃, c 0.11M); NMR (CDCl₃) δ 2.2 (m, 1, 2'-H), 3.1 (m, 1, 2'-H), 4.73 (m, 3, 4'-H and 5'-H), 5.38 (d, 1, 3'-H), 6.32 (t, 1, 1'-H, $J_{1',2'} = 6.5$ Hz), 7.17–8.05 (m, 8, aromatic), 8.2 (d, 1, 6-H, $J_{6,4} = 3.5$ Hz), 8.53 (d, 1, 4-H, $J_{4,6} = 3.5$ Hz); IR (CHCl₃) ν_{\max} 3005, 2165, 1730, 1670, 1595, 1505, 1400, 1265, 1095, 845 cm⁻¹; UV (CHCl₃) λ_{\max} 342 nm (ϵ 4200). Anal. Calcd for C₂₈H₂₆Cl₂N₂O₆Si: C, 57.44; H, 4.48; Cl, 12.11; N, 4.78. Found: C, 57.46; H, 4.48; Cl, 12.11; N, 4.73.

1-(2-Deoxy- α -D-ribofuranosyl)-5-ethynyl-2-pyrimidinone (13a).

To a flask containing 20 ml of cold saturated (at 0°C) anhydrous methanolic ammonia was added 0.26 g (0.44 mmol) of 9a; the flask was sealed and the mixture was stirred at 4°C for 20 hours. The resulting solution was concentrated to a syrup which was treated with acetone to yield the crystalline material. The product was collected by filtration, washed with acetone and dried to give 70 mg (66%) of the chromatographically homogeneous 13a; mp 160–162.5°C; NMR (DMSO-d₆) δ 1.82–2.88 (m, 2, 2'-H), 3.48 (d, 2, 5'-H), 4.23 (s, 1, C \equiv C-H), 4.35 (m, 2, 3'-H and 4'-H), 6.0 (dd, 1, 1'-H; $J_{1',2'} = 7$ Hz), 8.32 (d, 1, 6-H; $J_{6,4} = 3$ Hz), 8.57 (d, 1, 4-H); IR (KBr) ν_{\max} 3330, 3230, 2985, 1635, 1615, 1510, 1395, 1250, 1100, 1080, 980 cm⁻¹. Anal. Not performed.

1-(2-Deoxy- β -D-ribofuranosyl)-5-ethynyl-2-pyrimidinone (14a).

To 20 ml of cold anhydrous methanol presaturated with dry ammonia (at 0°C), was added 0.13 g (0.5 mmol) of 10a, and the mixture, after sealing the reaction vessel, was stirred at 4°C for 6 hours. The resulting solution was concentrated to an oil; the latter was treated with acetone and concentrated to a minimum volume with concomitant precipitation of the product. The mixture was treated with small amounts of acetone-ether and cooled. The product was collected by filtration, washed with acetone-ether and dried to yield 69 mg (55.9%) of 14a as an off-white powder; dec above 130°C;

NMR (DMSO- d_6 + D_2O) δ 2.26 (m, 2, 2'-H), 3.68 (m, 2, 5'-H), 3.97 (m, 1, 4'-H), 4.27 (m, 2, 3'-H and $C\equiv C-H$), 6.03 (t, 1, 1'-H; $J_{1,2}=6$ Hz), 8.63 (d, 1, 6-H, $J_{6,4}=3$ Hz), 8.73 (d, 1, 4-H, $J_{4,6}=3$ Hz); for the cycloadduct: 5.40 (s, 1, C_6-H), 5.82 (dd, 1, 1'-H; $J_{1,2}=5.5$ Hz), 6.65 (s, 1, C_4-H). IR (KBr) ν_{max} 3523 (shoulder), 3220 (broad), 2925 (shoulder), 2100, 1660, 1423, 1350, 1265, 1110, 1070, (shoulder), 925 cm^{-1} ; UV (MeOH) λ_{max} 332 nm (ϵ 3160). Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.36; H, 5.24; N, 11.60.

1-[3,5-Di-O-(p-chlorobenzoyl)-2-deoxy- α -D-ribofuranosyl]-5-phenylethynyl-2-pyrimidinone (9b) and 1-[3,5-di-O-(p-chlorobenzoyl)-2-deoxy- β -D-ribofuranosyl]-5-phenylethynyl-2-pyrimidinone (10b).

After 1.0 g (5.1 mmol) of **3b** was refluxed in 10 ml of hexamethyldisilazane and 0.5 ml of chlorotrimethylsilane for 90 minutes, the solution was cooled and concentrated to an oil. Residual solvent was then removed by co-evaporation with 15 ml of anhydrous 1,2-dichloroethane and the resulting oil was diluted with 10 ml of dry 1,2-dichloroethane. This solution was added to a cooled solution of 2.0 g (4.6 mmol) of the sugar halide **8**, in 40 ml of dichloroethane. A solution of 0.1 ml (0.85 mmol) of $SnCl_4$ in 25 ml of dichloroethane was then added, dropwise, to this mixture. The reaction mixture was maintained at $0^\circ C$, with exclusion of moisture, for 4 hours. Tlc (15% EtOAc/ CH_2Cl_2) showed two fluorescent major products (the α and β anomers). The mixture was diluted with 150 ml of 1,2-dichloroethane and 100 ml of saturated bicarbonate. After extraction, the organic extract was washed with water (2 x 100 ml), dried over magnesium sulfate and concentrated to an oil. The latter was subsequently chromatographed on 90 g of silica gel (using a gradient of 0-15% EtOAc/ CH_2Cl_2). The α , **9b**, and β , **10b**, anomers were obtained as syrups which solidified on standing. The more mobile β anomer was dried to give 1.35 g (49%) of white crystalline material. After recrystallization from acetonitrile-ether, 0.69 g (25%) of **10b** was obtained; mp $152-154^\circ C$; $[\alpha]_D^{26} = -81.9^\circ$ ($CHCl_3$, $c 2.2 \times 10^{-5} M$); NMR ($CDCl_3$) δ 2.0-2.70 (m, 1, 2'-H), 3.0-3.50 (m, 1, 2'-H), 4.75 (m, 3, 4'-H and 5'-H), 5.62 (d, 1, 3'-H), 6.33 (t, 1, 1'-H; $J_{1,2}=6.5$ Hz), 6.76-8.2 (m, 14, phenyl and 6-H), 8.27 (d, 1, 4-H; $J_{4,6}=3$ Hz), IR ($CHCl_3$) ν_{max} 3050, 1725, 1665, 1595, 1500, 1400, 1260, 1095 cm^{-1} . Anal. Calcd. for $C_{31}H_{22}Cl_2N_2O_6$: C, 63.17; H, 3.76; Cl, 12.03; N, 4.75. Found: C, 62.54; H, 3.80; Cl, 11.84; N, 4.69.

The α anomer, **9b**, was dried to yield 1.09 g (40%) of the crystalline product. An analytical sample was recrystallized from ethanol; mp $158.5-161^\circ C$; $[\alpha]_D^{26} = +157.4^\circ$ ($CHCl_3$; $c 2.3 \times 10^{-5} M$). NMR ($CDCl_3$) δ 2.57-3.50 (m, 2, 2'-H), 4.58 (d, 2, 5'-H), 5.05 (t, 1, 4'-H), 5.68 (d, 1, 3'-H), 6.37 (d, 1, 1'-H), 7.25-8.16 (m, 8, phenyl), 8.23 (d, 1, 6-H), 8.73 (d, 1,

4-H; $J_{4,6}=3$ Hz). IR (CDCl₃) ν_{\max} 3020, 1725, 1665, 1600, 1500, 1400, 1260, 1080 cm⁻¹. Anal. Calcd. for C₃₁H₂₂Cl₂N₂O₆: C, 63.17; H, 3.76; Cl, 12.03; N, 4.75. Found: C, 63.09; H, 3.84; Cl, 11.69; N, 4.63.

1-(2-Deoxy-β-D-ribofuranosyl)-5-(2-phenylethynyl)-2-pyrimidinone (14b/15b).

To a flask containing cold saturated (at 0°C) anhydrous methanolic ammonia, was added 0.35 g (0.59 mmol) of 10b; the flask was sealed and the mixture was stirred at 4°C for 22 hours. The resulting solution was concentrated to a syrup which was chromatographed on 20 x 20 silica gel plates (15% methanol/methylene chloride). The fluorescent band was extracted with 20% methanol/methylene chloride and the resulting solution was concentrated to a syrup. The latter was treated with acetone to provide a pale yellow crystalline material. A chromatographically pure material, 15b, 0.13 g (70%) was obtained after drying; mp 232-235°C. NMR (DMSO-d₆) δ 2.30 (m, 2, 2'-H), 3.82 (s, 2, 5'-H), 4.28 (s, 2, 3'-H and 4'-H), 5.52 (s, 1, 6-H), 5.85 (dd, 1, 1'-H; $J=6$ Hz and $J'=2$ Hz), 6.75 (s, 1, 4-H), 7.35 (s, 5, phenyl); IR (KBr) ν_{\max} 3470, 3210, 3070, 2940, 2200, 1650, 1460, 1260, 1110, 915, 750 cm⁻¹. Anal. Calcd. for C₁₇H₁₆N₂O₄: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.20; H, 5.18; N, 8.95.

1-[3,5-Di-O-(p-chlorobenzoyl)-2-deoxy-α-D-ribofuranosyl]-5-(1-propynyl)-2-pyrimidinone (9c) and 1-(3,5-di-O-(p-chlorobenzoyl)-2-deoxy-β-D-ribofuranosyl)-5-(1-propynyl)-2-pyrimidinone (10c).

Method A. Chlorotrimethylsilane (4.11 ml; 32.5 mmol) was introduced by syringe into a solution of 1.5 g (10.2 mmol) of 6 and 4.56 g (30.44 mmol) of NaI in 35 ml of anhydrous acetonitrile maintained under an atmosphere of dry nitrogen and removed from light. The mixture was stirred at 50°C for 2½ hours with periodic monitoring by tlc. The mixture was cooled in an ice bath and 3.5 g (8.14 mmol) of halogenose 8 were added. To this mixture was added 3 ml of 1 N trimethylsilyl triflate in 1,2-dichloroethane; the mixture was stirred at 0°C for 1 hour and then at room temperature for 2½ hours. The reaction mixture was then diluted with dichloromethane (150 ml) and saturated sodium bicarbonate (65 ml). The organic extract was subsequently washed with water (60 ml), dried over magnesium sulfate and concentrated to a residue which was subjected to flash chromatography on 80 g of silica gel. The fractions containing the slower moving α anomer were pooled and concentrated to a minimum volume with attendant precipitation. The mixture was cooled and filtered to give a white solid; the product was washed with diethyl ether and dried at 50°C to provide 1.1 g (26%) of 9c; mp 176-178°C; $[\alpha]_D^{35}=54.1^\circ$ (CHCl₃, c0.04M); NMR (CDCl₃) δ 1.98 (s, 3, C≡CH₃), 2.87 (m, 2, 2'-H), 4.57 (d, 2, 5'-H), 5.0 (t, 1, 4'-H), 5.67 (d, 1, 3'-H), 6.32 (d, 1, 1'-H, $J_{1,2}=6$ Hz), 7.2-8.2 (m, 9, 6-H and

phenyl), 8.63 (d, 1, 4-H, $J_{4,6}=3.5$ Hz); IR (CHCl₃) ν_{\max} 3020, 1725, 1660, 1595, 1500, 1400, 1260, 1205, 1090, 1015 cm⁻¹; UV (CHCl₃) λ_{\max} 342 nm (ϵ 2400). Anal. Calcd. for C₂₆H₂₀Cl₂N₂O₆: C, 59.22; H, 3.83; Cl, 13.44; N, 5.31. Found: C, 59.04; H, 3.84; Cl, 13.38; N, 5.28.

The fractions containing the faster moving β anomer 10c were pooled and concentrated to yield a foam which was subsequently dried. This material was barely enough for spectral characterization. NMR (CDCl₃) δ 1.97 (s, 3, -C \equiv C-CH₃), 2.2 (m, 1, 2'-H), 3.2 (m, 1, 2'-H), 4.8 (m, 3, 4'-H and 5'-H), 5.60 (m, 1, 3'-H), 6.34 (t, 1, 1'-H, $J_{1',2'}=6$ Hz), 7.38-8.1 (m, 8, phenyl), 8.19 (d, 1, 6-H), 8.6 (d, 1, 4-H, $J_{4,6}=3$ Hz).

Method B. For the α -anomer (9c). A mixture of 1.0 g (1.62 mmol) of 11, 25 mg (8.1 mol %) of CuI, 24 mg (2.1 mol %) of (ϕ_3P)₂PdCl₂, 20 ml of dry triethylamine and 20 ml of anhydrous acetonitrile in a Parr bottle was shaken, under an atmosphere of 85% propyne (15 psi), in a Parr hydrogenator for 21 hours. Tlc (15% ethyl acetate/dichloromethane) showed a highly fluorescent spot as the major component of the mixture; no starting material was present. The mixture was concentrated to a residue which was dissolved in dichloromethane (100 ml). The solution was washed with water (30 ml), dried over magnesium sulfate and concentrated to a dark oil. The latter was subjected to chromatography on 80 g of silica gel (eluted with 15% ethyl acetate in dichloromethane), and the desired fractions were pooled, concentrated to a minimum volume with concomitant precipitation and the mixture was then treated with a small amount of diethyl ether. The mixture was cooled, the product collected by filtration, washed with cold diethyl ether and dried to give 0.4 g (47%) of an off-white powder; mp 177-180°C; $[\alpha]_D^{25} = +56.97^\circ$ (CHCl₃; c 0.19M); NMR and IR: identical with those of 9c obtained by Method A.

For the β -anomer (10c). A mixture of 1.44 g (2.34 mmol) of 12, 34 mg (7.6 mol %) of CuI, 39 mg (2.38 mol %) of (ϕ_3P)₂PdCl₂, distilled acetonitrile (30 ml) and dry triethylamine (10 ml) was shaken, at room temperature, under an atmosphere of 85% propyne (16 psi), in a Parr hydrogenator for 20½ hours. On TLC (15% ethyl acetate in methylene chloride), the major product appeared as a fluorescent spot (small amounts of the α anomer could also be seen). The mixture was concentrated to a residue which was subjected to flash chromatography on 80 g silica gel (eluted with 12% ethyl acetate in methylene chloride). The desired fractions were concentrated to a foam and dried to give 0.30 g (24%) of a white product, identified as 10c. NMR (CDCl₃) δ 1.95 (s, 3, C \equiv C-CH₃), 2.23 (m, 1, 2'-H), 3.17 (m, 1, 2'-H), 4.75 (m, 3, 4'-H and 5'-H), 5.63 (m, 1, 3'-H), 6.32 (t, 1, 1'-H, $J_{1',2'}=6.5$ Hz), 7.3-8.1 (m, 8, phenyl), 8.17 (d, 1, 6-H, $J_{6,4}=2$ Hz), 8.57 (d, 1, 4-H, $J_{4,6}=3$ Hz).

This was used, without further characterization, in the synthesis of 14c.

1-(2-Deoxy- α -D-ribofuranosyl)-5-(1-propynyl)-2-pyrimidinone (13c)

A suspension of 500 mg (0.95 mmol) of 9c in 25 ml of cold, anhydrous methanolic ammonia (saturated at 0°C) was sealed in a flask and was stirred at 4°C for 12 hours and the resulting solution was concentrated to a syrup. The latter was treated with a minimum amount of ethanol and chilled to produce the crystalline product. The product was collected by filtration, washed with cold ethanol-ether and dried to give 120 mg (50%) of off-white material; shrinks and softens at 68-75°C; NMR (DMSO- d_6) δ 1.77-2.9 (m, 2, 2'-H), 2.02 (s, 3, -C \equiv C-CH $_3$), 3.42 (m, 2, 5'-H), 4.30 (m, 2, 3'-H and 4'-H), 6.00 (d, 1, 1'-H; $J_{1,2}=7$ Hz), 8.25 (d, 1, 6-H; $J_{6,4}=3$ Hz), 8.57 (d, 1, 4-H); IR (KBr) ν_{\max} 3300 (broad), 2900 (shoulder), 2230, 1640, (broad), 1500, 1395, 1250, 1100 (broad) cm^{-1} ; Anal. Calcd. for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_4 \cdot \frac{1}{2}\text{H}_2\text{O}$: C, 56.58; H, 5.74; N, 11.00. Found: C, 56.53; H, 5.72; N, 10.75.

1-(2-Deoxy- β -D-ribofuranosyl)-5-(1-propynyl)-2-pyrimidinone (14c)

To a cold, anhydrous, saturated (at 0°C) solution of methanolic ammonia (15 ml), 300 mg (0.57 mmol) of 10c was added and the flask was sealed. The mixture was stirred at 4°C for 4 hours. Tlc (10% MeOH/ CH_2Cl_2) showed several minor fluorescent products. The solution was concentrated, in vacuo, to an oil which was chromatographed on 20 x 20 cm silica gel plates (10% MeOH/ CH_2Cl_2). The major fluorescent band was extracted with a solution of 20% methanol in methylene chloride and the extract was concentrated to a syrup. The latter was dried to give 14c as a pale yellow, chromatographically homogeneous foam (82 mg, 58%); NMR (DMSO- d_6 + D_2O) δ 1.18 (t, ethanol -CH $_3$), 1.83-2.67 (m, 5, 2'-H and -C \equiv C-CH $_3$), 3.53-4.5 (ethanol, H_2O and sugar protons), 6.08 (t, 1, 1'-H, $J_{1,2}=6$ Hz), 7.97 (dd, 2, 4-H and 6-H; $J_{4,6}=3$ Hz); [for the cycloadduct 15c: 5.41 (s, 1, 6-H), 5.85 (dd, 1, 1'-H, $J_{1,2}=5.5$ Hz), 6.53 (s, 1, 4-H)]; IR (KBr) ν_{\max} 3350 (broad), 2920 (shoulder), 2600, 2363, 2236, 1650, 1500, 1250, 1090 cm^{-1} . Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_4 \cdot 0.4 \text{H}_2\text{O}$: C, 55.98; H, 5.79; N, 10.88. Found: C, 56.30; H, 5.78; N, 10.11.

1-(2-Deoxy-3,5-di-O-acetyl- β -D-ribofuranosyl)-5-(1-propynyl)-2-pyrimidinone (19), 1-(2-deoxy-3,5-di-O-acetyl- α -D-ribofuranosyl)-5-(1-propynyl)-pyrimidinone (20) and 1-(2-deoxy-3,5-di-O-acetyl- α -D-ribofuranosyl)-5-(1-propynyl)-2-pyrimidinone (18).

2-Hydroxy-5-iodopyrimidine, 1, (5.0 g, 22.54 mmol) was refluxed in 15 ml of hexamethyldisilazane and 0.5 ml of chlorotrimethylsilane for 90 minutes, and the resulting solution, subsequent to cooling, was concentrated to an oil. Residual solvent was then removed by co-evaporation with

1,2-dichloroethane (30 ml). The oil was diluted with 20 ml of anhydrous dichloroethane and added to a solution of the mixture of 2-deoxy-D-ribose triacetates [16 + 17] (prepared by the reaction of 2-deoxy-D-ribose with acetic anhydride in pyridine at 0°C - 25°C)², in 60 ml of dry dichloroethane. The resulting solution was cooled in an ice bath and to this cooled solution was added, dropwise, a solution of 2.9 ml (24.78 mmol) of SnCl₄ in 15 ml of anhydrous dichloroethane. The reaction mixture was stirred, with exclusion of moisture, at 4°C for 22 hours. Tlc (ethyl acetate) showed 2 spots; a preponderance of the more mobile component was evident. The mixture was diluted with methylene chloride (200 ml) and cold saturated NaHCO₃ (80 ml). After extraction, the organic extract was dried over anhydrous magnesium sulfate and concentrated to a dark oil. This was used in the next step without further purification.

Propyne (generated by the dropwise addition of 21 ml of 1,2-dibromopropane to a refluxing mixture of 36 g of KOH and 80 ml of n-BuOH)⁴ was bubbled through a mixture of the oil obtained from the first step 0.16 g (1 mol % based on 1) of (Ø₃P)₂PdCl₂ and 0.14 g (3.2 mol %) of CuI in dry triethylamine (20 ml) and anhydrous acetonitrile (20 ml) under nitrogen, at room temperature. The reaction was complete (as indicated by tlc; ethyl acetate) after three hours. The mixture was concentrated to a syrup which was diluted with methylene chloride (125 ml); this solution was then washed with a saturated solution of sodium bicarbonate (25 ml), dried over magnesium sulfate and concentrated to a residue. On tlc (ethyl acetate) this mixture showed two products (R_f 0.29 and 0.40); the more mobile component was in greater abundance. The mixture was then subjected to flash chromatography (50% ethyl acetate/CH₂Cl₂) on 100 g of silica gel. The more mobile component was obtained as an oil which was dried to give 1.3 g (17%) of a pale yellow syrup. On tlc (30% acetone/CHCl₃), this material appears as two spots (R_f 0.66 and 0.74). A small amount of this mixture was chromatographed on 20 x 20 cm silica gel plates (3-developments with 10% acetone/CH₂Cl₂). The two fluorescent bands were extracted with 20% methanol/methylene chloride, concentrated and dried. The more mobile component 19, was obtained as a chromatographically homogeneous foam

$[\alpha]_D^{27} = +74.2$ (CHCl₃; c 1.94 x 10⁻⁵M). NMR (CDCl₃) δ 2.03 (s, 6, COCH₃ and C≡C-CH₃), 2.20 (s, 3, acetyl), 1.8-2.7 (m, 2, 2'-H), 3.97 (d, 1, 5'-H), 4.10 (s, 1, 5'-H), 5.07 (m, 1, 3'-H), 5.58 (m, 1, 4'-H), 6.05 (dd, 1, 1'-H, J_{1',2'} = 10 Hz), 8.05 (d, 1, 6-H, J_{4,6} = 3.5 Hz), 8.58 (d, 1, 4-H); IR (CHCl₃) ν_{max} 3010, 2950, 1750, 1670, 1510, 1370, 1230, 1060 cm⁻¹.

The less mobile component, 20, was obtained as an oil; $[\alpha]_D^{28} = -32.2^\circ$ (CHCl₃; c 4.4 x 10⁻⁵M); NMR (CDCl₃) δ 2.03 (s, 3, C≡C-CH₃), 2.06 (s, 3, acetyl), 2.25 (s, acetyl), 1.8-2.5 (m, 2, 2'-H), 3.87 (d, 1, 5'-H), 4.33

(d, 1, 5'-H), 5.23 (m, 2, 3'-H and 4'-H), 5.82 (dd, 1, 1'-H, $J_{1',2'}=10$ Hz), 8.03 (d, 1, 6-H, $J_{6,4}=3$ Hz); 8.62 (d, 1, 4-H); IR (CHCl₃) ν_{\max} 3020, 2950, 1745, 1670, 1510, 1400, 1370, 1240 cm⁻¹.

On tlc (20% acetone/CHCl₂), the original propynylation mixture showed three spots (R_f 0.39, 0.46 and 0.52). The least mobile component of this mixture, **18**, (obtained as a chromatographically homogeneous material from the flash chromatography) was obtained as an oil (0.14 g, 1.86%); $[\alpha]_D^{27} = -32.2^\circ$ (CHCl₃; c1.88 x 10⁻⁴M); NMR (CDCl₃) δ 1.93 (s, 3, C \equiv C-CH₃), 2.03 (s, 3, acetyl), 2.10 (s, 3, acetyl), 2-3.1 (m, 2, 2'-H), 4.25 (m, 2, 5'-H), 4.77 (t, 1, 4'-H), 5.28 (d, 1, 3'-H), 6.20 (dd, 1, 1'-H, $J_{1',2'}=6$ Hz), 8.02 (d, 1, 6-H, $J_{6,4}=3$ Hz), 8.60 (d, 1, 4-H); IR (CHCl₃) ν_{\max} 3010, 1750, 1670, 1500, 1400, 1370, 1240, 1100 cm⁻¹.

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22. In some cases, when this instrument did not show the "characteristic" stretching frequency for the C≡C bond, the Nicolet Model 1180 was used which showed a weak signal in the 2150-2250 cm^{-1} region. All the major absorption peaks (i.e., the frequencies listed) were similar when compared on the two instruments.

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