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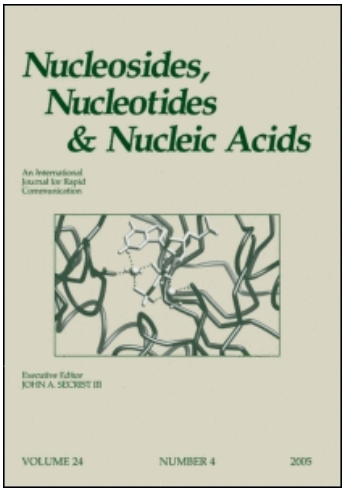

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Synthesis of the Pyrido[4,3-D]pyrimidine Congeners of Inosine and of Adenosine - A New Class of 6:6 Bicyclic C-Ribofuranosides

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NUCLEOSIDES & NUCLEOTIDES, 11(1), 61-83 (1992)

SYNTHESIS OF THE PYRIDO[4,3-d]PYRIMIDINE CONGENERS OF INOSINE AND OF ADENOSINE – A NEW CLASS OF 6:6 BICYCLIC C-RIBOFURANOSIDES[1].

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Abstract: The synthesis of the pyrido[4,3-d]pyrimidine congeners (**7** and **8**) of inosine and adenosine from the known precursor 3-dimethylamino-2-(2,3-O-isopropylidene-5-O-trityl-D-ribofuranosyl)acrylonitrile (**10**) is described. The synthetic sequence involves a modified Thorpe-Ziegler annulation to a 4-amino-3-cyanotetrahydropyridine derivative (**22**) followed by aromatization to an α, β mixture of the desired 5-ribosyl-4-amino-3-cyanopyridine intermediates (**25** and **26**). Further annulation to the pyrido[4,3-d]pyrimidine ring system and simultaneous detritylation and deisopropylidenation completes the synthesis.

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We have reported recently the synthesis of some pyrrolo[3,2-d]-,[2-4] thieno[3,2-d]-,[5,6] and furo-[3,2-d]pyrimidine[7] C-nucleosides (figure 1) that are isosteric with the naturally-occurring purine ribonucleosides inosine (for **1** - **3**) and adenosine (for **4** - **6**). In designing these novel "purine-like" C-nucleosides, we confined structural modifications to the replacement of the original imidazole ring in the purine system by a variety of 5-membered π-excessive heterocycles. Several of these C-nucleosides exhibit significant biological activities[8-17] as a consequence of their ability to enter purine nucleoside metabolic pathways.[9-11,13,14]

As an extension of the above synthetic program, we have begun to investigate the biochemical consequences of a similar replacement of the imidazole moiety of purine ribonucleosides by various six-membered heterocycles. We wish to report here the synthesis of two 8-β-D-ribofuranosyl derivatives of the pyrido[4,3-d]pyrimidine system, **7** and **8**, which are congeners of inosine and adenosine, respectively. To the

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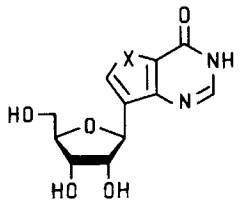
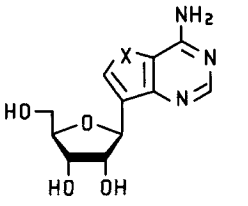
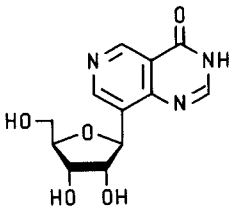


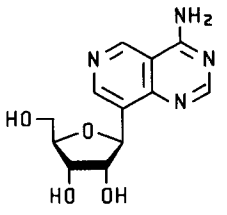
1, X = NH (9-Deazainosine)
2, X = S **3**, X = O



4, X = NH (9-Deazaadenosine)
5, X = S **6**, X = O



7



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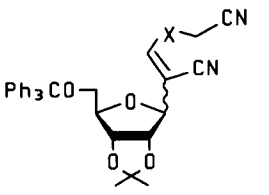

9 X = N-COOEt, O, S

Figure 1

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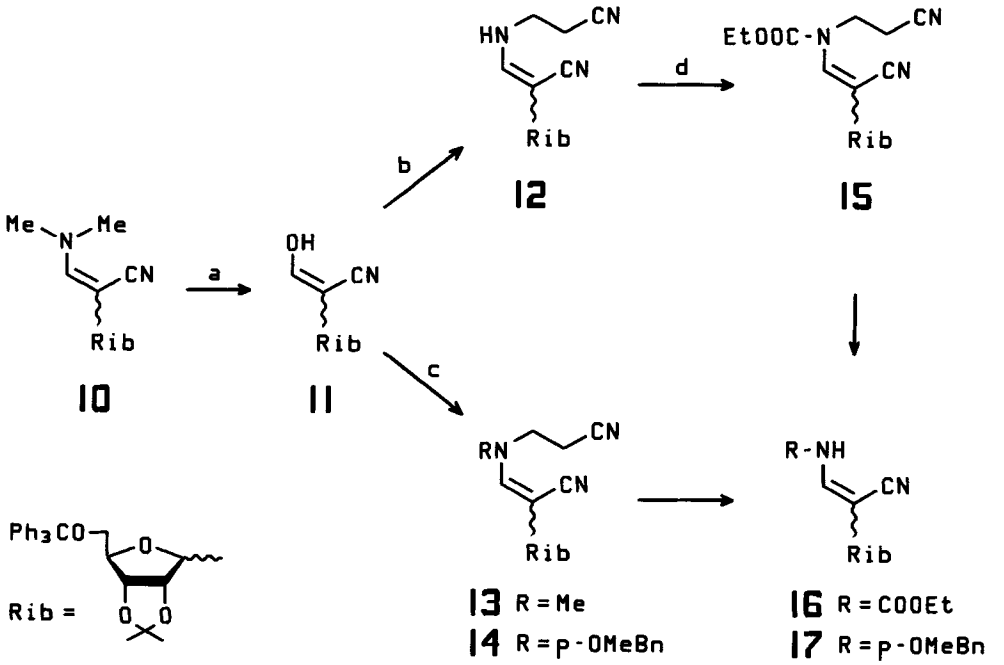
best of our knowledge, they also represent the first examples of 6:6 bicyclic purine-like C-nucleosides incorporating the fused pyrimidine moiety in its normal orientation.

The synthetic approach we investigated was based on modified Thorpe-Ziegler annulations akin to the procedures we had developed[2-7] for the preparation of **1** - **6** via intermediates **9**, readily obtainable from versatile precursor **10**.[18] One obvious approach to the pyrido[4,3-d]pyrimidine system was the annulation of **12** (scheme 1) or of its derivatives **13**, **14**, or **15**. The desired intermediate **12** was readily obtained from **11** by reaction with the primary amine β-aminopropionitrile in a buffered system. Attempted annulation of **12** under a variety of mild basic conditions (e.g., t-BuOK, THF, 25°C) was unsuccessful and led only to anomerization of the starting material, while stronger bases [e.g., $(Me_3Si)_2NLi$/THF, 25°C] led to decomposition. Since some of these difficulties were presumably due to proton abstraction of the relatively acidic unsubstituted NH group,[19] attempts at annulation using instead its derivative **15** were next made. This compound (obtained by treatment

Scheme 1



a = CF_3COOH, H_2O, CH_2Cl_2, 25°C; **b** = H_2N-CH_2-CH_2-CN, MeOH, H_2O, 25°C; **c** = R-NH-CH_2-CH_2-CN (where R = Me or p-CH_2-C_6H_4-OMe), I_2, Ph_3P, Et_3N, CH_2Cl_2, 25°C; **d** = ClCOOEt, Et_3N, p-dimethylaminopyridine, CH_2Cl_2, 0-25°C.

of **12** with ClCOOEt) was found, however, to undergo ready β-elimination to give **16** (e.g., t-BuOK, THF) or decarbethoxylation to give **12** (e.g., NaOEt) or both (e.g., NaH, THF).[20] It was at first thought that the susceptibility of **15** to undergo base-catalyzed β-elimination to give **16** was mainly due to the strong electronegative effect of its N-COOEt blocking group. Less electronegative benzylic N-blocking groups (e.g., p-methoxybenzyl as in **14**) therefore were investigated next. Neither **14** nor its N-Me congener **13** (used in some of these studies as a simpler model) could be readily obtained by direct reaction of **11** with the secondary amines 3-(p-methoxybenzylamino)- or 3-methylaminopropionitrile under the mild conditions described above in our synthesis of **12**. In an exploratory evaluation of possible methods leading to tertiary enamines (such as **13** or **14**) we found that the reaction of 3-methylamino-

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propionitrile with **11** mediated by triphenylphosphine and iodine in dichloromethane readily afforded enamine **13**[21] in good yield. This method was readily applicable to the preparation of the desired N-(p-methoxybenzyl) intermediate **14**.[22] All attempts to ring-close **14** under basic conditions that had been used with some degree of success in the annulation of **9** (X = N-Bn or NCOOR) led, however, to the same type of β-elimination observed previously, namely the formation of **17**,[23] while other conditions[24] gave no reaction.

The results clearly indicate that the extended conjugation present in enaminonitriles **14** and **15** overwhelmingly favors the β-elimination reaction over annulation, and suggested instead the possible utilization of a saturated system such as **20**, or some suitable N-substituted derivative such as **21** (Scheme 2). A number of 3-amino-4-cyano-tetrahydropyridine derivatives have, in fact, been synthesized via reactions akin to the modified Thorpe-Ziegler annulation.[25] The synthetic sequence adopted (Scheme 2, **11** → **22**) is nonstereoselective but gives rise, ultimately, to only two isomers (i.e., the α and β pair **26** and **25**, respectively) after aromatization of the intermediate tetrahydropyridinyl system. This strategy provided intermediate **21** in four steps from 2-formylacetonitrile **11**. Alcohol **18**, obtained by borohydride reduction of **11** afforded, upon treatment with methanesulfonyl chloride at 0°C and in the presence of an excess of triethylamine, an intermediate sulfonate ester that underwent smooth *in situ* elimination when the temperature of the mixture was raised to 25°C. The Michael addition of β-aminopropionitrile to ribosylated acrylonitrile **19** thus obtained[26], afforded secondary amine **20** which was finally N-benzylated under relatively mild basic conditions.[27] Intermediate **21**, obtained as the expected mixture of diastereomers, was readily annulated upon treatment with potassium t-butoxide in t-butanol at reflux temperature for half an hour to give the desired ribosylated tetrahydropyridines **22** in 60% yield. Also obtained were two minor products separable by preparative TLC and characterized as isomers having structure **23** (22% yield).[28a] The conversion of **21** into **22** was found to be critically dependent on the solvent, as less polar solvents (e.g., toluene or THF) led to increased amounts[28b] of the undesired products **23**. Aromatization of **22** to the desired 5-ribosylated pyridine C-nucleosides **25** and **26** was achieved in 56% overall yield (**25**/**26** = 3:8) by treatment with a large amount of palladium-on-carbon (10%) in boiling 95% ethanol[29]. The two products (**25** and **26**) were readily separable by flash chromatography on silica gel. Assignment of

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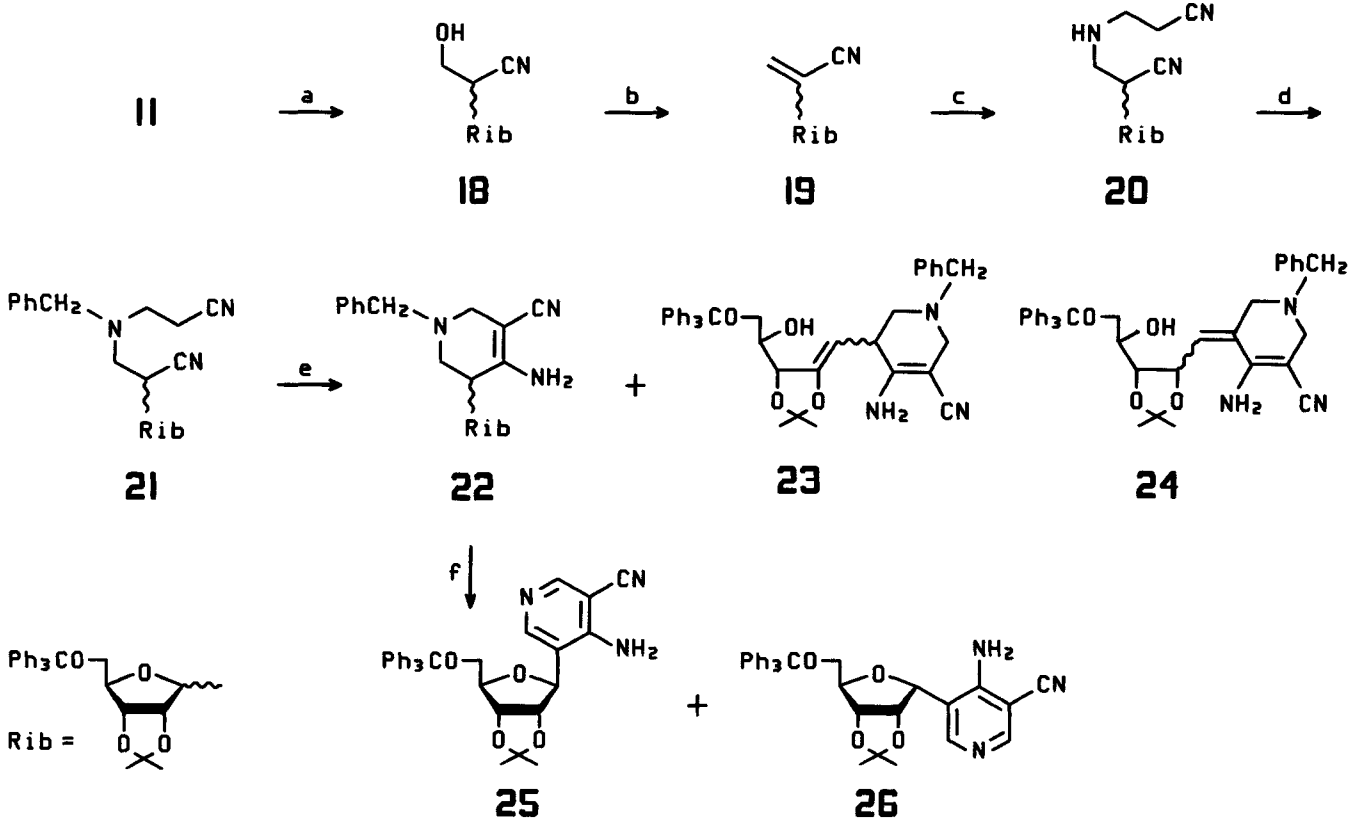
Scheme 2



a = $NaBH_4$, EtOH, 0°C; **b** = CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0°C, then 25°C; **c** = $H_2N\text{-}CH_2\text{-}CH_2\text{-}CN$, MeOH, 25°C; **d** = $PhCH_2Br$, $NaHCO_3$, EtOH, Δ; **e** = $(CH_3)_3COK$, t-BuOH, Δ, ½ hr; **f** = 10% Pd-C, EtOH, Δ.

the anomeric configurations of **25** and **26** was based on a comparison of their ^{1}H NMR spectra. Thus, the spectrum of the α-isomer **26** exhibited a signal for H-1' appearing further downfield (δ 5.27) than that of the β-isomer **25** (δ 4.75)[30] as well as a smaller Δδ value for the difference in the chemical shifts of its isopropylidene methyl groups (0.18 ppm vs 0.24).[31] The multiplicity of the H-4' signal (pseudo-triplet for **26**, multiplet for **25**) was also consistent with the empirical rules derived from previous studies on isopropylidenated nucleosides.[18,32]

Studies on the elaboration of the pyrido[4,3-d]pyrimidine system from o-aminonitriles **25** and **26** (Scheme 3) were initially directed towards the adenosine C-nucleoside analog **8**. Unlike the case of 4-ribosylated 3-amino-2-cyano-pyrroles, -thiophenes, and -furans, treatment of o-aminonitrile **26** (used in all pilot experiments because of its ready availability) with formamidine acetate did not lead to formation of the fused pyrimidine ring. Thus, the desired pyrido[4,3-d]pyrimidine product was not obtained even under forced conditions.[33] However, treatment of **26** with triethyl orthoformate in the presence of acetic anhydride afforded imidate **27α** (R = Et) which, upon treatment with saturated methanolic ammonia,[34] gave the desired pyrido[4,3-d]pyrimidine **28α** in poor yield together with a predominant amount of the starting material **26** produced by ammonolysis of the imidate ester. The use of trimethyl orthoformate to generate imidate **27α** (R = Me), followed (without isolation) by ammonia treatment,[35] provided **28α** in better yield with only minor ammonolysis to **26**. A similar sequence from **25** afforded the desired β-isomer **28β** via **27β** (R = Me). Both **28β** and **28α** could be readily deprotected (6% HCl in MeOH) to the corresponding pyrido[4,3-d]pyrimidine C-nucleosides **8** and **29**, which were obtained in 55% and 41% overall yields from **25** and **26**, respectively.

Syntheses of the corresponding inosine analogs **7** and **32** were carried out by utilization of the readily available o-aminonitriles **25** and **26**, respectively. Preliminary studies on the more abundant α-isomer **26** showed that it could be readily converted into the corresponding o-aminoamide intermediate **30α** (H_2O_2/EtOH, aq. NH_3). Annulation of the latter with triethyl orthoformate/acetic anhydride[36,37] afforded pyrido[4,3-d]pyrimidine C-nucleoside **31α** in excellent yield. Application of the same procedure to o-aminoamide **30β** gave a similarly good yield of the desired blocked β C-nucleoside **31β**. Deprotection of both isomers **31α** and **31β** by treatment with 6% HCl in methanol gave **32** and

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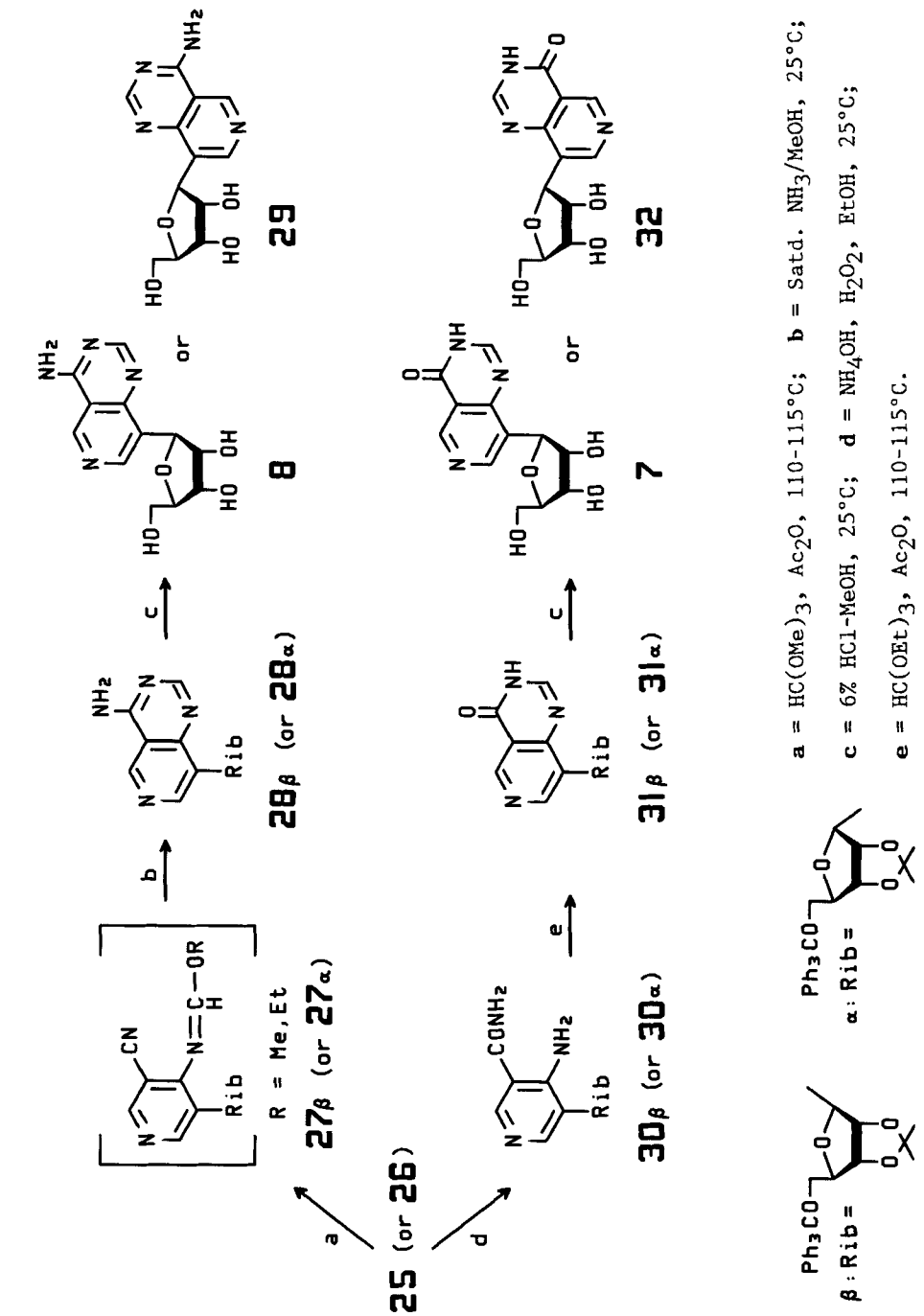
Scheme 3



inosine analog **7** (in 65% and 66% overall yields from **26** and **25**, respectively).

The same ^{1}H NMR criteria that had been used to determine the anomeric configuration of C-nucleoside precursors **25** and **26** were also found to apply consistently to the α,β pair of isomers of the adenosine analog **28** (for **28α**: δ H-1' = 6.21, Δδ = 0.12, H-4' pseudotriplet, while for **28β**: δ H-1' = 5.80, Δδ = 0.33, H-4' multiplet). The same relationships held true for the α,β pair of isomers of the inosine analog **31** (for **31α**: δ H-1' = 6.23, Δδ = 0.10 , H-4' pseudotriplet, while for **31β**: δ H-1' = 5.73, Δδ = 0.31, H-4' multiplet) and for their aminoamide intermediates **30** (for **30α**: δ H-1' = 5.26, Δδ = 0.17, H-4' pseudo-triplet, while for **30β**: δ H-1' = 4.76, Δδ = 0.25, H-4' multiplet).

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The approach described above for the synthesis of pyrido[4,3-d]-pyrimidine C-nucleosides **7** and **8** (a modified Thorpe-Ziegler annulation to a nonaromatic heterocycle followed by aromatization, and finally ring-closure of a second fused heterocycle) should be applicable, in principle, to a number of novel 6:6 bicyclic C-nucleoside analogs.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 137B Infracord spectrophotometer. UV spectra were recorded on a Gilford Response II spectrometer. Unless stated otherwise, ^{1}H NMR spectra were recorded on a JEOL FX-90Q (90 MHz) spectrometer. Nicolet (300 MHz) and Varian XL-200 (200 MHz) spectrometers were used in a few cases, as indicated in the spectral data. Chemical shifts are reported as δ values with Me_4Si as the internal standard. High Resolution (chemical ionization) mass spectra were recorded on a VG 7070E spectrometer at Rockefeller University (Mass Spectrometric Biotechnology Resource) by Dr. Frank H. Field and his coworkers. Microanalyses were performed by M.H.W. Laboratories, Phoenix, AZ. Thin-layer chromatography was performed on 250 μm silica gel GH plates (Analtech, Inc., Newark, DE.) or on RP-18, $F_{254}s$ (250 μm) plates (EM Science), and the substances were visualized with short-wave (254 nm) UV light and/or by spraying with 10% ethanolic sulfuric acid and charring. Preparative TLC was performed on 1,000 μm layers of silica gel (20 X 20 cm, Uniplate™ by Analtech, Inc.) and the products were visualized by short-wave UV light. Flash column chromatography was performed on Merck silica gel 60 (230-400 mesh, ASTM). Light petroleum

ether (bp 30-60°C) was used whenever this solvent was required. Reversed phase column chromatography was performed on 40μm Bakerbond™ Octadecyl (C_{18}) low pressure chromatography packing (J. T. Baker Chemical Company, Philipsburgh, NJ). Palladium on activated carbon (10%) was purchased from Alfa Products (Catalog no. 89109), Danvers, MA.

N-[2-(2,3-O-Isopropylidene-5-O-trityl-D-ribofuranosyl)-2-cyanovinyl]-3-aminopropionitrile (12). To a solution of (dimethylamino)-acrylonitrile **10** (9.60) g, 18.80 mmol) in CH_2Cl_2 (170 mL) was added a solution of trifluoroacetic acid (10 mL) in water (335 mL). The two-phase reaction mixture was stirred vigorously at ambient temperature for 5 h, and the organic layer was washed thoroughly with water and then with 0.2% aq. $NaHCO_3$ soln. It was then dried (Na_2SO_4), filtered, and evaporated to dryness in vacuo to afford 2-formylacetonitrile **11** as a white foam. Without further purification, **11** was dissolved in a mixture of methanol (115 mL) and water (3.9 mL), and to this solution was added 3-aminopropionitrile.1/2 fumarate (3.20 g, 25.0 mmol) and sodium acetate (4.71 g, 57.4 mmol). The reaction mixture was then stirred for 24 h at ambient temperature. A white precipitate was formed during this period. The mixture was evaporated to dryness in vacuo, and the residue was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (twice). The organic layers were combined, washed successively with water (twice), 0.2% aq. $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated in vacuo to give a crude product as a white foam. It was purified by flash chromatography using petroleum ether-EtOAc (80:20) and petroleum ether-EtOAc (60:40) as successive eluants. After evaporation of the appropriate fractions, enaminopropionitrile **12** was obtained as a mixture of isomers (7.82 g, white foam) in 77% yield.

An analytical sample of the major isomer (one of the α anomers, isolated as a white foam) was obtained by preparative TLC, using multiple developments with petroleum ether-EtOAc (40:60) and isolation of the slowest moving band: IR ($CHCl_3$) 3450 (NH), 2260 (C≡N), 2210 cm^{-1} (C≡N); ^1H NMR ($CDCl_3$) δ 1.33 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.57 (t, 2H, J_{CH_2,CH_2} = 6.6 Hz, CH_2-CN), 3.25 (m, H-5',H-5") overlapping NH-CH_2 q at 3.50 (total = 4H, J_{NH,CH_2} = 6.6 Hz), 4.24 (t, 1H, H-4'), 4.62 (d, 1H, H-1'), 4.70 (narrow m, 2H, H-2',3'), 5.19 (m, 1H, NH, exchanges with D_2O), 6.81 (d, 1H, $J_{NH,CH}$ = 13.2 Hz, olefinic H), 7.35 (m, 15H, $3C_6H_5$); HRMS (CI) m/e $(M-H)^-$ 534.2361 (Calcd. for $C_{33}H_{32}N_3O_4$, 534.2393).

Anal. Calcd. for $C_{33}H_{33}N_3O_4$: C, 74.00; H, 6.21; N, 7.84. Found: C, 73.84; H, 6.35; N, 7.66.

N-[2-(2,3-O-Isopropylidene-5-O-trityl-D-ribofuranosyl)-2-cyanovinyl]-N-methyl-3-aminopropionitrile (13). Solid I_2 (0.253 g, 1.00

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mmol) was gradually added to a mixture of 2-formylacetonitrile **11** (0.241 g, 0.50 mmol), triphenylphosphine (0.288 g, 1.10 mmol), 3-methylamino-propionitrile (0.093 g, 1.10 mmol), and triethylamine (0.310 ml, 2.20 mmol) in dry CH_2Cl_2 (2 mL). The homogeneous, deeply colored, reaction mixture was stirred for 16 h at ambient temperature. Monitoring of the reaction progress by TLC (EtOAc-petroleum ether, 60:40) was hindered by the similar mobilities of 2-formylacetonitrile **11** and dinitrile **13**. The mixture was subjected to preparative TLC (EtOAc-petroleum ether 60:40, multiple developments) to give the dinitrile **13** as a mixture of isomers isolated as a white foam, yield = 0.230 g (84%). An analytical sample of the faster-moving isomer (isolated as a white foam) was obtained by preparative TLC (EtOAc-petroleum ether 55:45, multiple developments): ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.68 (m, 2H, $C\underline{H}_2$-CN), 3.22 (s, 3H, N-$C\underline{H}_3$), 3.26 (m, 2H, H-5',H-5"), 3.65 (m, 2H, N-CH_2), 4.16 (m, 2H, H-1',4'), 4.63 (m, 2H, H-2',3'), 6.33 (s, 1H, olefinic $\underline{H}$), 7.40 (m, 15H, $3C_6\underline{H}_5$); HRMS (CI) m/e MH^+ 550.2694 (calcd. for $C_{34}H_{36}N_3O_4$, 550.2706).

N-[2-(2,3-O-Isopropylidene-5-O-trityl-D-ribofuranosyl)-2-cyanovinyl]-N-(4-methoxybenzyl)-3-aminopropionitrile (14). Solid I_2 (8.694 g, 34.25 mmol) was added in small portions to a magnetically stirred mixture of 2-formylacetonitrile **11** (8.28 g, 17.1 mmol), triphenylphosphine (9.936 g, 37.88 mmol), 3-(4-methoxybenzylamino)propionitrile (7.245 g, 38.081 mmol), and triethylamine (10.69 mL, 76.70 mmol) in dry CH_2Cl_2 (70 mL) at 25°C. The reaction was exothermic and the mixture was cooled initially with cold water. It was stirred for 18 h at 25° C and the mixture was then diluted with CH_2Cl_2, washed with water (thrice), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography using successively EtOAc-petroleum ether (20:80), EtOAc-petroleum ether (25:75), and EtOAc-petroleum ether (30:70) as eluants to give the 4-methoxy-benzyl derivative **14** as a mixture of isomers isolated as a white foam; yield = 10.86 g (97%).

An analytical sample of the fastest moving isomer (a β-epimer) was obtained as a white foam by preparative TLC (EtOAc-petroleum ether 40:60) of the above material: IR ($CHCl_3$) 2260 (C≡N), 2210 cm^{-1} (C≡N); ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H, $C\underline{H}_3$), 1.56 (s, 3H, $C\underline{H}_3$), 2.62 (t, 2H, $C\underline{H}_2$-CN), 3.27 (apparent d, 2H, H-5', H-5"), 3.72 (t, 2H, N-$C\underline{H}_2$), 3.81 (s, 3H, $OC\underline{H}_3$), 4.08 (q, 1H, H-4'), 4.21 (d, 1H, H-1', $J_{1',2'}$ = 4.7 Hz), 4.46 (s, 1H, $C\underline{H}_2$-Ph), 4.61 (m, 2H, H-2',3'), 6.76 (s, 1H, olefinic $\underline{H}$), 6.90 and 7.16 (two 2H d, $C_6\underline{H}_4$OMe), 7.45 (m, 15H, $3C_6\underline{H}_5$).

Anal. Calcd. for $C_{41}H_{41}N_3O_5$: C, 75.09; H, 6.30; N, 6.41. Found: C, 74.91; H, 6.47; N, 6.20.

N-Carbethoxy-N-[2-(2,3-O-isopropylidene-5-O-trityl-D-ribofuran-osyl)-2-cyanovinyl]-3-aminopropionitrile (15). Triethylamine (0.737 g,

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7.28 mmol) and 4-dimethylaminopyridine (0.242 g, 1.98 mmol) were added successively to a magnetically-stirred solution of enaminopropionitrile **12** (0.979 g, 1.83 mmol) in dichloromethane (25 mL). The mixture was cooled to 0°C and then ethyl chloroformate (0.523 mL, 5.47 mmol) was added dropwise under an argon atmosphere. The temperature of the reaction mixture was slowly raised to 25°C and stirring continued for 18 h. The reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography using EtOAc-petroleum ether (20:80) as eluant to give N-carbethoxy derivative **15** as a mixture of isomers (foam): yield = 1.01 g (91%); IR ($CHCl_3$) 2260 (C≡N), 2225 (C≡N), 1740 cm^{-1} (COOEt); ^1H NMR ($CDCl_3$) δ 1.33 and 1.36 (2t, 3H, J_{CH_2,CH_3} = 7.1 Hz, CH_2-$C\underline{H}_3$), 1.32 (s, 3H, $C\underline{H}_3$), 1.53 (s, 3H, $C\underline{H}_3$), 2.80 and 2.83 (2t, 2H, $J_{CH_2\text{-}CN,\ N\text{-}CH_2}$ = 6.3 Hz, $C\underline{H}_2$-CN), 3.24 (m, 2H, H-5', H-5"), 4.27 (m, 6H, H-1',4' N-$C\underline{H}_2$ and O$C\underline{H}_2$), 7.37 (m, 15H, $3C_6\underline{H}_5$), 4.70 (m, 2H, H-2',3'), 7.60 and 7.69 (2s, 1H, olefinic $\underline{H}$); HRMS (CI) m/e $(M-H)^-$ 606.2697 (calcd. for $C_{36}H_{36}N_3O_6$, 606.2604).

Anal. Calcd. for $C_{36}H_{37}N_3O_6$: C, 71.15; H, 6.14; N, 6.91. Found: C, 70.95; H, 6.14; N, 6.75.

2-(2,3-O-Isopropylidene-5-O-trityl-D-ribofuranosyl)-3-(carbethoxyamino)acrylonitrile (16). 3-Aminopropionitrile derivative **15** (0.600 g, 0.987 mmol) was added under an argon atmosphere to a stirred suspension of potassium t-butoxide (0.120 g, 1.07 mmol) in dry THF (20 mL). The mixture was stirred for 16 h at ambient temperature and then concentrated in vacuo. The residue was dissolved in CH_2Cl_2. The solution was then cooled to 0°C and neutralized with aqueous 0.1 N HCl while stirring. After separation, the aqueous layer was extracted again with CH_2Cl_2 (twice) and the combined organic extracts were washed successively with dilute aq. NaCl solution, 2% aq. $NaHCO_3$ solution, then dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography using successively EtOAc-petroleum ether (10:90) and EtOAc-petroleum ether 15:85) as eluants to give product **16** as a mixture of isomers isolated as a white foam; yield = 0.44 g (80%).

An analytical sample of the fast-moving isomer was obtained by preparative TLC (EtOAc-petroleum ether 35:55, multiple developments) and was isolated as a white solid: IR ($CHCl_3$) 3460 (NH), 2230 (C≡N), 1755 cm^{-1} (COOEt); ^1H NMR ($CDCl_3$) δ 1.30 (t, 6H, J_{CH_2,CH_3} = 7.1 Hz, CH_2-$C\underline{H}_3$ and $C\underline{H}_3$), 1.53 (s, 3H, $C\underline{H}_3$), 3.25 (m, 2H, H-5', H-5"), 4.22 (m, 4H, H-1',4' and O-$C\underline{H}_2$), 4.57 (m, 2H, H-2',3'), 7.34 (m, 16H, olefinic $\underline{H}$ and $3C_6\underline{H}_5$; HRMS (CI) m/e $(M-H)^-$ 553.2338 (calcd. for $C_{33}H_{33}N_2O_6$, 553.2339). Anal. Calcd. for $C_{33}H_{34}N_2O_6 \cdot 0.25\ H_2O$: C, 70.89; H, 6.22; N, 5.01. Found: C, 70.86; H, 6.41; N, 4.77.

2-(2,3-O-Isopropylidene-5-O-trityl-D-ribofuranosyl)-3-(4-methoxybenzylamino)acrylonitrile (17). A mixture of (4-methoxy-benzylamino)-

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propionitrile **14** (0.065 g, 0.10 mmol) and DBN (0.025 g, 0.20 mmol) in dry DMF (1 mL) was heated at 90-100°C for 20 h. The mixture was concentrated to dryness in vacuo at 50°C and the residue dissolved in CH_2Cl_2, washed thoroughly with H_2O, dried (Na_2SO_4) and concentrated in vacuo. The residue was subjected to preparative TLC (EtOAc-petroleum ether 35:65, multiple developments) and the major product band was isolated to give aminoacrylonitrile **17** as a white foam: yield = 0.005 g (8%); ^1H NMR ($CDCl_3$) δ 1.32 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 3.26 (m, 2H, H-5', H-5"), 3.80 (s, 3H, OCH_3), 4.07 (m, 4H, H-1',4' and $CH_2C_6H_5$), 4.57 (m, 2H, H-2',3'), 6.86 (d, upfield part of C_6H_4OMe) and 6.98 (s, olefinic H, total 3H), 7.2 - 7.5 (m, 17H, $3C_6H_5$ and downfield part of C_6H_4OMe); HRMS (CI) m/e MH^+ 603.2864 (calcd. for $C_{38}H_{39}N_2O_5$, 603.2859).

3-Hydroxy-2-(2,3-O-Isopropylidene-5-O-trityl-D-ribofuranosyl)-propionitrile (18). Sodium borohydride (6.17 g, 163.1 mmol) was added in small portions to a magnetically-stirred solution of 2-formylacetonitrile **11** (39.95 g, 82.62 mmol) in absolute ethanol (192 mL) at 0°C. The reaction mixture was stirred for 1 h and neutralized carefully by dropwise addition of glacial acetic acid. The mixture was concentrated in high vacuum at ambient temperature. The residue was dissolved in CH_2Cl_2 and washed with water (thrice), then with saturated aq. NaCl (twice). The organic layer was dried (Na_2SO_4), concentrated in vacuo, and the residue purified by flash chromatography using petroleum ether-EtOAc (90:10) and petroleum ether-EtOAc (80:20) as successive eluants to give 3-hydroxypropionitrile **18** as a mixture of isomers isolated as a white solid; yield = 31.84g (78%): IR ($CHCl_3$) 3685 (OH), 2260 cm^{-1} (C≡N); ^1H NMR ($CDCl_3$) δ 1.32, 1.34, 1.50, 1.52 (4s, 6H, isopropylidene), 2.17, 2.38 (2t, 2H, OH, exch. with D_2O), 3.25 (m, 3H, CH-CN, H-5' and H-5"), 4.10 (m, 3H, CH_2-OH and H-4'), 4.70 (m, 3H, H-1',2', 3'), 7.37 (m, 15 H, $3C_6H_5$).

Anal. Calcd. for $C_{30}H_{31}NO_5$: C, 74.21; H, 6.44; N, 2.88. Found: C, 74.14; H, 6.63; N, 2.77.

2-(2,3-O-Isopropylidene-5-O-trityl-D-ribofuranosyl)acrylonitrile (19). Methanesulfonyl chloride (7.54 g, 65.8 mmol) was added dropwise to a cold (0°C), magnetically-stirred solution of 3-hydroxypropionitrile **18** (29.1 g, 59.2 mmol) and triethylamine (13.3g, 131.4 mmol) in dry CH_2Cl_2 (210 mL). The reaction mixture was maintained for 1 h at 0°C and then for another 1 h at ambient temperature. The mixture was diluted with CH_2Cl_2 then washed with water (thrice). The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give crude **19** as a foam. This was purified by flash chromatography using EtOAc-petroleum ether (5:95) and EtOAc-petroleum ether (10:90) as successive eluants to give **19** as a solid containing the α:β anomers in a 2:1 ratio; yield = 27.45 g (99%). IR ($CHCl_3$) 2240 (C≡N), 1610 cm^{-1} (C=C).

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Anal. Calcd. for $C_{30}H_{29}NO_4$: C, 77.06; H, 6.25; N, 3.00. Found: C, 76.95; H, 6.38; N, 2.91.

A solution of the above material in hexane-ethyl acetate (3:1) readily deposited crystals of **19α** on standing; mp 133 - 134°C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.32 (s, 3H, $C\underline{H}_3$), 1.50 (s, 3H, CH_3), 3.38 and 3.25 (two dd, 4H, H-5' and H-5", J_{gem} = 10.2 Hz, $J_{4',5'} = J_{4',5''}$ = 3.7 Hz), 4.34 (t, 1H, H-4'), 4.72 (dd, 1H, H-3', $J_{2',3'}$ = 5.9 Hz, $J_{3',4'}$ = 0.7 Hz), 4.82 (broad d, 1H, H-1'), 4.93 (dd, 1H, H-2', $J_{1',2'}$ = 4.4 Hz), 6.08 (narrow m, 2H, $=CH_2$), 7.22 - 7.48 (m, 15H, $3C_6\underline{H}_5$).

Following removal of **19α**, concentration of the filtrate afforded a syrup enriched with **19β** (α:β ≈ 1:2), which gave the following ^{1}H NMR spectrum (200 MHz, $CDCl_3$): δ1.32 (s, 3H, $C\underline{H}_3$), 1.55 (s, 3H, $C\underline{H}_3$), 3.39 and 3.19 (two dd, overlapping α signals, H-5' and H-5", $J_{4',5'}$ = 3.9 Hz, $J_{4',5''}$ = 5.3 Hz), 4.23 (m, 1H, H-4'), 4.44 (broad d, 1H, H-1', $J_{1',2'}$ = 4.7 Hz), 4.60 (8-line m, 2H, H-2' and H-3', $J_{2',3'}$ = 6.5 Hz, $J_{3',4'}$ = 3.6 Hz), 6.12 and 6.03 (two narrow m, 1H each, $=CH_2$), 7.22 - 7.48 (m, 15H, $3C_6\underline{H}_5$).

N-[2-(2,3-O-Isopropylidene-5-O-trityl-D-ribofuranosyl)-2-cyanoethyl]-3-aminopropionitrile (20). A mixture of acrylonitrile **19** (27.45 g, 58.71 mmol) and 3-aminopropionitrile (9.198 g, 131.2 mmol) in dry methanol (200 mL) was stirred for 72 h. The mixture was concentrated in vacuo and the residue was purified by flash chromatography using EtOAc-hexane (40:60) and then EtOAc-hexane (45:55) as successive eluants to give product **20** as a mixture of isomers (colorless foam); yield = 30.39g (96%). An analytical sample of the faster-moving isomer (an α anomer) was obtained by preparative TLC of the above material (EtOAc-petroleum ether 40:60) and was obtained as a white foam: IR ($CHCl_3$) 3380 (NH), 2260 cm^{-1} (C≡N); ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3H, $C\underline{H}_3$), 1.50 (s, 3H, $C\underline{H}_3$), 2.45 (t, 2H, $J_{CH_2CN,\ CH_2N}$ = 7.1 Hz, $C\underline{H}_2$-CN), 3.10 (m, 7H, $C\underline{H}$-CN, $C\underline{H}_2$-NH-$C\underline{H}_2$, H-5' and H-5"), 4.20 (t, 1H, H-4'), 4.39 (dd, 1H, H-1', $J_{1',2'}$ = 3.9 Hz, $J_{1',C\underline{H}\text{-CN}}$ = 9.1 Hz), 4.72 (d, 1H, H-3', $J_{2',3'}$ = 6.1 Hz), 4.89 (dd, 1H, H-2'), 7.32 (m, 15H, $3C_6\underline{H}_5$).

Anal. Calcd. for $C_{33}H_{35}N_3O_4$: C, 73.72; H, 6.56; N, 7.82. Found: C, 73.76; H, 6.34; N, 7.55.

One of the β-anomers of **20** (slower moving) was also obtained by preparative TLC; ^{1}H NMR (200 MHz, $CDCl_3$) δ1.33 (s, 3H, $C\underline{H}_3$), 1.55 (s, 3H, $C\underline{H}_3$), 2.47 (t, 2H, $C\underline{H}_2$CN, J = 6.6 Hz), 3.0 (m, 5H, $C\underline{H}$-CN and $C\underline{H}_2$-NH-$C\underline{H}_2$), 3.35 (8-line m, 2H, H-5' and H-5"), 4.05 (t, 1H, H-1', $J_{1',2'}$ = $J_{1',C\underline{H}\text{-CN}}$ = 4.4 Hz), 4.16 (m, 1H, H-4'), 4.61 (m, 2H, H-2',3'), 7.2 - 7.5 (m, 15H, $3C_6\underline{H}_5$).

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N-Benzyl-N-[2-(2,3-O-isopropylidene-5-O-trityl-D-ribofuranosyl)-2-cyanoethyl]-3-aminopropionitrile (21). A mixture of 3-aminopropionitrile **20** (29.94 g, 55.69 mmol), sodium bicarbonate (5.14 g, 61.18 mmol), benzyl bromide (10.47 g, 61.21 mmol) in absolute ethanol (90 mL), was heated to reflux for 2 h. The reaction mixture was then concentrated in high vacuum and the residue was partitioned between CH_2Cl_2 and 10% aq. $NaHCO_3$. The aq. layer was thrice extracted with CH_2Cl_2 and the combined organic layers washed with water, dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography using EtOAc-petroleum ether 20:80 afforded **21** as a mixture of isomers (white foam), yield = 18.97 g (54%, 76% on the basis of recovered **20**): IR ($CHCl_3$) 2265 cm^{-1} (C≡N); ^1H NMR ($CDCl_3$) δ 1.33 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 2.41 (m, 2H, CH_2-CN), 3.05 (m, 7H, CH_2-N-CH_2, CH-CN, H-5' and H-5"), 3.81 (m, 2H, CH_2-Ph), 4.22 (m, 2H, H-1',4'), 4.71 (m, 2H, H-2',3'), 7.34 (m, 20H, $4C_6H_5$). Anal. Calcd. for $C_{40}H_{41}N_3O_4$: C, 76.53; H, 6.58; N, 6.69. Found: C, 76.49; H, 6.65; N, 6.52.

Further elution with EtOAc-petroleum ether 50:50 afforded 8.70 g of unreacted starting material **20**.

4-Amino-1-benzyl-5-(2,3-O-isopropylidene-5-O-trityl-D-ribofuranosyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile (22). A mixture of potassium t-butoxide (2.413 g, 21.50 mmol) in dry t-butanol (100 mL) was heated to reflux under an argon atmosphere for 10 min. A solution of N-benzylaminopropionitriles **21** (13.50 g, 21.50 mmol) in warm, dry t-butanol (100 mL) was added dropwise at reflux temperature and then heating was continued for half an hour. The mixture was cooled to 0°C, diluted with water, and stirred vigorously for 15 min. and then extracted thrice with EtOAc. The combined organic layers were washed with dil. aq. NaCl (twice), dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography of the residue using, successively, EtOAc-petroleum ether (90:10) and then EtOAc-petroleum ether (80:20), afforded enaminonitrile **22** as a mixture of isomers (yield = 8.12 g, 60%). An analytical sample of the faster-moving isomer of **22** (one of the α-anomers) was obtained by preparative TLC (EtOAc-petroleum ether, 20:80, multiple developments) as a colorless solid: IR ($CHCl_3$) 3550, 3430 (NH_2), 2210 cm^{-1} (C≡N); ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.64 (m, 3H, H-5 and H-6), 2.97 (d, 1H, $J_{H\text{-}2a,H\text{-}2b}$ = 13.2 Hz, H-2a) 3.21 (d, 1H, H-2b), 3.11 (dd, 1H, $J_{5',5''}$ = 10.2 Hz, $J_{4',5'}$ = 4.8 Hz, H-5'), 3.19 (dd, 1H, $J_{4',5''}$ = 3.9 Hz, H-5"), 3.42 and 3.68 (2d, 2H, J_{gem} = 12.8 Hz, N-CH_2-Ph), 4.18 (apparent t, 1H, H-4'), 4.28 (dd, 1H, $J_{1',2'}$ = 3.4 Hz, $J_{1',5}$ = 8.8 Hz, H-1'), 4.34 (dd, 1H, $J_{2',3'}$ = 5.9 Hz, H-2'), 4.62 (dd, 1H, $J_{3',4'}$ = 1.0 Hz, H-3'), 5.02 (broad s, 2H, NH_2, exch. in D_2O), 7.35 (m, 20H, $4C_6H_5$); HRMS (CI) m/e $(M-H)^-$ 626.3028 (Calcd. for $C_{40}H_{40}N_3O_4$, 626.3019).

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Anal. Calcd. for $C_{40}H_{41}N_3O_4$: C, 76.53; H, 6.58; N, 6.69. Found: C, 76.62; H, 6.67; N, 6.58.

Further elution of the column with EtOAc-petroleum ether (40:60) afforded a mixture of two isomeric by-products (2.93 g, 22%) identified as **23** on the basis of IR, NMR, and high-resolution mass spectrometry. Analytical samples of each isomer of **23** were obtained as foams by subjecting the mixture to preparative TLC (three developments with CH_2Cl_2-MeOH 100:2 and then final development with CH_2Cl_2-MeOH 100:2.5).

For **23a** (slower-moving component): IR ($CHCl_3$) 3630 (OH), 3550, 3430 (NH_2), 2200 cm^{-1} (C≡N); ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 2.30 (dd, 1H, $J_{H\text{-}5,H\text{-}6a}$ = 5.5 Hz, $J_{6a,6b}$ = 11.8 Hz, H-6a), 2.40 (broad m, 1H, OH, exch. in D_2O), 2.63 (dd, 1H, $J_{H\text{-}5,H\text{-}6b}$ = 4.7 Hz, H-6b), 3.05 (broad s, 2H, H-2), 3.30 (m, 3H, H-5, H-5' and H-5"), 3.57 (m, 2H, N-CH_2-Ph), 3.82 (m, 1H, H-4'), 3.70 (m, 2H, NH_2, exch. in D_2O), 4.25 (dd, 1H, $J_{1',3'}$ = 1.4 Hz, $J_{1',5}$ = 9.1 Hz, H-1'), 4.65 (dd, 1H, $J_{3',4'}$ = 4.1 Hz, H-3'), 7.30 (m, 20H, $4C_6H_5$); HRMS (CI) m/e $(M-H)^-$ 626.3067 (calcd. for $C_{40}H_{40}N_3O_4$, 626.3019).

Anal. Calcd. for $C_{40}H_{41}N_3O_4$: C, 76.53; H, 6.58; N, 6.69. Found: C, 76.63; H, 6.67; N, 6.61.

For **23b** (faster-moving component): IR ($CHCl_3$) 3625 (OH), 3550, 3435 (NH_2), 2200 cm^{-1} (NH_2); ^1H NMR ($CDCl_3$) δ 1.34 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 2.38 (m, 3H, OH and H-6), 3.07 (broad s, 2H, H-2), 3.31 (m, 3H, H-5, H-5' and H-5"), 3.57 (apparent d, 2H, N-CH_2-Ph), 3.77 (m, 1H, H-4'), 4.50 (m, 3H, NH_2 and H-1', changes to dd after exchange with D_2O, $J_{1',3'} \simeq 1$ Hz and $J_{1',5}$ = 9.0 Hz), 4.70 (dd, 1H, $J_{3',4'}$ = 5.8 Hz, H-3'), 7.34 (m, 20H, $4C_6H_5$).

Anal. Calcd. for $C_{40}H_{41}N_3O_4$: C, 76.53; H, 6.58; N, 6.69. Found: C, 76.74; H, 6.42; N, 6.73.

4-Amino-5-(2,3-O-isopropylidene-5-O-trityl-β-D-ribofuranosyl)-pyridine-3-carbonitrile (25) and 4-Amino-5-(2,3-O-isopropylidene-5-O-trityl-α-D-ribofuranosyl)pyridine-3-carbonitrile (26). The isomeric mixture of cyclic enaminonitrile **22**, obtained in the previous step, (7.613 g, 12.13 mmol) was dissolved in warm 95% ethanol (300 mL), and the solution was cooled to ambient temperature. Palladium on activated carbon (10%, 30.45 g) was carefully added under an atmosphere of N_2. The mixture was heated to reflux for 1 h under N_2. It was then filtered and the catalyst was washed thoroughly with hot alcohol, then with hot $CHCl_3$. The filtrates were combined and concentrated to dryness *in vacuo*. Flash chromatography using successively petroleum ether-EtOAc (90:10), petroleum ether-EtOAc (85:15), and petroleum ether-EtOAc

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(80:20) as eluants gave the β-isomer **25** (1.03 g, 15%) as a white, analytically-pure solid: IR ($CHCl_3$) 3550, 3425 (NH_2), 2240 cm^{-1} (C≡N); ^1H NMR ($CDCl_3$) δ 1.37 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 3.52 (m, 2H, H-5', H-5"), 4.26 (m, 1H, H-4'), 4.75 (m, 3H, H-1',2',3'), 5.56 (broad s, 2H, NH_2, exch. with D_2O), 7.31 (m, 15H, $3C_6H_5$), 8.35 (s, 1H, H-6), 8.42 (s, 1H, H-2); HRMS (CI) m/e MH^+ 534.2456 (calcd. for $C_{33}H_{32}N_3O_4$, 534.2393).

Anal. Calcd. for $C_{33}H_{31}N_3O_4 \cdot 0.4H_2O$: C, 73.29; H, 5.93; N, 7.77. Found: C, 73.19; H, 6.15; N, 8.12.

Further successive elutions of the column with petroleum ether-EtOAc (75:25), then petroleum ether-EtOAc (70:30) afforded the α-isomer **26** as a white solid: yield 2.86 g (41%); IR ($CHCl_3$) 3590, 3475 (NH_2), 2240 cm^{-1} (C≡N); ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.32 (m, 2H, H-5', H-5"), 4.40 (apparent t, 1H, H-4'), 4.73 (apparent d, 1H, H-3'), 4.91 (dd, 1H, $J_{1',2'}$ = 3.8 Hz, $J_{2',3'}$ = 6.0 Hz, H-2'), 5.27 (d, 1H, H-1'), 5.76 (broad s, 2H, NH_2, exch. with D_2O), 7.36 (m, 15H, 3 C_6H_5), 8.16 (s, 1H, H-6), 8.40 (s, 1H, H-2).

Anal. Calcd. for $C_{33}H_{31}N_3O_4 \cdot 0.4H_2O$: C, 73.29; H, 5.93; N, 7.77. Found: C, 73.25; H, 5.95; N, 8.07.

4-Amino-8-(2,3-O-isopropylidene-5-O-trityl-α-D-ribofuranosyl)-pyrido[4,3-d]pyrimidine (28α). o-Aminonitrile **26** (0.620 g, 1.16 mmol) was added to trimethyl orthoformate (6.1 mL) and acetic anhydride (6 mL), and the mixture was stirred continuously for 4 h at 110-115°C. The mixture was then evaporated to dryness in high vacuum. The crude imino ester (**27α**) thus obtained was dissolved without purification in saturated (0°C) methanolic ammonia (75 mL) and stirred in a closed pressure-resistant vessel for 5 h at ambient temperature. The reaction mixture was then concentrated in vacuo and the residue was subjected to flash chromatography using hexane-EtOAc (30:70) to give first some of the o-aminonitrile **26** (0.155 g). Further successive elution with hexane-EtOAc (50:50) and then with CH_2Cl_2-MeOH (92:8) afforded pyridopyrimidine **28α** as a white solid: yield 0.340 g (70% on the basis of recovered **26**); IR ($CHCl_3$) 3600, 3480 cm^{-1} (NH_2); ^1H NMR ($CDCl_3$) δ 1.23 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 3.37 (two dd, 2H, $J_{4',5'}$ = 4.7 Hz, $J_{4',5"}$ = 4.4 Hz, $J_{5',5"}$ = 10 Hz, H-5',H-5"), 4.47 (apparent t, 1H, H-4'), 4.80 (d, 1H, $J_{2',3'}$ = 6 Hz, H-3'), 5.33 (dd, 1H, $J_{1',2'}$ = 4.1 Hz, H-2'), 6.21 (d, 3H, H-1' and NH_2, NH_2 exch. with D_2O), 7.53 (m, 15H, $3C_6H_5$), 8.72 (s, 1H, H-2), 9.01 (s, 1H, H-5), 9.21 (s, 1H, H-7).

Anal. Calcd. for $C_{34}H_{32}N_4O_4 \cdot 2H_2O$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.55; H, 5.98; N, 9.19.

4-Amino-8-(2,3-O-isopropylidene-5-O-trityl-β-D-ribofuranosyl)-pyrido[4,3-d]pyrimidine (28β). This compound was prepared from o-amino-

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nitrile **25** by a procedure essentially identical to that used in the synthesis of **28α**, except that treatment of **25** with trimethyl orthoformate/acetic anhydride (1:1 v/v) was carried out for 9 h to give imino ester **27β**, which afforded **28β** as a white solid upon treatment with saturated methanolic ammonia: yield = 67% on the basis of recovered **25**; IR ($CHCl_3$) 3600, 3480 (NH_2), 1625, 1615 cm^{-1} (C≡N); ^{1}H-NMR ($CDCl_3$) δ 1.34 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 3.42 (apparent d, 2H, H-5', H-5"), 4.34 (m, 1H, H-4'), 4.87 (dd, 2H, H-2', $J_{2',3'}$ = 6.4Hz), 4.72 (dd, 1H, H-3', $J_{3',4'}$ = 4.7 Hz), 5.80 (d, 1H, $J_{1',2'}$ = 3.3 Hz, H-1'), 6.23 (broad m, 2H, NH_2, exch. with D_2O), 7.35 (m, 15H, $3C_6H_5$), 8.67 (s, 1H, H-2), 8.96 (s, 1H, H-5), 9.21 (s, 1H, H-7); HRMS (CI) m/e MH^+ 561.2599 (calcd. for $C_{34}H_{33}N_4O_4$, 561.2502)

4-Amino-5-(2,3-O-isopropylidene-5-O-trityl-α-D-ribofuranosyl)-pyridine-3-carboxamide (30α). A solution of H_2O_2 (18 mL, 30% aq.) was added dropwise to a mixture of o-aminonitrile **26** (1.50 g, 2.81 mmol) and aq. conc. NH_4OH (60 mL) in ethanol (113 mL). The mixture was stirred at ambient temperature for 2.5 h, then diluted with water (800 mL), and the mixture was repeatedly extracted with EtOAc (4 x 150 mL). The organic layers were combined, washed successively with dil. NaCl soln. (until washings gave neutral pH), then dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography of the residue using CH_2Cl_2 and then CH_2Cl_2-MeOH (95:5) as successive eluants gave o-aminoamide **30α** as an analytically-pure white solid: yield = 1.51 g (97%); IR ($CHCl_3$) 3550, 3490, 3400 (NH_2, $CONH_2$), 1670 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 1.29 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 3.35 (m, 2H, H-5', H-5"), 4.40 (apparent t, 1H, H-4'), 4.74 (d, 1H, $J_{2',3'}$ = 6.0 Hz, H-3'), 4.94 (dd, 1H, $J_{1',2'}$ = 3.6 Hz, H-2'), 5.26 (d, 1H, H-1'), 5.87 (broad s, 2H, NH_2, exch. with D_2O), 7.08 (broad s, $CONH_2$, exch. with D_2O), 7.34 (m, 15H, $3C_6H_5$), 8.15 (s, 1H, H-6), 8.47 (s, 1H, H-2); HRMS (CI) m/e $(M-H)^-$ 550.2198 (calcd. for $C_{33}H_{32}N_3O_5$, 550.2342).

4-Amino-5-(2,3-O-isopropylidene-5-O-trityl-β-D-ribofuranosyl)-pyridine-3-carboxamide (30β). This compound was prepared from o-aminonitrile **25** (0.600 g, 1.12 mmol) by the procedure described above for its α-isomer **30α**, and was obtained in 98% yield (0.61 g) as a white amorphous solid after flash chromatography: IR ($CHCl_3$) 3600, 3500, 3480 (NH_2, $CONH_2$), 1670 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 1.35 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 3.46 (m, 2H, H-5', H-5"), 4.23 (m, 1H, H-4'), 4.76 (narrow m, 3H, H-1',2',3'), 5.97 (broad s, 2H, NH_2, exch. with D_2O), 7.03 (s, 2H, $CONH_2$, exch. with D_2O), 7.34 (m, 15H, $3C_6H_5$), 8.28 (s, 1H, H-6), 8.50 (s, 1H, H-2); HRMS (CI) m/e MH^+ 552.2496 (calcd. for $C_{33}H_{34}N_3O_5$, 552.2498).

Anal. Calcd. for $C_{33}H_{33}N_3O_5 \cdot 1.5\ H_2O$: C, 68.49; H, 6.27; N, 7.26. Found: C, 68.75; H, 6.13; N, 7.10.

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8-(2,3-O-Isopropylidene-5-O-trityl-α-D-ribofuranosyl)pyrido[4,3-d]-pyrimidin-4-(3H)-one (31α). Acetic anhydride (14 mL) was added to a solution of o-aminoamide **30α** (1.42 g, 2.57 mmol) in triethyl orthoformate (14.2 mL) and the mixture was heated at 110-115°C for half an hour. The reaction mixture was evaporated to dryness in high vacuum at 50°C, and the residue was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc (thrice). The organic layers were combined, washed with 10% aq $NaHCO_3$ solution (thrice), then with brine (twice), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash chromatography using CH_2Cl_2 and then CH_2Cl_2-MeOH (95:5) as successive eluants to give **31α** (1.355 g, 94%) as an amorphous solid: IR ($CHCl_3$) 3450 (NH), 1720 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 1.23 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 3.39 (two dd, 2H, H-5', H-5"), 4.45 (apparent t, 1H, H-4'), 4.80 (apparent d, 1H, H-3'), 5.28 (dd, 1H, $J_{1',2'}$ = 4.4, $J_{2',3'}$ = 6.0 Hz, H-2'), 6.23 (d, 1H, H-1'), 7.38 (m, 15H, $3C_6H_5$), 8.23 (s, 1H, H-2), 9.13 (s, 1H, H-7), 9.51 (s, 1H, H-5), 11.76 (broad s, 1H, NH, exch. with D_2O); HRMS (CI) m/e $(M-H)^-$ 560.2344 (calcd. for $C_{34}H_{30}N_3O_5$, 560.2185).

Anal. Calcd. for $C_{34}H_{31}N_3O_5 \cdot H_2O$: C, 70.45; H, 5.74; N, 7.25. Found: C, 70.65; H, 5.75; N, 7.05.

8-(2,3-O-Isopropylidene-5-O-trityl-β-D-ribofuranosyl)pyrido[4,3-d]-pyrimidin-4-(3H)-one (31β). This compound was prepared from o-amino-amide **30β** (0.600 g, 1.09 mmol), triethyl orthoformate (6.1 mL) and acetic anhydride (6 mL) by the method described above for the α-isomer **31α**. It was obtained as an analytically-pure solid after flash chromatography; yield = 605 mg (99%): IR ($CHCl_3$) 3450 (NH), 1710 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 1.34 (s, 3H, CH_3), 1.65 (s, 1H, CH_3), 3.41 (apparent d, 2H, H-5', H-5"), 4.33 (m, 1H, H-4'), 4.75 (m, 2H, H-2',3'), 5.73 (d, 1H, $J_{1',2'}$ = 3 Hz, H-1'), 7.37 (m, 15H, $3C_6H_5$), 8.14 (s, 1H, H-2), 9.07 (s, 1H, H-7), 9.50 (s, 1H, H-5), 11.24 (broad s, 1H, NH, exch. with D_2O). Anal. Calcd. for $C_{34}H_{31}N_3O_5 \cdot 1.5\ H_2O$: C, 69.37; H, 5.82; N, 7.14. Found: C, 69.18; H, 5.63; N, 6.81.

8-β-D-Ribofuranosylpyrido[4,3-d]pyrimidin-4-(3H)-one (7). Pyrido-[4,3-d]pyrimidine **31β** (0.565 g, 1.01 mmol) was deprotected by dissolving it in 6% methanolic hydrogen chloride (10 mL) and stirring the solution at ambient temperature for 1 h. The mixture was concentrated in vacuo to dryness and the residue was triturated with diethyl ether and decanted five times. The crude hydrochloride salt was then dissolved in water, neutralized with aqueous ammonia and the product was purified by reversed phase column chromatography using water as eluant. The desired fractions were combined and lyophilized to give free nucleoside **7** as a white solid; yield = 0.19 g (68%): UV (H_2O) λ max 278.5 (ε 2,400), 232.5

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nm (ε 6,700); ^{1}H-NMR (DMSO-d_6) δ 3.65 (m, 2H, H-5', H-5"), 3.97 (m, 3H, H-2',3',4'), 4.94 (m, 3H, 2',3',5'-hydroxyls, exch. with D_2O), 5.45 (d, 1H, $J_{1',2'}$ = 3.8 Hz, H-1'), 8.33 (s, 1H, H-2), 9.05 (s, 1H, H-7), 9.21 (s, 1H, H-5), 12.67 (broad s, 1H, NH, exch. with D_2O).

Anal. Calcd. for $C_{12}H_{13}N_3O_5 \cdot H_2O$: C, 48.49; H, 5.09; N, 14.14. Found: C, 48.59; H, 4.82; N, 14.11.

8-α-D-Ribofuranosylpyrido[4,3-d]pyrimidin-4-(3H)-one (32). This compound was prepared by unblocking nucleoside **31α** (1.11 g, 1.98 mmol) in 6% methanolic hydrogen chloride (20 mL) using the method described above for **7**. C-Nucleoside **32** was obtained as a white solid after reversed phase chromatography; yield = 0.395 g (71%): UV (H_2O) λ max 278 (ε 3,300), 230.5 nm (ε 8,500); ^{1}H-NMR (DMSO-d_6) δ 3.58 (m, 2H, H-5', H-5"), 3.97 (m, 1H, H-4'), 4.21 (m, 2H, H-2',3'), 4.55 - 5.00 (m, 3H, 2',3'and 5'-hydroxyls, exch. with D_2O), 5.67 (d, 1H, $J_{1',2'}$ = 2.5 Hz, H-1'), 8.30 (s, 1H, H-2), 8.82 (s, 1H, H-7), 9.18 (s, 1H, H-5), 12.7 (broad s, 1H, NH, exchanges with D_2O).

Anal. Calcd. for $C_{12}H_{13}N_3O_5 \cdot 0.9\ H_2O$: C, 48.78; H, 5.05; N, 14.22. Found: C, 49.00; H, 5.01; N, 13.92.

4-Amino-8-β-D-ribofuranosylpyrido[4,3-d]pyrimidine (8). This compound was prepared by treatment of **28β** with 6% methanolic hydrogen chloride under conditions identical to those utilized for the synthesis of **7**. This procedure afforded **8** in 82% yield as a white solid: UV (H_2O) λ max 303 (ε 9,900), 244 nm (ε 10,900); ^{1}H-NMR (DMSO-d_6) δ 3.63 (broad m, 2H, H-5', H-5"), 3.98 (m, 3H, H-2',3',4'), 4.81 (d, 1H, $J_{OH,CH}$ = 4.4 Hz, CH-OH, exch. with D_2O), 5.22 (m, 2H, CH_2-OH and CH-OH, exch. with D_2O), 5.39 (d, 1H, $J_{1',2'}$ = 4.9 Hz, H-1'), 8.33 (broad s, 2H, NH_2, exch. with D_2O), 8.53 (s, 1H, H-2), 8.89 (s, 1H, H-7), 9.47 (s, 1H, H-5); HRMS (CI) m/e $(M-H)^-$ 277.0978 (calcd. for $C_{12}H_{13}N_4O_4$, 277.0937).

Anal. Calcd. for $C_{12}H_{14}N_4O_4 \cdot 1.6\ H_2O$: C, 46.93; H, 5.65; N, 18.24. Found: C, 46.74; H, 5.65; N, 17.89.

4-Amino-8-α-D-ribofuranosylpyrido[4,3-d]pyrimidine (29). This compound was obtained by treatment of **28α** with 6% methanolic hydrogen chloride under conditions identical with those described for the synthesis of **7**. This procedure afforded **29** in 58% yield as a white solid after reversed phase column chromatography: UV (H_2O) λ max 303.5 (10,100), 239.5 nm (ε 9,800); ^{1}H-NMR (DMSO-d_6) δ 3.58 (m, 2H, H-5', H-5"), 3.93 (m, 1H, H-4'), 4.24 (m, 2H, H-2',3'), 4.5 - 5.0 (m, 3H, 2',3'and 5'-hydroxyls, exch. with D_2O), 5.69 (d, 1H, $J_{1',2'}$ = 2.5Hz, H-1'), 8.23 (broad s, 2H, NH_2, exch. with D_2O), 8.51 (s, 1H, H-2), 8.71 (s, 1H, H-7), 9.43 (s, 1H, H-5); HRMS (CI) m/e $(M-H)^-$ 277.0981 (calcd. for $C_{12}H_{13}N_4O_4$, 277.0937).

Anal. Calcd. for $C_{12}H_{14}N_4O_4 \cdot H_2O$: C, 48.65; H, 5.44; N, 18.91. Found: C, 48.48; H, 5.28; N, 18.71.

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1) Support of this investigation by funds from the American Cancer Society (grant CH-305) and from the Department of Health and Human Services (grant CA-24634) is gratefully acknowledged. Additional support from the Cancer Center Support Grants CA-13330 (for work carried out at Montefiore Medical Center) and CA-08748 (for work carried out at Memorial Sloan-Kettering Cancer Center) is also acknowledged.

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19) Although in our previous work[2-4] intermediate **9** (X = NH) did not afford the desired o-aminonitrile pyrrole, several of its derivatives (X = NBn, NCOOR) readily undergo ring closure under a variety of conditions.

20) This reagent (NaH/THF, 25°C, 16 h) converts **9** (X=NCOOEt) into the desired pyrrole in moderate-to-good yields.

21) The reaction of **11** with secondary amines under these conditions was originally developed in our laboratory for the synthesis of the N-alkylated pyrrolo[3,2-d]pyrimidines corresponding to **1** and **4** (unpublished results). The role of Ph_3P-I_2 is to generate the reactive intermediate $(Ph)_3P^+O$-CH=C(Rib)CN I^-, which is more susceptible to nucleophilic substitution than **11** itself.

22) Attempts to obtain **14** by direct N-alkylation of **12** with p-methoxybenzyl chloride under a variety of conditions were not satisfactory, in contrast to the facile carbethoxylation of **12** with ClCOOEt, which affords **15**.

23) These conditions included NaOEt (1eq)/EtOH + DMF, 25°C; t-BuOK (1eq)/THF, 25°C, and DBN/DMF, 90-100°C.

24) These conditions included t-BuONa/t-BuOH, 25°C or reflux; Cs_2CO_3 /THF, 25°C or reflux; and lithium diisopropylamide/THF.

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28) a) These two minor products are presumably formed from **24**, which, somewhat surprisingly, must isomerize under the reaction conditions used. The structures assigned to **23** rest on the following spectral evidence. The IR signals at 2200 cm^{-1} are indicative of an isolated 3,4 enaminonitrile double bond (cf 2210 cm^{-1} for **22**). In the ^{1}H-nmr spectra of **23**, the C6-methylene protons appear as 8-line multiplets that feature substantial couplings (4 - 5 Hz) to the C5 methine protons. For each isomer, H-3' and the vinylic proton (H-1') appear as double doublets with small allylic couplings to each other ($J_{1',3'} \approx 1$ Hz) and larger vicinal couplings to H-4' ($J_{3',4'} = 4 - 6$ Hz) or H-5 ($J_{1',5} \approx 9$ Hz), respectively. The relatively high chemical shift ($\delta \approx 4.25$) seen for H-1' is appropriate for a vinyl ether. The observed chemical shift and coupling constant patterns, which were confirmed by homodecoupling measurements, do not accommodate structure **24**. For example, H-5 would be absent in **24**, and the H-6 resonances would reveal only small allylic couplings instead of the 4-6 Hz vicinal couplings actually observed. b) In addition to **23a** and **23b**, a third **23** isomer was isolated from the reaction of **21** with potassium t-butoxide in THF.

29) a) A similar type of aromatization was observed by Danishefsky et al. in the facile debenzylation and dehydrogenation of an N-benzyl-1,2,3,4-tetrahydroquinoline with Pd/C (5%) at room temperature and atmospheric pressure in absolute ethanol. Danishefsky, S.; Cavanaugh, R.; J. Org. Chem., **1968**, 33, 2959. b) It is also possible to convert **22** into a mixture of **25** + **26** (albeit in somewhat lower yield) via a two-step process involving first hydrogenolytic debenzylation using Pd-C (10%)/ammonium formate in dry methanol (Ram, S.; Spicer, L. D; Tetrahedron Lett., **1987**, 28, 515) followed by aromatization of the N-debenzylated enamine product under the conditions described herein for the direct conversion of **22** → **25** + **26**.

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