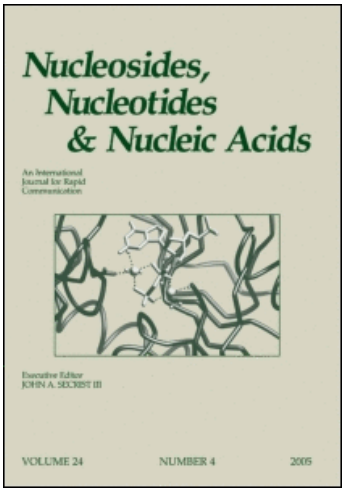

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STUDIES ON THE SYNTHESIS OF FURO[3,2-d]PYRIMIDINE C-NUCLEOSIDES: NEW INOSINE ANALOGUES WITH ANTIPROTOZOAN ACTIVITY.[1]

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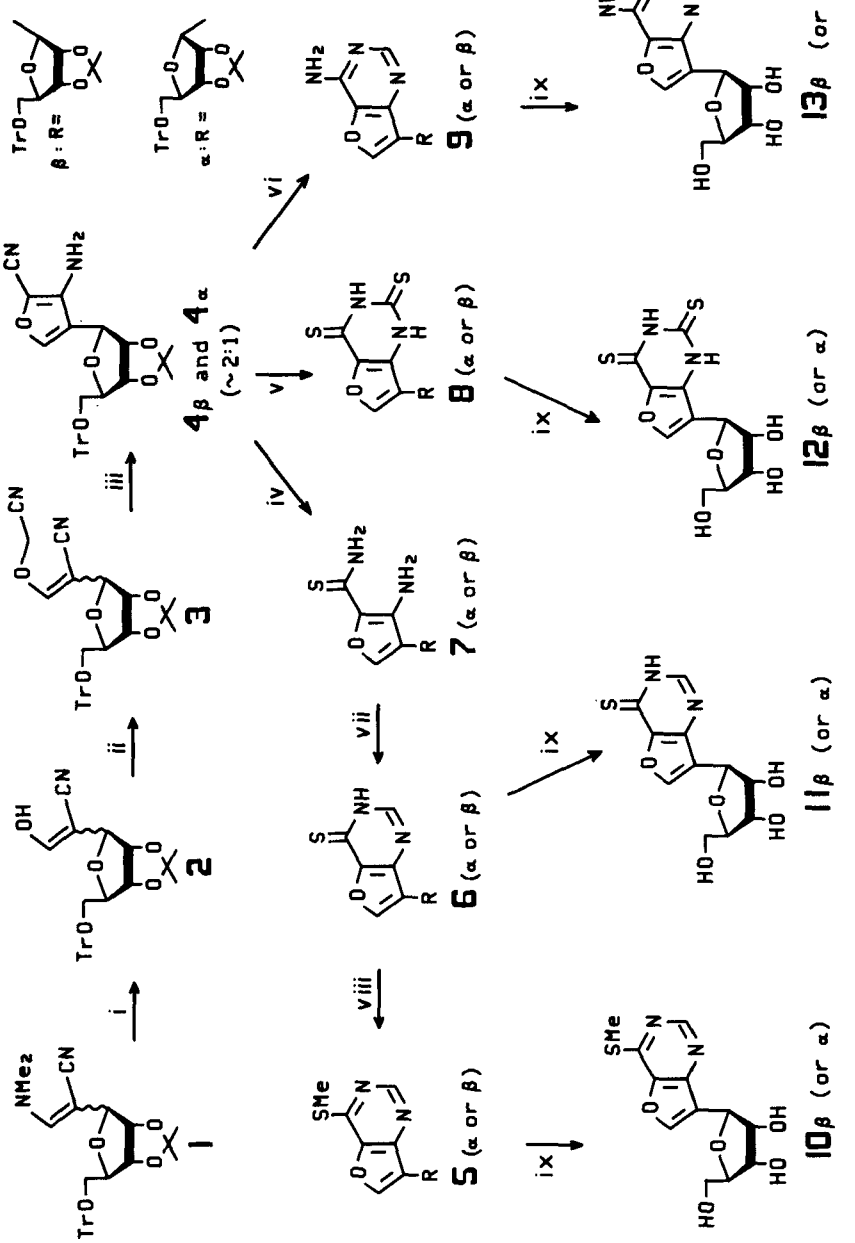
Abstract: Methods are described for the synthesis of the α and β anomers of 7-D-ribofuranosylfuro[3,2-d]pyrimidines substituted at C-4 with either amino, oxo, thiono, or methylthio groups. The analogous 2,4-dithiono compounds are also described. The key steps involve the LDA-promoted cyclizations of the cyano ethers **3** and **14** to give, respectively, the substituted furan C-nucleosides **4** and **16**. After separation of anomers, these compounds were subjected to a number of pyrimidine-ring-forming reactions to give the desired bicyclic C-nucleosides. The adenosine analogue **13** is markedly cytotoxic to mouse L1210 cells in vitro, and the inosine analogue **20** shows activity against the pathogenic protozoans Leishmania donovani and Trypanosoma gambiense.

The parasitic protozoans Leishmania sp. and Trypanosoma sp. are unable to synthesize purine nucleotides de novo and are thus dependent on purine salvage for their growth.[2] This deficiency is being exploited in the development of drugs, and it has been found that several analogues of the purine nucleoside inosine effectively inhibit the proliferation of these organisms. Examples include allopurinol riboside,[3,4,5a] Formycin B,[4,5] and 9-deazainosine.[5,6] The latter compound, a catabolically-stable C-nucleoside developed in this laboratory, is capable of late-stage cures of African trypanosomiasis in a murine model when used in combination with α-difluoromethylornithine.[7a] 9-Deazainosine is also active against Pneumocystis carinii pneumonia in rats.[8]

The selectivity of inosine analogues that are active against these parasitic protozoans results from their differential metabolism.

Scheme 1



i) CF_3COOH / CH_2Cl_2, H_2O ; ii) $ClCH_2CN$, KF, 18-Crown-6 / DMF, 20° ; iii) LDA / THF, -70° ; iv) H_2S / Pyridine; v) CS_2 / Pyridine ; vi) NH_2-CH=NH.CH_3COOH / EtOH ; vii) $HC(OEt)_3$; viii) MeI, K_2CO_3 / MeOH ; ix) 6% HCl / MeOH

Leishmania and trypanosomes possess a phosphotransferase activity that converts inosine analogues into their corresponding nucleoside 5'-monophosphates.[3] Mammalian cells are less effective at phosphorylating these compounds. More significantly, their adenylosuccinate synthetase/lyase enzyme systems have different substrate specificities compared to mammalian cells and are able to convert these IMP analogues into the corresponding analogues of AMP.[3] For example, 9-deazainosine is converted into the phosphorylated derivatives of 9-deazaadenosine by both leishmania and trypanosomes, but not by mammalian cells.[7] Since 9-deazaadenosine[9] and its nucleotides are acutely cytotoxic compounds, the formation of these adenosine nucleotide analogues in these protozoans is responsible for the differential toxicity of 9-deazainosine. As a consequence of these metabolic differences, inosine analogues are often relatively non-toxic to mammalian cells at levels that are lethal to the parasites.

The foregoing "amination hypothesis" of inosine analogue cytotoxicity[7b] has led to the general strategy that whenever an adenosine congener is found to be a cytotoxic compound, the corresponding inosine analogue is a good candidate for evaluation as an antiprotozoal agent. In a preliminary report,[10] we have recently described the oxa equivalent of 9-deazaadenosine, namely the furo[3,2-d]pyrimidine C-nucleoside **13β** (Scheme 1). This compound is apparently recognized metabolically as an adenosine analogue, and it is indeed appreciably cytotoxic towards mammalian cells *in vitro*. This has prompted the synthesis of the corresponding inosine congener, which, together with the details of the synthesis of **13β** and some additional analogues, forms the subject of the present paper.

Our synthetic approach to furo[3,2-d]pyrimidine C-nucleosides starts with the 3-dimethylaminoacrylonitrile **1**. This versatile intermediate has been used in the synthesis of oxazinomycin[11] as well as a variety of purine-like C-nucleosides.[6,9,12] The controlled hydrolysis of enamine **1** with trifluoroacetic acid in a two-phase system (water-CH_2Cl_2) affords the blocked 2-(D-ribofuranosyl)-2-formylacetonitrile **2** in excellent yield. Conversion of **2** into the cyano ether **3** was achieved by treating the mixed isomers with chloroacetonitrile in dry DMF in the presence of potassium fluoride and 18-crown-6. The resulting α,β/*cis-trans* isomers of **3** were obtained in a combined yield of 84%. They can be separated by

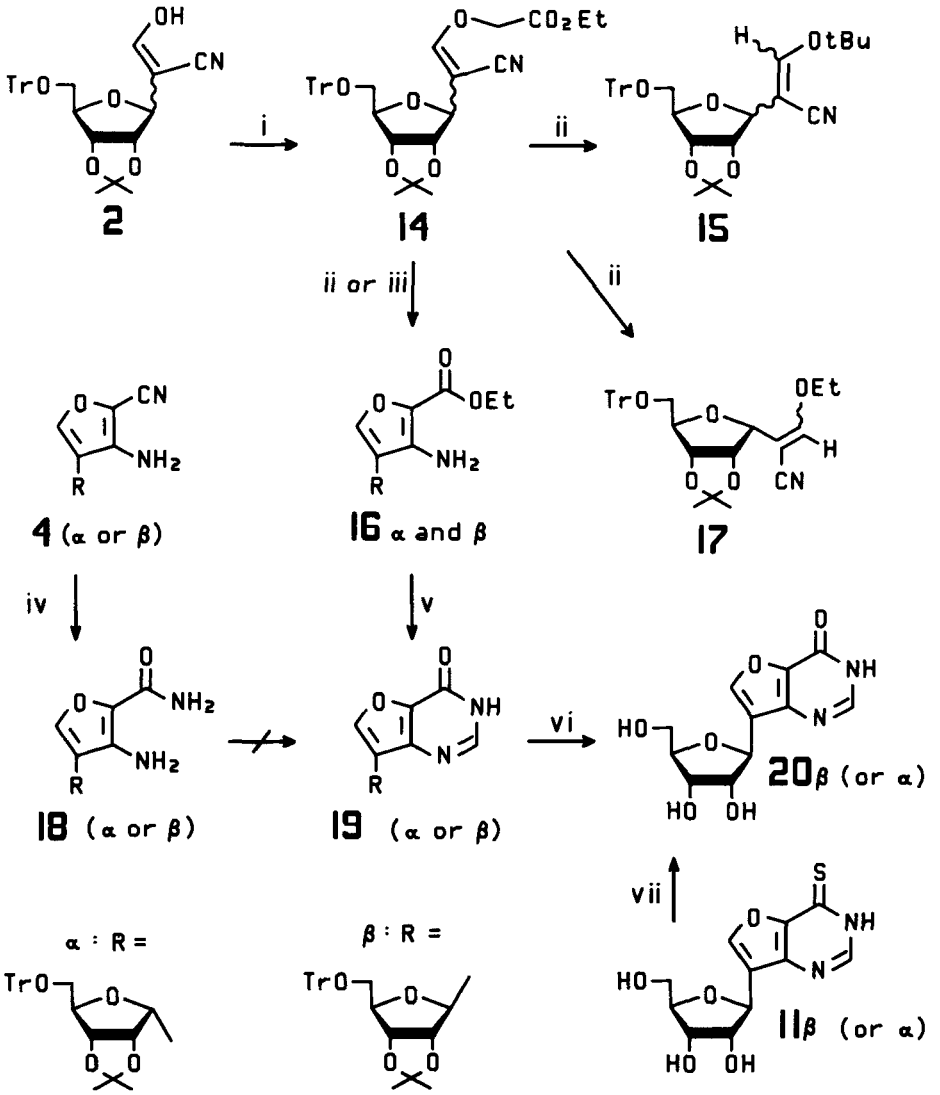
silica gel chromatography, but this offers no advantage over using the mixed isomers in the following annulation step.

Because of our earlier experiences with the synthesis of ribosyl pyrroles[6,9] and thiophenes,[12a] we expected that **3** would readily undergo Thorpe-Ziegler cyclization to give **4** when exposed to bases such as sodium ethoxide or DBN. In practice, these bases as well as the stronger bases potassium t-butoxide and n-butyl lithium proved to be unsatisfactory with **3**. However, cyclization does occur when **3** is treated with a fourfold excess of LDA in tetrahydrofuran at -70°, and the resulting aminonitriles **4** are formed in a β:α ratio of about 2:1, judging from the nmr spectrum of the crude product. After a quite difficult separation by column chromatography, the epimers **4β** and **4α** were isolated in yields of 22% and 17.5%, respectively.

The aminonitriles **4** are versatile intermediates for obtaining a number of furo[3,2-d]pyrimidine C-nucleosides, as shown in Scheme 1. For example, treatment of the separated epimers with formamidine acetate in refluxing ethanol affords the protected 4-amino derivatives **9α** or **9β** in yields of better than 75%. Similarly, annulation of the **4** epimers with carbon disulfide in hot pyridine leads to the dithiones **8α** or **8β**, again in excellent yields. For the synthesis of the 4-thiones **6**, the epimers of **4** were first converted into the thioamides **7α** and **7β** by treatment with hydrogen sulfide in pyridine. Treatment of the **7** epimers with triethyl orthoformate then affords **6α** or **6β**, which were each methylated to give the corresponding 4-methylthio derivatives **5**. No instances of anomerization were noted in any of these reactions. Each of the epimers was subsequently deblocked by treatment with 6% hydrochloric acid in methanol. The nucleosides **10** - **13** were obtained in excellent yield, again with no evidence of anomerization.

At the outset, we envisaged that the aminonitrile **4β** would also serve as the source of the inosine congener **20β** (Scheme 2) via the amide **18β**. In practice, **4** can be converted satisfactorily into amide **18** by reaction with alkaline hydrogen peroxide, but the subsequent reaction of **18** with triethyl orthoformate, somewhat surprisingly, leads only to decomposition and affords none of the expected **19**. We have therefore examined an alternative approach from **2** that proceeds via the esters **14** and **16**. This route parallels that shown in Scheme 1 for the synthesis of **4** and it uses many of the same techniques. Thus, alkylation of **2**

Scheme 2



i) $ClCH_2COOEt$, KF, 18-Crown-6 / DMF, 20° ; ii) KOt-Bu / t-BuOH, CH_2Cl_2, 20° ; iii) LDA / THF, -70° ; iv) H_2O_2 / NH_4OH ; v) NH_2-CH=NH.CH_3COOH / EtOH ; vi) 6% HCl / MeOH ; vii) HCl / DMSO

with chloroethylacetate to afford **14** was carried out in the presence of potassium fluoride and 18-Crown-6 in DMF, as had been done in the synthesis of the analogous nitrile **3**. As with **3**, the base-promoted cyclization of **14** proved to be difficult. The strong base LDA was again the most satisfactory of those tried, and by conducting the reaction at -75° it was possible to obtain the α-and β-anomers of the amino-esters **16** in about 20% yield each following separation by silica gel column chromatography. Conversion of the separate anomers of **16** into the furo[3,2-d]pyrimidin-4(3H)-ones **19** by reaction with formamidine acetate, and final deblocking to give **20α** and **20β**, was then accomplished using standard procedures.

In an attempt to improve the yield of the amino-esters **16**, we have also examined the reaction of **14** with potassium t-butoxide in some detail. On treatment with four equivalents of the base in a mixture of t-butanol and dichloromethane at room temperature, **14** does in fact cyclize to give a mixture of **16α** and **16β**. The difficulty is that several side products are also formed, and these complicate the separation process. For example, the desired β-anomer of **16** could not be separated from the t-butyl ether **15**, a compound that is formed in about 13% yield presumably by Michael addition of butoxide ion to **14** followed by loss of ethyl glycolate. In most runs, the presence of **15** also adversely affects the separation of **16α**. Treatment of the mixture of **15** and **16β** with formamidine acetate readily affords a mixture of **15** and **19β**, which can be separated chromatographically. From the amount of **19β** obtained, we estimate that **16β** must have been formed from **14** in about 25% yield, which is only a slight improvement over the LDA method. A second unexpected product, namely the ethyl ether **17**, was obtained from **14** in 25% yield from the column chromatography fractions. This compound is probably formed in a manner analogous to that of **15**, except that ethanol derived ultimately from the ethyl ester group must have been involved. The substantial formation of by-products such as **15** and **17** from **14**, together with the demanding column separations, makes the butoxide approach to the inosine congener **20** much less practical than the LDA approach. However, we have also developed an entirely different route to **20** as follows.

During the routine characterization of the hydrochloride salts of the thiones **11** by ^{1}H-nmr spectroscopy, we made the serendipitous observation that these compounds are converted slowly into the inosine

congeners **20** simply on standing in DMSO-d_6 at the probe temperature. This process takes place in several discrete steps. For example, the original proton resonances of **11β** are completely replaced within a 2.5 hr period by those of an intermediate compound. The resonances of a second intermediate then appear over the course of several days, together with those of the product **20β**. The entire process is markedly accelerated by the addition of hydrochloric acid, and it represents a synthetically-useful route for obtaining the inosine congeners. Thus, both **20α** and **20β** were obtained in yields of about 80% from their respective thiones **11** when the reactions were conducted on a preparative scale in ordinary DMSO. On checking the literature we found that similar findings had already been reported by Mikolajczyk and Luczak[13] with regard to the formation of uracil from mono- and dithiouracils. Their reactions, which were conducted with an equivalent amount of sulfuric acid in DMSO at 80°, also proceed in good yield. The mechanism of these transformations is not known with any certainty, but the finding that the conversions **11α,β** → **20α,β** occur stepwise suggests that it might be possible to isolate the intermediates for structural identification.

The configurations at C-1' of the nucleosides shown in Schemes 1 and 2 were determined by using a number of ^{1}H-nmr criteria that have been developed from studies of both C- and N-nucleosides. These criteria include the empirical rules that H1' of the α-isomers resonates downfield of H1' of the β-isomers;[14] that H4' in the 2',3'-O-isopropylidene-5'-O-trityl derivatives appears as a pseudotriplet for the α-isomers and a higher multiplet for the β-isomers;[15] and that the Δδ value of the isopropylidene methyl resonances is <0.15 ppm for the α-isomers and >0.15 ppm for the β-isomers.[16] The various values noted for the epimer pairs in the present study are consistent with these observations. For example, the Δδ values average 0.15 ppm for compounds assigned the α-configuration, and 0.23 ppm for compounds assigned the β-configuration.[17]

We have also taken the opportunity afforded by the availability of numerous anomeric pairs of C-nucleosides to examine the effects of the C1'-configuration on their ^{13}C-nmr spectra. The appropriate data are gathered in Table 1. In a definitive study of the chemistry of C-glycosyl compounds with epimerizable substituents, the Syntex group[18] established a correlation between the ^{13}C-nmr shifts of the isopropylid-

TABLE 1

^{13}C-NMR data for certain Furo[3,2-d]pyrimidine (**5,6,8,9,19**) and Furan (**4,7,18**) C-Nucleosides.

	Ribosyl					Isopropylidene			Base		
Cmpd.	C1'	C2'	C3'	C4'	C5'	Me	Me	C	C7	C2	C6
5α	75.8	81.6	83.7	83.4	63.8	26.4	25.2	112.8	118.0	153.1	148.8
5β	78.7	84.5	82.7	84.3	64.2	27.5	25.6	114.4	120.8	153.2	147.5
6α	75.8	81.7	83.6	83.4	64.4	26.3	25.1	112.8	119.3	144.3	151.3
6β	78.3	84.6	82.6	84.2	64.1	27.5	25.6	114.6	121.8	144.4	149.9
8α	75.8	82.9	83.9	82.9	64.5	26.6	24.1	112.6	113.1	170.7	148.9
8β	78.5	84.7	82.4	84.1	63.6	27.5	25.5	115.6	115.6	171.4	146.7
9α	75.6	81.5	83.6	83.3	63.4	26.3	25.1	112.6	117.9	153.4	147.7
9β	78.8	84.5	82.7	84.3	64.3	27.6	25.7	114.4	121.0	153.8	146.6
19α	75.8	81.4	83.7	83.4	64.2	26.3	25.2	112.8	119.0	144.7	149.3
19β	78.5	84.7	82.6	84.2	64.2	27.5	25.7	114.5	121.8	144.7	147.9
									C4	2-subst	C5
4α	76.7	82.8	83.5	83.2	64.6	26.2	24.6	112.9	114.3	110.5	144.9
4β	78.8	84.3	81.7	83.5	63.2	27.4	25.5	115.1	116.9	110.3	143.0
7α	76.6	82.8	83.4	83.2	64.7	26.3	24.7	112.9	115.0	180.5	141.9
7β	79.2	84.4	82.0	83.6	63.5	27.6	25.6	115.2	118.0	180.7	139.7
18α	76.7	82.9	83.3	83.3	64.7	26.3	24.7	112.8	115.0	162.6	141.9
18β	79.2	84.4	81.9	83.6	63.5	27.6	25.6	115.1	117.9	162.5	139.9

Solvent: $CDCl_3$. Data were obtained at 22.52MHz on a JEOL FX90Q, except for **19α** and **19β**, which were measured at 50.31MHz on a Varian XL-200 spectrometer. Selective decoupling measurements carried out with the epimer pairs **5α,5β** and **6α,6β**, and with the α-C-ribosyl compound **17** (see experimental), were used to confirm the assignments of the ribosyl carbon atoms. The splittings due to $J_{C6,H1'}$ in the coupled spectra were used to differentiate the C-6 resonances from C-2.

ene methyl groups and the anomeric configuration. Thus, in the β series, methyl signals appear at 25.5 ± 0.2 and 27.5 ± 0.2 ppm, while in the α series they are at 24.9 ± 0.3 and 26.3 ± 0.2 ppm. Later work by the same group,[19] and by Cousineau and Secrist,[20] found a similar correlation for the central isopropylidene carbon, which resonates at 114.5 ± 0.6 ppm for β anomers, and 112.7 ± 0.6 ppm for α anomers. The values found for the present compounds are generally in excellent agreement with these ranges, with the exception of **8α** and **8β**, where the methyl shifts and the chemical shift of the central carbon, respectively, are slightly outside the ranges given above. The value of 115.2 ppm noted for the chemical shift of the central isopropylidene carbon of **7β** is also slightly larger than expected.

A number of studies of both N- and C-glycosyl compounds have established that the anomeric carbon in the isomer having a cis relationship between the aglycon and the C2'-oxygen substituent resonates at higher field than the isomer having a trans relationship.[18,21] This shielding effect, which results from steric crowding, means that the α anomer of D-ribofuranosyl compounds is expected to have the smaller C1' chemical shift. From the data in Table 1, it is seen that C1' in the α anomers does, in fact, occur an average of 2.7 ppm upfield of C1' in the β anomers. Comparable upfield shifts are evident for C2' and C7 (or C4 for the furans) in the α series. It will also be noted that whereas C2' in the α series resonates upfield of C3', the sequence is reversed in the β series. We have also noted this alternation with the anomer pairs of 5-(2',3'-O-isopropylidene-D-ribofuranosyl)thieno[3,4-d]pyrimidine,[22] and the same phenomenon is apparent on examination of the Syntex data.[18,23]

With regard to the biological activities of the furo[3,2-d]pyrimidine C-nucleosides, we noted in the introduction that the adenosine congener **13β** is markedly cytotoxic towards mammalian cells. For example, the IC_{50} value against mouse L1210 cells averages 0.004 μg/ml (about 13 nM).[24] This value is about a log order higher than the IC_{50} values found for the corresponding pyrrolo- and thieno[3,2-d]pyrimidine C-nucleosides in the same system.[9,12d] On the other hand, the thione **11β** - an analogue of 6-mercaptopurine riboside - shows an average IC_{50} value of 7 μg/ml in the L1210 system, and is therefore not considered to be active.

The antiprotozoan activity of compounds **11β** and **20β** were evaluated against the hemoflagellates Trypanosoma cruzi, T. gambiense and Leishmania donovani. Neither of the compounds is active against T. cruzi, but they do show activity against T. gambiense and L. donovani. The inosine congener **20β** is the most promising since it shows IC_{50} values of 0.02 and 0.15 μg/ml, respectively, against T. gambiense and L. donovani while showing relatively little toxicity towards human U937 cells (IC_{50} of 10 μg/ml). The thione **11β** is somewhat less active, with IC_{50} values of 0.7 μg/ml against both L. donovani and T. gambiense. However, the IC_{50} value of about 4 μg/ml noted for **11β** against U937 cells means that the therapeutic index is not as good as that of **20β**. The adenosine congener **13β** is very active against L. donovani (IC_{50} of 0.001 μg/ml), but, as expected, it is toxic to U937 cells (IC_{50} of 0.1 μg/ml).

From the results obtained to date, it appears that the biological activities of the furo[3,2-d]pyrimidine C-nucleosides broadly parallel those of other purine-like C-nucleosides. That is, the adenosine analogues tend to be much more toxic than the inosine analogues to mammalian cells, whereas both types of analogues tend to be toxic to the above blood parasites. Whether or not the antiprotozoan activity of the inosine congener **20β** results from the parasite's ability to convert it into the nucleotide forms of **13β** remains to be determined. Further studies on the furo[3,2-d]pyrimidine system would appear to be warranted, including the development of more efficient synthetic approaches.[26]

EXPERIMENTAL SECTION

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined at 89.61 MHz (proton) and 22.52 MHz (^{13}C) on a JEOL FX90Q spectrometer. Proton chemical shifts were measured relative to internal tetramethylsilane whereas ^{13}C chemical shifts were measured relative to the solvent absorbance and then corrected to the TMS scale. The designation ψt in the descriptions of proton spectra refers to a doublet of doublets that has the appearance of a triplet. First order values are given for coupling constants and chemical shifts. Ultraviolet spectra were recorded on a Gilford Response II spectrophotometer. Tlc analyses were carried out with Analtech silica gel GF plates (250μm), and separated materials were visualized with uv light and/or by spraying with 10% ethanolic sulfuric acid followed by heating. Merck silica gel (230-400

mesh ASTM) was used for preparative column chromatography. All evaporations were carried out under reduced pressure in a rotary evaporator. Microanalyses were performed by MHW Laboratories, Phoenix, Arizona. Drug sensitivity studies against Trypanosoma cruzi (Peru strain), T. gambiense (TH114 strain) and Leishmania donovani (Sudan 1 strain) were performed as previously described.[25]

2-(2,3-O-Isopropylidene-5-O-trityl-D-ribofuranosyl)-2-formylacetonitrile (2). A solution of trifluoroacetic acid (40 ml) in water (1000 ml) was added to a solution of the dimethylaminoacrylonitrile derivative[11] **1** (40 g, 78.56 mmol) in dichloromethane (700 ml), and the mixture was stirred vigorously at room temperature for 6 hr. The organic layer was separated and washed thoroughly with water. After drying over sodium sulfate, the dichloromethane solution was evaporated to dryness to afford **2** as a foam in 90% yield. This material was used without further purification.

Synthesis of the 2-(D-ribofuranosyl)cyano ethers 3. The protected 2-(D-ribofuranosyl)-2-formylacetonitrile **2** (4.00 g, 8.28 mmol), potassium fluoride (0.96 g, 16.58 mmol) and 18-crown-6 (1.75 g, 6.62 mmol) were dissolved in dry dimethylformamide (80 ml), and the solution was stirred under an atmosphere of nitrogen at 20°. Chloroacetonitrile (1.88 g, 24.84 mmol) was added dropwise, and the reaction mixture was stored for 20 hr. The solution was evaporated to dryness (oil pump) and the residue was subjected to flash chromatography, with benzene-ethyl acetate (9:1) being used as the developing solvent. The individual isomers of **3** can be separated by this procedure, but the mixture of α,β/cis-trans isomers (3.62 g, 84%) obtained as a foam by concentrating the appropriate fractions was used for the following step. Anal. Calcd. for $C_{32}H_{30}N_2O_5$: C, 73.56; H, 5.75; N, 5.36. Found: C, 73.45; H, 5.87; N, 5.15.

3-Amino-2-cyano-4-(2,3-O-isopropylidene-5-O-trityl-β-D-ribofuranosyl)-furan (4β) and the α isomer (4α). The cyano ether **3** (8 g, 15.31 mmol) was dissolved in 200 ml of dry THF and the solution was stirred and cooled to -70° under a nitrogen atmosphere. A solution of LDA (6.57 g, 61.3 mmol) in 50 ml of dry THF was added dropwise while the temperature was maintained at -70°. After 2 hr, the flask was removed from the cooling bath and the reaction was quenched by the addition of 5 ml of water. Stirring was continued for an additional hour at room temperat-

ure before the reaction mixture was evaporated to dryness. The residue was partitioned between dichloromethane (20 ml) and water, and the organic layer was separated and washed with three additional batches of water. The dichloromethane layer was then dried over sodium sulfate, the filtrate and washings were evaporated to dryness, and the residue was fractionated by flash chromatography using petroleum ether-ether, 10:1.

The faster moving product, **4β**, (Rf 0.64, toluene-ethyl acetate; 9:1) was obtained as a colorless foam (1.75 g, 22%) after evaporation of the appropriate fractions; ^{1}H-nmr ($CDCl_3$)[27] δ 1.36 and 1.57 (2s, MeCMe), 3.31 and 3.42 (7-line m, H5'a and H5'b), 4.18 (m, H4'), 4.53 - 4.79 (overlapping m, H1', H2' and H3'), 7.18 - 7.44(m, trityl and H5), 4.16 (bs, NH_2, ex D_2O), $J_{4',5'a} = J_{4',5'b} = 4.2$Hz, $J_{3',4'} = 4.0$Hz, $J_{5'gem} = 11$Hz. Anal. Calcd. for $C_{32}H_{30}N_2O_5$: C, 73.56; H, 5.75; N, 5.36. Found: C, 73.59; H, 6.04; N, 5.16.

The slower moving isomer, **4α**, (Rf 0.45, toluene-ethyl acetate; 9:1) was also obtained as a colorless foam (1.40 g, 17.5%); ^{1}H-nmr ($CDCl_3$)[27] δ 1.34 and 1.49 (2s, MeCMe), 3.35 and 3.24 (7-line m, H5'a and H5'b), 4.29 (ψt, H4'), 4.78 (d, H3'), 4.88 (dd, H2'), 5.12 (d, H1'), 7.48 - 7.22 (m, trityl and H5); 4.27 (bs, NH_2, ex D_2O), $J_{1',2'} = 4.5$, $J_{2',3'} = 5.8$, $J_{3',4'} < 0.5$, $J_{4',5'a} = J_{4',5'b} = 4.2$, $J_{5'gem} = 10.2$ Hz. Anal. Calcd. for $C_{32}H_{30}N_2O_5$: C, 73.56; H, 5.75; N, 5.36. Found: C, 73.42; H, 5.89; N, 5.19.

4-Amino-7-(2,3-O-isopropylidene-5-O-trityl-β-D-ribofuranosyl)furo[3,2-d]pyrimidine (9β). Formamidine acetate (1.58 g, 15.19 mmol) was added to a solution of **4β** (0.80 g, 1.52 mmol) in ethanol (25 ml), and the reaction was heated under reflux for 48 hr. Following removal of the solvent, the residue was partitioned between dichloromethane and water, and the organic layer was washed several times with water. The dichloromethane layer was dried over sodium sulfate, solids were removed by filtration, and the filtrate was evaporated to dryness. Pure **9β** (670 mg, 80%) was obtained following flash chromatography (dichloromethane-methanol, 12:1) and crystallization from a mixture of carbon tetrachloride and petroleum ether; mp 95°; ^{1}H-nmr ($CDCl_3$)[27] δ 1.37 and 1.61 (2s, MeCMe), 3.30 and 3.26 (m, H5'a and H5'b), 4.34 (m, H4'), 4.76 (dd, H3'), 5.11 (dd, H2'), 5.25 (dd, H1'), 7.18 - 7.58 (m, trityl), 7.73 (d, H6), 8.45 (s, H2), 5.2 (bs, NH_2, ex D_2O), $J_{1',2'} = 4.0$, $J_{1',6} = 1.0$, $J_{2',3'} = 6.2$, $J_{3',4'} = 3.6$, $J_{4',5'a} = 4.0$, $J_{4',5'b} = 5.0$, $J_{5'gem} = 10.2$Hz. Anal. Calcd. for $C_{33}H_{31}N_3O_5$: C, 72.13; H, 5.65; N, 7.65. Found: C, 72.14; H, 5.62; N, 7.41.

4-Amino-7-(2,3-O-isopropylidene-5-O-trityl-α-D-ribofuranosyl)furo[3,2-d]pyrimidine (9α) was obtained in 75% yield from **4α** by using the procedure described above for the β isomer; mp 116-117°, ^{1}H-nmr ($CDCl_3$)[27] δ 1.30 and 1.45 (2s, MeCMe), 3.25 (ψd, H5'a,b), 4.36 (ψt, H4'), 4.77 (d, H3'), 4.90 (dd, H2'), 5.40 (dd, H1'), 7.2 - 7.5 (m, trityl), 7.90 (d, H6), 8.44 (s, H2), ~5.4 (bs, NH_2, ex D_2O), $J_{1',2'}$ = 3.6, $J_{1',6}$ = 1.0, $J_{2',3'}$= 6.2, $J_{3',4'}$ < 0.5, $J_{4',5'a}$ = $J_{4',5'b}$ = 5.0, $J_{5'gem}$ = 10.2Hz. Anal. Calcd. for $C_{33}H_{31}N_3O_5$: C, 72.13; H, 5.65; N, 7.65. Found: C, 72.16; H, 5.57; N, 7.41.

3-Amino-4-(2,3-O-isopropylidene-5-O-trityl-β-D-ribofuranosyl)furan-2-thiocarboxamide (7β). The furan C-nucleoside **4β** (400 mg, 0.77 mmol) was dissolved in a mixture of pyridine (40 ml) and triethylamine (11 ml), and H_2S gas was bubbled through the solution for 20 min at room temperature. The reaction mixture was then heated in a sealed steel vessel at 60° for 16 hr. After removal of solvents, the residue was subjected to flash chromatography using dichloromethane-methanol, 98:2 as eluant. The thiocarboxamide **7β** was obtained as a pale yellow, tlc-homogeneous foam in 85% yield (360 mg); ^{1}H-nmr ($CDCl_3$) δ 1.35 and 1.58 (2s, MeCMe), 3.31 and 3.41 (8-line m, H5'a and H5'b), 4.24 (m, H4'), 4.74 (overlapping m, H1', H2' and H3'), 6.28 (bs, NH_2, ex D_2O), 6.56 (bs, thioamide, ex D_2O), 7.12 (s, H5), 7.22 - 7.48 (trityl). Anal. Calcd. for $C_{32}H_{32}N_2O_5S$: C, 69.06; H, 5.75; N, 5.03; S, 5.75. Found: C, 69.19; H, 5.77; N, 5.14; S, 5.62.

3-Amino-4-(2,3-O-isopropylidene-5-O-trityl-α-D-ribofuranosyl)furan-2-thiocarboxamide (7α) was obtained in 85% yield from **4α** by using the procedure described above for **7β**; ^{1}H-nmr ($CDCl_3$) δ 1.33 and 1.49 (2s, MeCMe), 3.15 and 3.47 (7-line m, H5'a and H5'b), 4.32 (ψt, H4'), 4.93 (dd, H2'), 4.80 (d, H3'), 5.15 (d, H1'), 6.30 (bs, NH_2, ex D_2O), 6.63 (bs, thioamide, ex D_2O), 7.22 - 7.48 (m, trityl and H5), $J_{1',2'}$ = 3.6, $J_{2',3'}$ = 6.0, $J_{3',4'}$ <0.5Hz. Anal. Calcd. for $C_{32}H_{32}N_2O_5S$: C, 69.06; H, 5.75; N, 5.03; S, 5.75. Found: C, 68.92; H, 5.79; N, 4.82; S, 5.96.

7-(2,3-O-Isopropylidene-5-O-trityl-β-D-ribofuranosyl)furo[3,2-d]pyrimidine-4(3H)-thione (6β). A solution of **7β** (300 mg, 0.54 mmol) in triethyl orthoformate was (7ml) heated at 90° for 1.5 hr. The reaction mixture was then evaporated to dryness and the residue was purified by flash chromatography using dichloromethane-methanol, 15:1, as eluant. Pure **6β** was obtained as a pale yellow foam (280 mg, 92%); ^{1}H-nmr ($CDCl_3$)

δ 1.36 and 1.60 (2s, MeCMe), 3.28 (m, H5'a and H5'b), 4.37 (m, H4'), 4.75 (dd, H3'), 5.02 (dd, H2'), 5.21 (dd, H1'), 7.19 - 7.52 (trityl), 7.94 (d, H6), 8.00 (s, H2), 12.38 (bs, NH, ex D_2O), $J_{1',2'}$ = 3.8, $J_{1',6}$ = 0.7, $J_{2',3'}$ = 6.2, $J_{3',4'}$ = 3.6Hz. Anal. Calcd. for $C_{33}H_{30}N_2O_5S$: C, 69.96; H, 5.30; N, 4.95; S, 5.65. Found: C, 70.13; H, 5.09; N, 5.04; S, 5.86.

7-(2,3-O-Isopropylidene-5-O-trityl-α-D-ribofuranosyl)furo[3,2-d]pyrimidine-4(3H)-thione (6α) was obtained in 82% yield from **7α** by using the procedure described above for **6β**; mp 155-156°; ^{1}H-nmr ($CDCl_3$) δ 1.29 and 1.40 (2s, MeCMe), 3.14 - 3.48 (8-line m, H5'a and H5'b), 4.35 (ψt, H 4'), 4.79 (d, H3'), 5.05 (dd, H2'), 5.55 (dd, H1'), 7.19 - 7.52 (m, trityl), 8.10 (s, H2), 8.12 (d, H6), $J_{1',2'}$ = 3.8, $J_{1',6}$ = 0.8, $J_{2',3'}$ = 6.0, $J_{3',4'}$ < 0.5 . Anal. Calcd. for $C_{33}H_{30}N_2O_5S$: C, 69.96; H, 5.30; N, 4.95; S, 5.65. Found: C, 69.77; H, 5.49; N, 5.08; S, 5.67.

4-Methylthio-7-(2,3-O-isopropylidene-5-O-trityl-β-D-ribofuranosyl)-furo[3,2-d]pyrimidine (5β). Methyl iodide (151 mg, 1.06 mmol) and potassium carbonate sesquihydrate (25 mg) were added to a solution of **6β** (150 mg, 0.265 mmol) in methanol (25 ml), and the mixture was stirred at room temperature for 45 min. The reaction mixture was then evaporated to dryness and the residue was partitioned between water and dichloromethane. The organic phase was washed three times with water and then dried over sodium sulfate. The residue obtained after removal of solvent was purified by flash chromatography, using dichloromethane-methanol, 49:1, as the eluant. Pure **5β** (148 mg) was obtained in 96% yield; ^{1}H-nmr ($CDCl_3$) δ 1.37 and 1.61 (2s, MeCMe), 2.71 (s, SMe), 3.25 (m, H5'a,b), 4.37 (m, H4'), 4.76 (dd, H3'), 5.11 (dd, H2'), 5.23 (dd, H1'), 7.17 - 7.47 (m, trityl), 7.79 (d, H6), 8.81 (s, H2), $J_{1',2'}$= 3.8, $J_{2',3'}$= 6.3, $J_{3',4'}$= 3.6, $J_{1',6}$ = 1.1Hz. Anal. Calcd. for $C_{34}H_{32}N_2O_5S$: C, 70.34; H, 5.52; N, 4.83; S, 5.52. Found: C, 70.06; H, 5.60; N, 4.59; S, 5.32.

4-Methylthio-7-(2,3-O-isopropylidene-5-O-trityl-α-D-ribofuranosyl)-furo[3,2-d]pyrimidine (5α) was obtained in 87% yield from **6α** by using the procedure described above for **5β**; ^{1}H-nmr ($CDCl_3$) δ 1.29 and 1.42 (2s, MeCMe), 2.70 (s, SMe), 3.29 (ψd, H5'a,b), 4.38 (ψt, H4'), 4.81 (d, H3'), 5.04 (dd, H2'), 5.53 (dd, H1'), 7.23 - 7.52 (m, trityl), 7.99 (d, H6), 8.84 (s, H2), $J_{1',2'}$ = 3.6, $J_{1',6}$ = 0.8, $J_{2',3'}$ = 5.8, $J_{3',4'}$ <0.5Hz. Anal: Calcd. for $C_{34}H_{32}N_2O_5S$: C, 70.34; H, 5.52; N, 4.83; S, 5.52. Found: C, 70.14; H, 5.61; N, 4.65; S, 5.37.

7-(2,3-O-Isopropylidene-5-O-trityl-β-D-ribofuranosyl)furo[3,2-d]-pyrimidine-2,4(1H,3H)-dithione (8β). Carbon disulfide (210 mg, 0.95 mmol) was added to a solution of **4β** (500 mg, 0.95 mmol) in dry pyridine (80 ml), and the mixture was heated under reflux for 2 hr.[28] After cooling and removal of solvent, several portions of toluene were added to and evaporated from the residue in order to remove residual pyridine. The crude product was subjected to flash chromatography using dichloromethane-methanol, 15:1, as the solvent system. Pure **8β** (480 mg) was obtained as a pale yellow solid in 85% yield; mp 135-136°; ^{1}H-nmr ($CDCl_3$) δ 1.37 and 1.61 (2s, MeCMe), 3.15 - 3.52 (8-line m, H5'a and H5'b), 4.39 (m, H4'), 4.61 - 4.82 (overlapping m, H2' and H3'), 4.88 (unresolved m, broadened by virtual coupling, H1'), 7.20 - 7.71 (m, trityl), 7.73 (d, H6), 9.86 and 10.53 (2bs, N1-H and N3-H, ex D_2O), $J_{1',6}$ = 1.4 Hz. Anal. Calcd. for $C_{33}H_{31}N_2O_5S_2$: C, 66.11; H, 5.18; N, 4.67; S, 10.68. Found: C, 66.05; H, 5.05; N, 4.59; S, 10.72.

7-(2,3-O-Isopropylidene-5-O-trityl-α-D-ribofuranosyl)furo[3,2-d]-pyrimidine-2,4(1H,3H)-dithione (8α) was obtained in 92% yield from **4α** by using the procedure described above for **8β**; ^{1}H-nmr ($CDCl_3$) δ 1.34 and 1.61 (2s, MeCMe), 3.30 - 3.39 (7-line m, H5'a and H5'b), 4.38 (ψt, H4'), 4.8 - 4.9 (overlapping m, H2' and H3'), 5.29 (d, H1'), 7.22 - 7.38 (m, trityl), 7.67 (s, H6), 9.87 and 10.80 (2bs, N1-H and N3-H), $J_{1',2'}$ = 2.7Hz. Anal. Calcd. for $C_{33}H_{31}N_2O_5S_2$: C, 66.11; H, 5.18; N, 4.67; S, 10.68. Found: C, 66.25; H, 5.32; N, 4.67; S, 10.49.

Synthesis of the 2-(D-ribofuranosyl)ethoxycarbonyl ethers 14. The protected 2-ribofuranosyl)-2-formylacetonitrile **2** (8.00 g, 16.56 mmol), potassium fluoride (2.5 g, 43.1 mmol) and 18-crown-6 (3.50 g, 13.16 mmol) were dissolved in dry dimethylformamide (120 ml). Chloroethyl-acetate (5.07 g, 41.38 mmol) was added dropwise to the stirred solution, and the reaction mixture was stored at 20° for 5 hr. The reaction mixture was evaporated to dryness (oil pump) and a solution of the residue in 3 ml of benzene was applied to a flash chromatography column. Elution with benzene-ethyl acetate (4:1) afforded a mixture of α,β / cis-trans isomers (6.5 g, 69%) as a rigid foam that was used directly in the following step. Anal. Calcd. for $C_{34}H_{35}NO_7$: C, 71.71; H, 6.15; N, 2.49. Found: C, 71.65; H, 6.29; N, 2.47.

Ethyl-3-amino-4-(2,3-O-isopropylidene-5-O-trityl-β-D-ribofuranosyl)-furan-2-carboxylate (16β) and the α isomer (16α). A solution of LDA (1.14 g, 10.64 mmol) in THF (10 ml) was added dropwise over a period of

30 min to a stirred solution of **14** (1.5 g, 2.63 mmol) in dry THF (40 ml) at -75°. The reaction mixture was maintained at this temperature for an additional 1 hr. Following the addition of water (3 ml) to quench the reaction, the mixture was subjected to the work-up procedure described above for the synthesis of **4β** and **4α**. Following flash chromatography (petroleum ether-ether, 3:1), the faster moving isomer, **16β**, was obtained as a foam in 21% yield (320 mg); ^{1}H-nmr ($CDCl_3$) δ 1.57 and 1.35 (2s, MeCMe overlapped by t of ethyl Me), 3.27 - 3.40 (m, 7-line m, H5'a,b), 4.19 - 4.43 (m, H4' overlapping ethyl CH_2), 4.75 - 4.78 (m, NH_2, ex D_2O, overlapping H1', H2', H3'), 7.22 - 7.45 (m, trityl). Anal. Calcd. for $C_{34}H_{35}NO_7$: C, 71.71; H, 6.15; N, 2.49. Found: C, 71.70; H, 6.08; N, 2.47.

The slower moving isomer, **16α**, was obtained in 20% yield (306 mg) as a pale yellow foam; ^{1}H-nmr ($CDCl_3$) δ 1.50 and 1.36 (2s, MeCMe overlapped by t of ethyl Me), 3.28 (m, H5'a,b), 4.23 - 4.66 (m, H4' overlapping ethyl CH_2), 4.83 - 4.91 (m, NH_2, ex D_2O, overlapping H2',H3'), 5.15 (d, H1'), 7.23 - 7.48 (m, trityl). Anal. Calcd. for $C_{34}H_{35}NO_7$: C, 71.71; H, 6.15; N, 2.49. Found: C, 71.43; H, 6.31; N, 2.48.

7-(2,3-O-Isopropylidene-5-O-trityl-β-D-ribofuranosyl)furo[3,2-d]pyrimidin-4(3H)-one (19β). A solution of the β C-nucleoside **16β** (260 mg, 0.46 mmol) in ethanol (25 ml) was treated with formamidine acetate (1 g, 9.6 mmol), and the mixture was heated under reflux for 4 days. Work-up of the reaction mixture as described for the synthesis of **9β**, and flash chromatography using dichloromethane-methanol (97:3) as eluant, afforded pure **19β** (128 mg, 51%) as a foam; ^{1}H-nmr ($CDCl_3$) δ 1.61 and 1.38 (2s, MeCMe), 3.27 (m, H5'a,b), 4.36 (m, H4'), 4.76 (dd, H3'), 5.05 (dd, H2'), 5.19 (dd, H1'), 7.18 - 7.48 (m, trityl), 7.79 (d, H6), 8.02 (s, H2), $J_{1',2'}$ = 3.8, $J_{1',6}$ = 0.8, $J_{2',3'}$ = 6.3, $J_{3',4'}$ = 3.6 Hz. Anal. Calcd. for $C_{33}H_{30}N_2O_6$: C, 72.00; H, 5.49; N, 5.09. Found: C, 71.98; H, 5.59; N, 5.25.

7-(2,3-O-Isopropylidene-5-O-trityl-α-D-ribofuranosyl)furo[3,2-d]pyrimidin-4(3H)-one (19α) was obtained in 80% yield from **16α** by the procedure described above for **19β**; ^{1}H-nmr ($CDCl_3$) δ 1.31 and 1.44 (2s, MeCMe), 3.29 (m, H5'a,b), 4.35 (ψt, H4'), 4.80 (d, H3'), 5.02 (dd, H2'), 5.50 (dd, H1'), 7.23 - 7.52 (m, trityl), 7.99 (d, H6), 8.08 (s, H2), $J_{1',2'}$ = 3.6, $J_{2',3'}$ = 6.0, $J_{3',4'}$ <0.5Hz. Anal. Calcd. for $C_{33}H_{30}N_2O_6$: C, 72.00; H, 5.49; N, 5.09. Found: C, 71.63; H, 5.46; N, 5.19.

3-Amino-4-(2,3-O-isopropylidene-5-O-trityl-β-D-ribofuranosyl)furan-2-carboxamide (18β). Concentrated aqueous ammonia solution (35 ml) was added to a solution of **4β** (1 g, 1.91 mmol) in ethanol (60 ml). This solution was stirred at room temperature while 30% hydrogen peroxide (16 ml) was added dropwise. After an additional 30 min., at which time tlc (dichloromethane-methanol, 14:1) indicated the absence of starting material, the ethanol was removed by evaporation and the reaction mixture was diluted by the addition of 300 ml of water. The solution was extracted with dichloromethane (4 X 50 ml), the combined organic layers were washed with water and then dried over sodium sulfate. After removal of solvent, the residue was purified by flash chromatography (chloroform-methanol, 19:1), affording 850 mg (82%) of **18β**; ^{1}H-nmr ($CDCl_3$) δ 1.35 and 1.57 (2s, MeCMe), 3.23 - 3.40 (7-line m, H5'a,b), 4.21 (m, H4'), 4.76 (m, NH_2, ex D_2O, overlapping H1', H2' and H3'), 5.57 (bs, amide, ex D_2O), 7.21 - 7.48 (m, trityl), 7.13 (s, H5). Anal. Calcd. for $C_{32}H_{32}N_2O_6$: C, 71.11; H, 5.93; N, 5.19. Found: C, 71.21; H, 5.83; N, 5.16.

3-Amino-4-(2,3-O-isopropylidene-5-O-trityl-α-D-ribofuranosyl)furan-2-carboxamide (18α) was obtained in 80% yield from **4α** as described above for **18β**; ^{1}H-nmr ($CDCl_3$) δ 1.34 and 1.51 (2s, MeCMe), 3.14 - 3.34 (7-line m, H5'a,b), 4.31 (ψt, H4'), 4.77 - 4.97 (m, NH_2, ex D_2O, overlapping H2' and H3'), 5.16 (d, H1'), 5.50 (bs, amide, ex D_2O), 7.24 - 7.49 (m, trityl), $J_{1',2'}$ = 3.3Hz. Anal. Calcd. for $C_{32}H_{32}N_2O_6$: C, 71.11; H, 5.93; N, 5.19. Found: C, 71.33; H, 5.85; N, 5.17.

Reactions of the ethoxycarbonyl ethers 14 with potassium t-butoxide. A solution of potassium t-butoxide (5.13 g, 45.68 mmol) in t-butanol (20 ml) was added dropwise to a stirred solution of **14** (6.5 g, 11.42 mmol) in a mixture of t-butanol (50 ml) and dichloromethane (10 ml) over a period of 20 min at room temperature. Stirring was continued for a further 30 min period, at which time tlc- monitoring indicated the absence of starting material. Following removal of solvents, and a conventional work-up by partitioning between dichloromethane and water, the final residue was subjected to preparative column chromatography, using petroleum ether-ethyl acetate (4:1) as eluant. The following fractions were obtained.

1) The slowest moving material, obtained in 25% yield (1.65 g), was identified as the ethyl ether **17**; Rf 0.51 (toluene-ethyl acetate, 4:1); ^{1}H-nmr ($CDCl_3$) δ 1.25 (t, Me), 1.61 and 1.32 (2s, MeCMe), 3.28 (ddd,

H5'), 4.03 (q, CH_2), 4.29 (ψt, H4'), 4.68 (dd, H3'), 4.86 (dd, H2'), 5.35 (dd, H1'), 6.97 (d, =CH), 7.21 - 7.47 (m, trityl), $J_{1',2'}$ = 4.1, $J_{2',3'}$ = 6.1, $J_{3',4'}$ = 0.6, $J_{5'gem}$ = 10.1, $J_{4',5'a}$ = $J_{4',5'b}$ = 3.3, $J_{1',vinyl}$ = 0.9Hz; ^{13}C-nmr ($CDCl_3$) δ 143.5, 128.6, 127.9, 127,1 and 87.4 (trityl), 113.0, 25.6 and 24.8 (isopropylidene), 159.1 (=CH), 117.9 (CN), 91.0 (NC-C=), 83.3 (C3'), 83.1 (C4'), 81.9 (C2'), 75.5 (C1'), 71.1 (CH_2), 65.5 (C5'), 15.2 (Me); mass spectrum (CI), (MH^+) 512.2437 (calcd. 512.2428). Anal. Calcd. for $C_{32}H_{33}NO_5$: C, 75.12; H, 6.50; N, 2.73. Found: C, 75.21; H, 6.60; N, 2.71.

2) A small amount of material (800 mg) with Rf 0.59 (toluene-ethyl acetate, 4:1) proved to contain (nmr) a mixture of compounds that have not been identified.

3) The fastest moving material (2.5 g) proved to be a mixture of the t-butyl ether **15** and the desired **16β** (both Rf 0.61 in toluene-ethyl acetate, 4:1), usually accompanied by the isomer **16α** (Rf 0.60). In one run, a clear-cut separation of **15** and **16β** from **16α** was achieved, but this result could not be reproduced routinely. Treatment of a 500 mg portion of the mixture of **16β** and **15** with formamidine acetate in ethanol led to the formation of **19β**, which was readily separated from **15** by column chromatography using dichloromethane-methanol, 95:5. From the amount of **19β** isolated (180 mg), it is estimated that **16** must have been formed from **14** in about 25% yield. The t-butyl ether **15** was obtained in 13% yield (165 mg) as a mixture of isomers of uncertain anomeric configuration; ^{1}H-nmr ($CDCl_3$) δ 1.31 and 1.53 (2s, MeCMe), 1.34 (s, tBu), 3.28 (m, H5'), 4.00 - 4.86 (4H, overlapping m's, H4', H3' H2' and H1'), 7.15 (s, vinyl H), 7.21 - 7.50 (m, trityl). Anal. Calcd. for $C_{34}H_{37}NO_5$: C, 75.67; H, 6.91; N, 2.60. Found: C, 75.78; H, 6.96; N, 2.34.

Treatment of a mixture of **15**, **16α** and **16β** with formamidine acetate in ethanol leads satisfactorily to a mixture containing **19α** and **19β**. While these epimers are easily separated from **15**, the difficulty of separating **19α** and **19β** from each other by column chromatography makes this approach somewhat impractical.

General procedure for deblocking 5'-O-trityl-2',3'-O-isopropylidene C-Nucleosides. The blocked C-nucleoside (100 mg) was treated with 6% HCl/methanol (10 ml), and the mixture was stirred at room temperature. tlc- monitoring showed that deblocking was complete at 1 hr in each case. The reaction mixture was then evaporated to dryness and several batches of methanol were evaporated from the residue. The final residue

was dissolved in methanol (2 ml) and the product was precipitated by adding 10 ml of diethyl ether. The mixture was cooled in an ice bath for 1 hr before the precipitate was collected by centrifugation. The product was washed with several batches of fresh ether and dried *in vacuo* over P_2O_5 to afford the following deblocked nucleosides as the chromatographically pure hydrochloride salts.

4-Amino-7-β-D-ribofuranosylfuro[3,2-d]pyrimidine (13β) was obtained in 90% yield; mp 150-152°; ^{1}H-nmr (DMSO-d_6) δ 3.64 (m, H5'a,b), 3.91 - 4.07 (m, H2', H3' and H4'), 4.91 (m, H1', broadened by virtual coupling), 8.57 (s, H6), 8.67 (s, H2), 9.28 (bs, NH_2, ex D_2O), $J_{1',2'}$ ~ 6.3 Hz; ^{13}C-nmr (DMSO-d_6) δ 149.6 (C6 and C4), 147.9 (C2), 138.2 (C7a), 118.4 (C7), 85.6, 75.8, 75.2, 71.5 (ribosyl), 61.6 (C5'); UV (pH1) λ_{max} 227 (ε 11624), 269 (ε 15100), 274nm (ε 15400); λ_{min} 213 (ε 9800), 242nm (ε 7450); UV (pH 13) λ_{max} 247 (ε 7770), 272.5nm (ε 7650), λ_{min} 240.5 (ε 7880), 259.5nm (ε 6750). Anal. Calcd. for $C_{11}H_{13}N_3O_5$. HCl: C, 43.50; H, 4.61; N, 13.84. Found: C, 43.17; H, 4.92; N, 13.65.

4-Amino-7-α-D-ribofuranosylfuro[3,2-d]pyrimidine (13α) was obtained in 90% yield; ^{1}H-nmr (DMSO-d_6) δ 3.4 - 3.7 (ddd, H5'a,b), 4.26 - 4.05 (m, H2', H3' and H4'), 5.19 (d, H1'), 8.44 (s, H6), 8.64 (s, H2), 9.22 (bs, NH_2, ex D_2O), $J_{1',2'}$ = 2.5Hz; ^{13}C-nmr (DMSO-d_6) δ 151.2 (C4), 150.1 (C6), 147.5 (C2), 138.2 (C7a), 132.4 (C4a), 116.6 (C7), 82.6, 74.2, 72.8, 72.1 (ribosyl), 61.4 (C5'). Anal. Calcd. for $C_{11}H_{13}N_3O_5$. HCl: C, 43.49; H, 4.61; N, 13.84. Found: C, 43.51; H, 4.71; N, 13.79.

7-β-D-Ribofuranosylfuro[3,2-d]pyrimidine-4(3H)-thione (11β) was obtained in 97% yield; mp 190°; ^{1}H-nmr (DMSO-d_6)[29] δ 3.42 - 3.81 (m, H5'a,b), 3.86 - 4.04 (m, H3' and H4'), 4.22 (ψt, H2'), 4.79 (d, H1'), 8.27 (s, H6), 8.44 (s, H2), $J_{1',2'} = J_{2',3'}$ = 5.6Hz; UV (pH1) λ_{max} 207 (ε 14100), 259 (ε 9400), 335nm (ε 13500); λ_{min} 234 (ε 5210), 295nm (ε 4020); UV (pH 13) λ_{max} 261 (ε 7900), 315nm (ε 13120), λ_{min} 283 (ε 5070). Anal. Calcd. for $C_{11}H_{12}N_2O_5S$. HCl: C, 41.25; H, 4.06; N, 8.75; S, 10.00. Found: C, 41.50; H, 4.24; N, 8.60; S, 9.81.

7-α-D-Ribofuranosylfuro[3,2-d]pyrimidine-4(3H)-thione (11α) was obtained in 81% yield; mp 197-198°; ^{1}H-nmr (DMSO-d_6)[29] δ 3.21 - 3.53 (m, H5'a,b), 3.73 (m,H4'), 4.12 - 4.19 (m, H2' and H3'), 5.19 (d, H1'), 8.24 (s, H6), 8.37 (s, H2). Anal. Calcd. for $C_{11}H_{12}N_2O_5S$. HCl: C, 41.25; H, 4.06; N, 8.75; S, 10.00. Found: C, 41.40; H, 3.69; N, 8.66; S, 9.99.

4-Methylthio-7-β-D-ribofuranosylfuro[3,2-d]pyrimidine (10β) was obtained in 87% yield; mp 175°; ^{1}H-nmr (DMSO-d_6) δ 2.70 (s, SMe), 3.53 - 3.63 (m, H5'a,b), 3.72-4.09 (m, H3' and H4'), 4.31 (dd, H2'), 4.87 (d, H1'), 8.44 (s, H6), 8.85 (s, H2), $J_{1',2'}$ = 6.3, $J_{2',3'}$ = 4.9, $J_{3',4'}$ = 4.7Hz; UV (pH1) λ_{max} 212 (ε 14000), 242 (ε 7000), 317nm (ε 20800); λ_{min} 208 (ε 13000), 231nm (ε 6300); UV (pH 13) λ_{max} 244 (ε 9770), 294nm (ε 18000), λ_{min} 232 (ε 8250), 267nm (ε 9600). Anal. Calcd. for $C_{12}H_{14}N_2O_5S$. HCl: C, 43.11; H, 4.49; N, 8.38; S, 9.58. Found: C, 43.20; H, 4.70; N, 8.49; S, 9.37.

4-Methylthio-7-α-D-ribofuranosylfuro[3,2-d]pyrimidine (10α) was obtained in 82% yield; mp 181°; ^{1}H-nmr (DMSO-d_6) δ 2.70 (s, SMe), 3.49 - 3.60 (m, H5'a,b), 3.90 (m, H4'), 4.15 - 4.21 (m, H2' and H3'); 5.21 (m, H1'), 8.24 (d, H6), 8.85 (s, H2), $J_{1',2'}$ = 2.2, $J_{1',6}$ = 0.8Hz. Anal. Calcd. for $C_{12}H_{14}N_2O_5S$. HCl: C, 43.11; H, 4.49; N, 8.38; S, 9.58. Found: C, 43.55; H, 4.55; N, 8.60; S, 9.71.

7-β-D-Ribofuranosylfuro[3,2-d]pyrimidin-4(3H)-one (20β) was obtained in 90% yield; mp 190° (dec); ^{1}H-nmr δ 3.42 - 3.72 (m, H5'a,b), 3.86 - 4.04 (m, H3' and H4'), 4.23 (dd, H2'), 4.77 (d, H1'), 8.13 (s, H6), 8.24 (s, H2), $J_{1',2'}$ = 6.3, $J_{2',3'}$ = 4.9Hz; UV (pH2) λ_{max} 220 (ε 15100), 258nm (ε 8600), λ_{min} 208 (ε 11050), 240nm (ε 7200); UV (pH 13) λ_{max} 243 (ε 8500), 256nm (ε 8400). Anal. Calcd. for $C_{11}H_{12}N_2O_6$. HCl: C, 43.42; H, 4.28; N, 9.21. Found: C, 43.22; H, 4.31; N, 9.33.

7-α-D-Ribofuranosylfuro[3,2-d]pyrimidin-4(3H)-one (20α) was obtained in 87% yield; mp 214-215° (dec); ^{1}H-nmr (DMSO-d_6) δ 3.41 - 3.58 (m, H5'a,b), 3.72 - 4.57 (m, H2', H3' and H4'), 5.12 (m, H1'), 8.04 (d, H6), 8.11 (s, H2), $J_{1',2'}$ = 2.2, $J_{1',6}$ = 0.8Hz. Anal. Calcd. for $C_{11}H_{12}N_2O_6$. HCl: C, 43.42; H, 4.28; N, 9.21. Found: C, 43.61; H, 4.51; N, 9.10.

7-β-D-Ribofuranosylfuro[3,2-d]pyrimidine-2,4(1H,3H)-dithione (12β) was obtained in 95% yield; mp 235° (dec); ^{1}H-nmr (DMSO-d_6) δ 3.17 (ψd, H5'a,b), 3.63 - 3.96 (m, H2', H3' and H4'), 4.80 (d, H1'), 8.30 (s, H6), 12.99 and 13.51 (2bs, N1-H and N3-H, ex D_2O), $J_{1',2'}$ = 6.6Hz; UV (pH1) λ_{max} 202 (ε 28200), 272 (ε 28800), 357nm (ε 17500); λ_{min} 237 (ε 9600), 336nm (ε 13800); UV (pH 13) λ_{max} 252 (ε 24100), 275 (ε 23300), 340nm (ε 9700), λ_{min} 238 (ε 24100), 262 (ε 23300), 315nm (ε 9700). Anal. Calcd. for $C_{11}H_{13}N_2O_5S_2$. HCl: C, 37.34; H, 3.96; N, 7.92; S, 18.11. Found: C, 37.71; H, 3.95; N, 7.61; S, 18.19.

7-α-D-Ribofuranosylfuro[3,2-d]pyrimidine-2,4(1H,3H)-dithione (12α) was obtained in 92% yield; mp 225° (dec); ^{1}H-nmr (DMSO-d_6) δ 3.38 - 3.68 (7-line m, H5'a,b), 3.85 (m, H4'), 4.05 - 4.30 (m, H2' and H3'), 5.08 (d, H1'), 8.15 (s, H6), 13.10 and 13.49 (2bs, N3-H and N1-H, ex D_2O), $J_{1',2'}$ = 4.1Hz. Anal. Calcd. for $C_{11}H_{13}N_2O_5S_2$. HCl: C, 37.34; H, 3.96; N, 7.92; S, 18.11. Found: C, 37.61; H, 3.65; N, 7.99; S, 18.09.

Synthesis of the furo[3,2-d]pyrimidin-4(3H)-one C-nucleosides 20β and 20α from the corresponding 4-thiones 11β and 11α. A 1 ml portion of 12N HCl was added to a solution of the 4-thione **11β** (100 mg) in 10 ml of dimethylsulfoxide. The mixture was stored at room temperature for 1.5 hr, at which time tlc (dichloromethane-methanol, 6:1) indicated that the formation of **20β** was complete. The reaction mixture was evaporated to dryness (oil pump) and the residue was dissolved in 2 ml of methanol. The hydrochloride salt that precipitated on the addition of ether was collected by decantation and washed liberally with fresh ether. The dried product (85 mg, 84%) was identical (nmr, uv, mp) with the sample of **20β** obtained by deblocking **19β** as described above.

A similar reaction applied to **11α** (40 mg in 5 ml DMSO and 4 ml of 12N HCl) afforded 30 mg (79%) of the hydrochloride salt of **20α**, identical with the material prepared from **19α** as described above.

REFERENCES AND NOTES

¶ Present address for BAO and RSK.

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