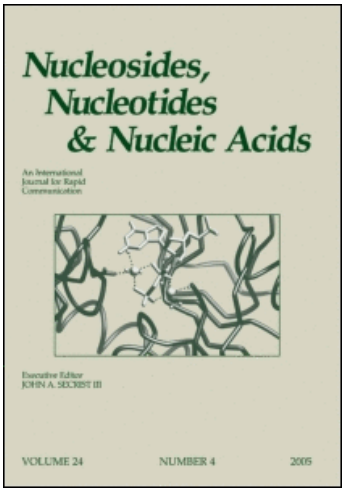

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C-Glycosylation of Substituted Heterocycles Under Friedel-Crafts Conditions (II): Ribosylation of Multi-Functionalized Thiophenes and Furans for the Synthesis of Purine-Like C-Nucleosides

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C-GLYCOSYLATION OF SUBSTITUTED HETEROCYCLES UNDER FRIEDEL-CRAFTS CONDITIONS (II): RIBOSYLATION OF MULTI-FUNCTIONALIZED THIOPHENES AND FURANS FOR THE SYNTHESIS OF PURINE-LIKE C-NUCLEOSIDES

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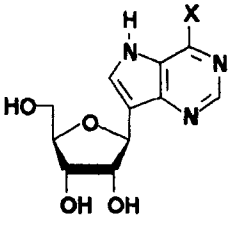
Abstract: In our continuing studies of the Friedel-Crafts glycosylation of preformed heterocycles, we have observed that while the $SnCl_4$ catalyzed glycosylation of methyl 4-(formylamino)thiophene-3-carboxylate (**5**) gives readily the C-nucleosides **7b** and **7a**, the corresponding Et_2AlCl catalyzed reaction gives exclusively the N-nucleoside **11**. These nucleosides can be further elaborated into the bicyclic thieno[3,4-d]-pyrimidine system. Similarly, methyl 4-(formylamino)furan-3-carboxylate (**19**) gave the expected C-nucleosides **20b** and **20a** upon glycosylation in the presence of $SnCl_4$. However, these nucleosides could not be converted into the furo[3,4-d]pyrimidine system. Interestingly, several of the N-formamido compounds exhibit pronounced rotational isomerism, which was demonstrated by ^1H NMR spectroscopy.

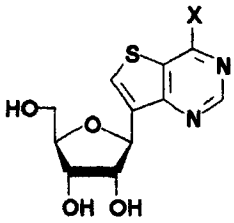
Several of the purine-like C-nucleoside analogs prepared in our laboratory (e. g. **1-3**) elicit a wide range of important biological effects. These include *in vivo* and/or *in vitro* antitumor activity for the adenosine analogues (X = NH_2)[1] and *in vivo* and/or *in vitro* activity against several pathogenic hemoflagellates for the inosine analogues (X = OH).[2] One of these (**1**, X = OH) has also exhibited significant activity against Pneumocystis carinii infections in the rat[3], growth inhibitory activity *in vitro* against Giardia lamblia[4] and was also found to be a good reversible inhibitor of purine nucleoside phosphorylase.[5] Prompted by these findings, we have begun investigating the synthesis of structurally related, potentially active purine-like C-nucleoside analogues which might be obtainable by shorter routes than those we had used for compounds **1-3**. As a result of these studies, we have reported our preliminary findings[6] on the Friedel-Crafts glycosylation of functionalized thiophenes which provide a direct synthesis of purine-like C-nucleosides such as **4** (X = S). We wish to report here a more detailed description of those studies and their possible extension to the synthesis of **4** (X = O).

The thieno[3,4-d]pyrimidine inosine analog **10b** was originally prepared in our laboratory[6] by the $SnCl_4$ catalyzed glycosylation of thiophene derivative **5** with ribose **6** to give intermediate **7b** and its anomer **7a**. Subsequent ring-closure of **7b** with methanolic NH_3 afforded the inosine analog **10b** in 9% overall yield (Scheme 1).



1

X = NH_2 or OH



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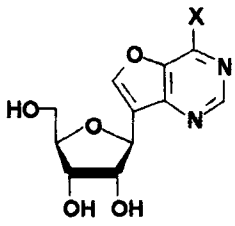
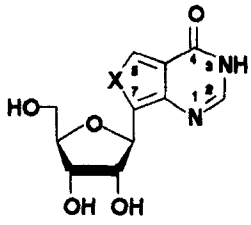
X = NH_2 or OH



3

X = NH_2 or OH

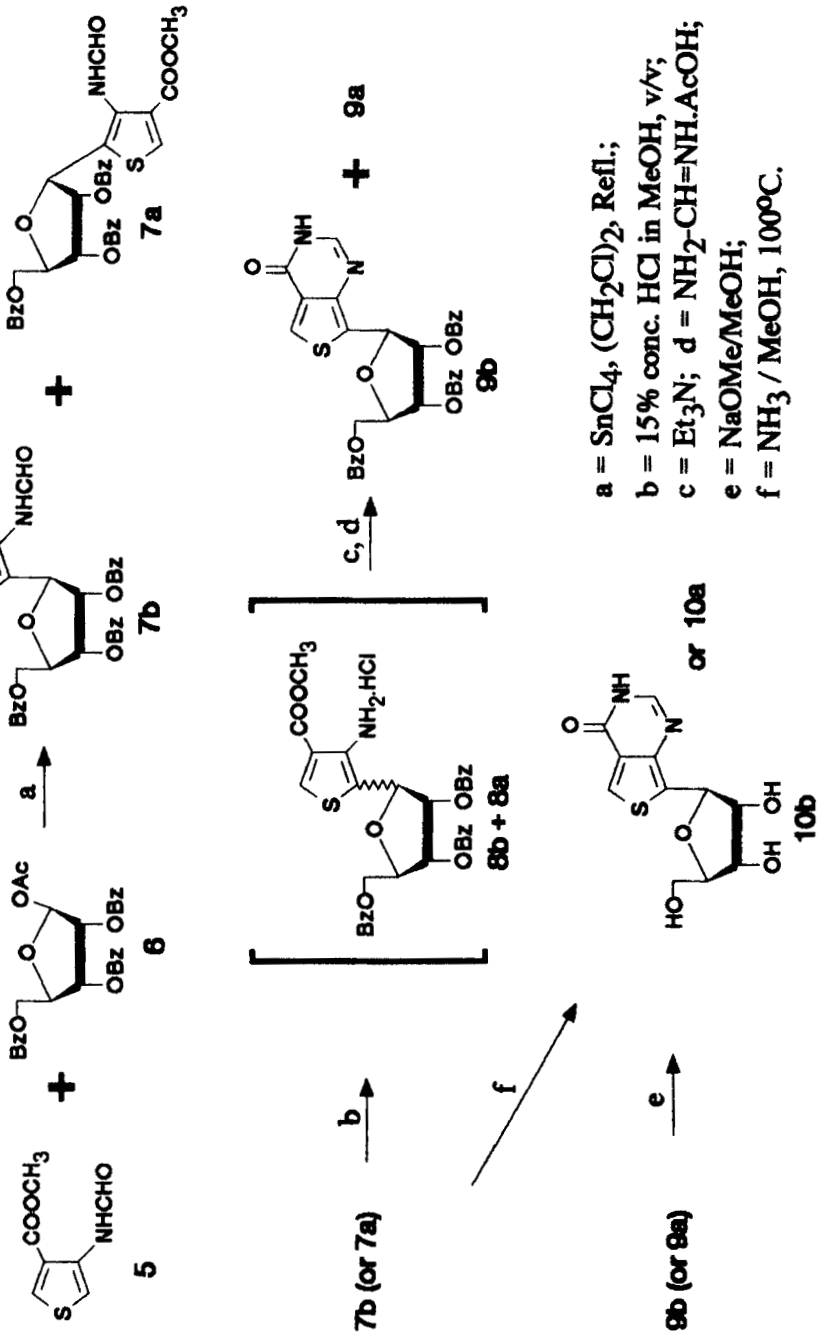


4

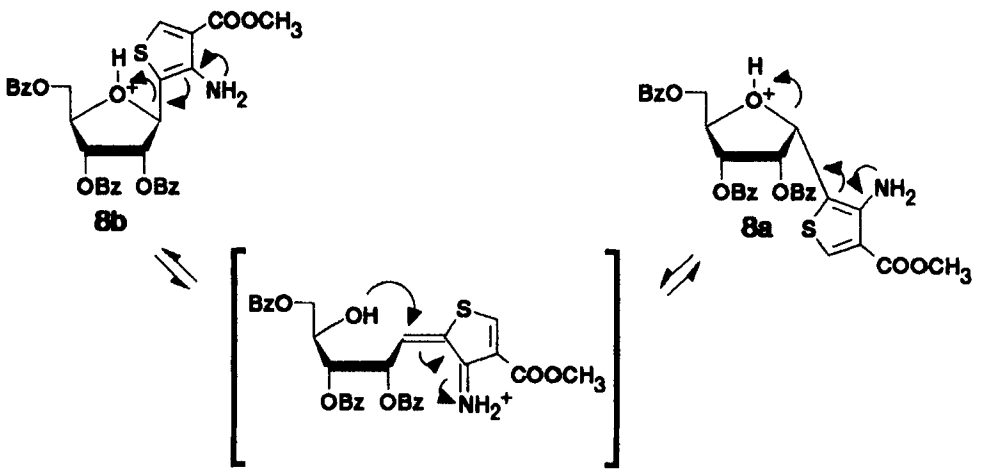
X = S, O

The promising in vitro studies of **10b** as an antiprotozoal agent[7] prompted us to investigate possible improvements in its synthesis. Thus, C-glycosylation of **5** by **6** was studied using a number of Lewis and proton acid catalysts[8] ($SnCl_4$, $AlCl_3$, 85% aq. H_3PO_4, Et_2AlCl, $ZnCl_2$) and a variety of solvents (1,2-dichloroethane, acetonitrile, nitromethane) in different molar ratios of **5**:**6**:catalyst. Phosphoric acid[9] was not effective in catalyzing the ribosylation. Both $ZnCl_2$ in 1,2-dichloroethane and $AlCl_3$ in nitromethane, although somewhat effective, gave very slow reactions. The combination of $SnCl_4$ with **5** and **6** in molar ratios of 2:2:1 respectively, in boiling 1,2-dichloroethane, was the most satisfactory. These conditions afforded **7b** and **7a** in ≈ 50% and ≈ 10% yield respectively, after recovery of unreacted thiophene **5** (≈78%). The use of Et_2AlCl as a catalyst, on the other hand, afforded the N-glycosylated compound **11**, (see below).

Scheme 1



Selective deformylation was investigated next since access to amino ester derivative **8** might also extend the scope of this approach to the synthesis of 2-substituted thieno[3,4-d]pyrimidines (**4**, X=S) via annulation with amidines or other similar dinucleophilic reagents. The formyl group of **7b** was thus selectively and efficiently removed using aqueous methanolic HCl[10] (15% concentrated hydrochloric acid in methanol) to give the anomeric mixture **8b** + **8a** in almost quantitative yield. Other conditions for the deformylation of **7b** (both in acids and bases) were much less satisfactory. Separation of anomers **8b** and **8a**, in their non-protonated form, was achieved by chromatography on silica gel (toluene-EtOAC, 9:1). However, each one anomerized rapidly to give a mixture of the α and β isomers in roughly 2:3 ratio. Anomerization possibly occurs by the mechanism shown below.



Reaction of the hydrochloride **8** with formamidine acetate and triethylamine in refluxing ethanol gave **9b** and **9a**, which were readily separated by silica gel flash chromatography and isolated in 44% and 24% yield, respectively.

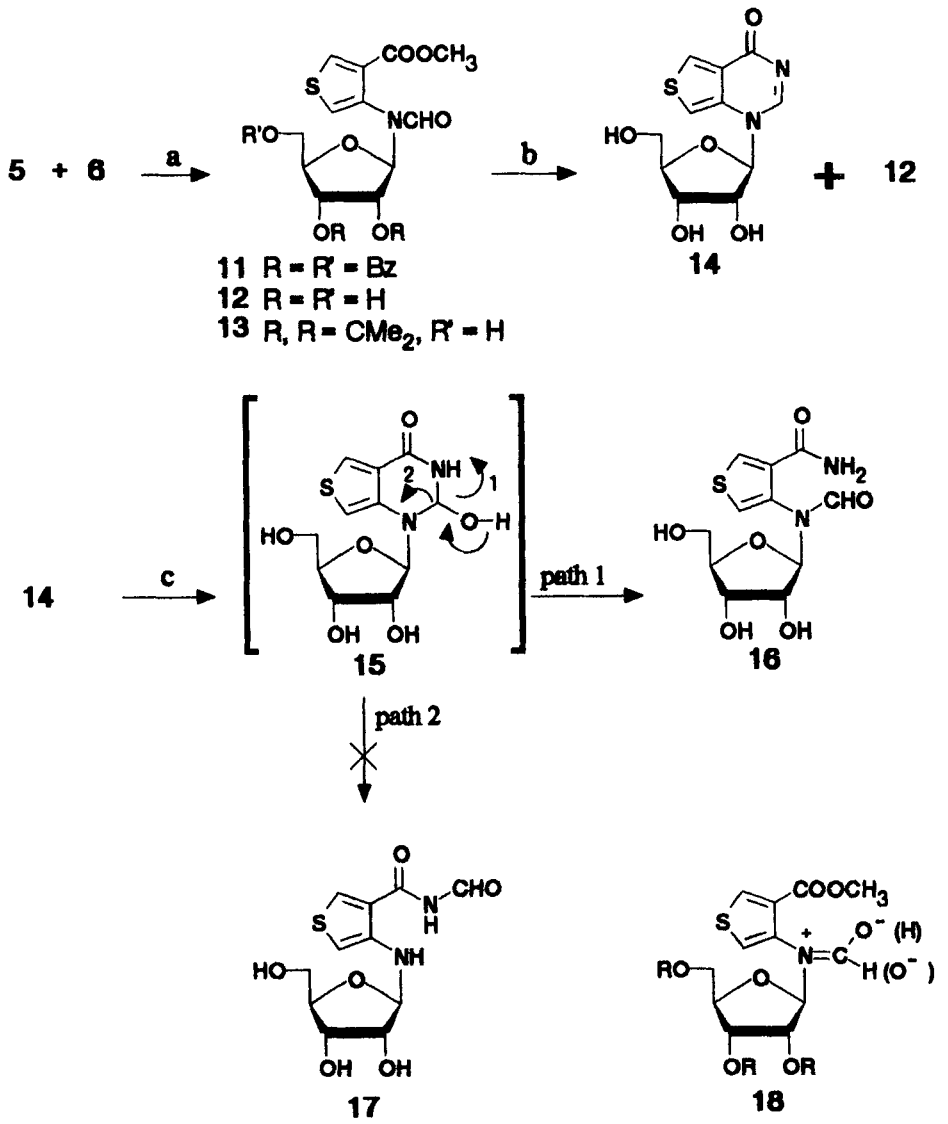
Debenzoylation of the ribose moiety of either **9b** or **9a** with $NaOCH_3$ in MeOH gave **10b** or **10a** in 86% and 92% yield, respectively. The overall yield of **10b** (18%) in this 3-step sequence, based on unrecovered **5**, was slightly better than the 2-step process we reported earlier.[6]

As mentioned above, the use of Et_2AlCl as a catalyst (Scheme 2) led surprisingly to the exclusive formation of the N-glycosylated product **11**, which was isolated in 58% yield by silica gel chromatography. The ^1H NMR of this compound in $CDCl_3$ was significantly different from that of **7b**. The NH signal observed in the spectrum of **7b** at δ 9.2 ppm was conspicuously absent from that of **11**. The spectrum of **11** was otherwise quite complex presumably due to restricted internal rotation about the -N-CHO bond resulting in two distinct rotamers. The benzoyl groups were removed with $NaOCH_3$ in MeOH to give **12** in very good yield. Its ^1H NMR spectrum in DMSO-$\underline{d}_6$ (containing some D_2O) also showed the presence of two rotamers as indicated by a set of two signals for H-1' appearing at δ 5.58 and 6.00 ppm in the approximate ratio of 3.6:1. The downfield region also displayed two sets of signals for each of H-2, H-5 and -N-CHO. Similarly, the ^{13}C NMR spectrum of **11** and **12** in $CDCl_3$ displayed two sets of signals for several of the carbon atoms (see experimental).

The conclusion that the multiple signals in the NMR spectra of **12** result from restricted rotation was confirmed by determining its ^1H NMR spectrum at 120°C. Under these conditions, all double resonances coalesced to give a single set of signals for all protons. The two rotamers could again be detected if that same solution was allowed to cool to 20°C. These observations provide convincing evidence for the existence of rotamers for **12** (and hence for **11**). Restricted internal rotation in amides (stabilized in our own system by mesomeric structures such as **18**) is a well documented phenomenon.[11]

To determine the anomeric configuration of **11** and **12**, we converted **12** into its isopropylidene derivative by treating it with acetone in the presence of p-toluenesulfonic acid. The ^{13}C NMR spectrum of the resulting **13** in $CDCl_3$ exhibited broad isopropylidene methyl signals at δ 25.4 and 27.3 ppm with a Δδ of 1.90 ppm. Furthermore, two signals (δ 114.0 and 114.7 ppm) were observed for the quaternary carbon of the isopropylidene group indicating the presence of two rotamers.[12] These values are in excellent agreement with those reported to be characteristic of the β-configuration in structures based on 2,3-$\underline{O}$-isopropylidene D-ribofuranose.[13] Moreover, unless **12** anomerizes instantly and completely during the isopropylidenation (a highly unlikely event for which there is no evidence) it follows that **11** and **12** also have the β configuration.

Scheme 2



All attempts to deformylate **11** under either acidic or alkaline conditions were unsuccessful. Under acidic conditions, deglycosylation occurred as would be expected for an N-glycoside. Under alkaline conditions, hydrolysis of the ester functions occurred instead. Attempted cyclization with ammonium formate in formamide[14] at 140-145°C resulted in partial debenzoylation and extensive decomposition. However, as in the case of **7b** (or **7a**) it was possible to cyclize **11** by treatment with methanolic NH_3 at 75°C to give the bicyclic N-nucleoside **14** in 19% yield.

In neutral aqueous solution, **14** was found to be unstable with a half-life of ≈ 1.9 h as determined by UV spectroscopy. Under these conditions, the UV maxima at λ 325.5 and 277 nm which are characteristic of structure **14** slowly disappear leaving a λ_{max} at 203 nm with a strong shoulder at 240 nm. Monitoring the reaction by silica gel TLC (CH_2Cl_2-MeOH, 5:1) showed the gradual disappearance of **14** (bright blue fluorescent spot at R_f = 0.30) and the appearance of a more polar non-fluorescent product (R_f = 0.24).

The ^1H NMR spectrum of the new product in DMSO-d_6 (containing some D_2O) at 20°C showed the presence of a formyl group which was confirmed by ^{13}C NMR spectroscopy. While it is possible to conceive of the formation of two different N-formyl compounds (**16** and **17**, Scheme 2), we have identified the product as the formamido-carboxamide **16** on the basis of ^{13}C NMR spectroscopy.

The fully decoupled ^{13}C NMR spectrum of **16** in DMSO-d_6 displays two signals for -N-CHO at δ 163.4 and 164.0 ppm (rotamers, see below). In the proton-coupled ^{13}C NMR spectrum, each of these signals appears as a doublet of doublets due to geminal coupling with the formyl hydrogen and long range coupling with H-1'. While the ^{13}C NMR spectrum of **17** would also be expected to give a doublet of doublets for the CHO, this signal would collapse to a simple doublet upon deuterium exchange of the amidic NH proton. No such change in the coupling pattern was observed upon addition of D_2O, thus indicating structure **16** to be the correct one.

It is interesting to note that the ^1H NMR spectrum of **16** in DMSO-d_6 - D_2O also displays two sets of signals for the formyl and thiophene protons. We have demonstrated conclusively that this phenomenon is again due to restricted rotation by obtaining the spectrum at 120°C

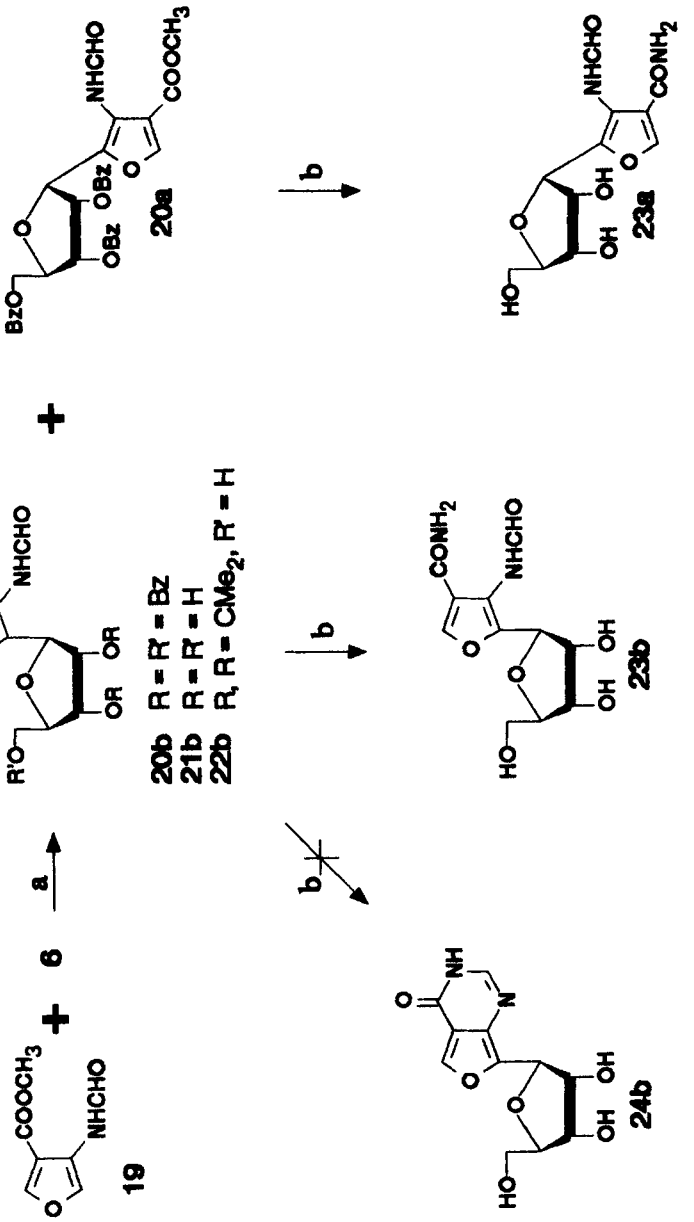
whereupon all previously doubled signals collapsed to a single set. As was shown in the case of **12**, this collapse of signals was also found to be reversible.

A plausible mechanism for the formation of **16** from **14** is shown in Scheme 2 in which covalent hydration at C-2 would give intermediate **15** which then undergoes pyrimidine ring-cleavage by pathway 1 to give **16**. We have previously observed similar covalent hydration of N-1 acetylated -4-pyrimidones and subsequent ring opening where the products can be accounted for by both pathways.[15]

In order to evaluate the scope of Friedel-Crafts C-glycosylation, the reaction of the furan formamido derivative **19** (obtained by Curtius rearrangement via the corresponding monoacid[16]) with the ribose derivative **6** was investigated using different catalysts and molar ratios of reactants (Scheme 3). While $ZnCl_2$ and BF_3-etherate gave very sluggish reactions, better yields were obtained here also using $SnCl_4$, **19** and the sugar **6** in a ratio of 2:2:1. Under these conditions, the readily separable nucleosides **20b** and **20a** were obtained in a total yield of 19% (β/α = 9.4). The large β/α ratio obtained, as in the case of ribosylation of thiophene **5**, suggests a common mechanism involving anchimeric participation by the 2-benzoyloxy group leading to a carboxonium intermediate. The substantially lower recovery of unreacted furan **19** (32%) as compared to the recovery of the thiophene **5** demonstrates its lower stability under these strongly acidic conditions. The relative instability of furans and thiophenes under acidic conditions is quite well known.[17]

From mechanistic considerations[6], glycosylation of **19** would be expected to proceed with the regiospecificity illustrated, and this has been verified by ^{13}C NMR studies. In the free base **19** the unsubstituted furan carbons resonate at δ 146.6 and 134.9 ($CDCl_3$) and the presence of an exchangeable three-bond coupling (7 Hz) to the NH group allows unambiguous assignment of the upfield signal to the CH "ortho" to the formylamino group. The site of glycosylation can be determined by observing which of these peaks shifts downfield following substitution of the corresponding carbon by the sugar. In the product **20b** and all compounds derived from it, the unsubstituted furan carbons resonate near 147 ppm while no CH resonances were observed around 135 ppm. This clearly indicates that ribosylation has occured on the carbon adjacent to the amide function. In addition, the 147 ppm resonances in the

Scheme 3



proton-coupled spectra appear as sharp doublets (J ≈ 211 Hz) with no observable coupling to the NH groups, which is again consistent only with structures in which the CH is adjacent to the methoxycarbonyl group.[18]

The assignment of the anomeric configuration of **20b** and **20a** could not be made directly from a comparison of the ^{1}H NMR chemical shifts of their C-1' protons. Therefore, **21b** (prepared by debenzoylation of **20b** with methanolic NH_3) was converted into its isopropylidene derivative **22b** under standard conditions (46% yield). The ^{13}C NMR spectrum of **22b** indicated the existence of two rotamers[12] and exhibited partially overlapping isopropylidene signals at δ 25.4, 25.6 and 27.5 ppm. These values are in excellent agreement with those originally established for the β isomers of 2,3-O-isopropylidene D-ribosyl compounds.[13]

All attempts to deformylate nucleoside **20b** under acidic conditions similar to those that gave **8** were unsuccessful, and resulted in extensive decomposition. Treatment of **20b** with methanolic NH_3 at 25°C afforded only the formamido-carboxamide **23b** (isolated in 16% yield) and **21b**. No trace of the expected furopyrimidine **24b** was observed. Use of higher temperatures (50-110°C) or longer reaction times during the attempted cyclization resulted in extensive decomposition. Again, the ^{1}H NMR spectrum of **23b** in DMSO-d_6 (containing some D_2O) indicated the presence of two rotamers freely interconvertible at 120°C. Compound **20a** afforded similarly the formamido-carboxamide **23a** (isolated in ≈ 10% yield) together with the debenzoylated derivative of **20a**. No furo-[3,4-d]pyrimidine nucleoside was observed.

In conclusion, we have shown that Friedel-Crafts glycosylation of heterocycles can provide an easy access to multifunctionalized C-nucleosides, as demonstrated by the synthesis of the thieno and furo nucleosides **7b** and **21b**, and that some are suitable for further elaboration into purine-like C-nucleosides. We are presently exploring the application of this methodology to the pyrrole and other 5-membered heterocyclic systems and examining alternative procedures for obtaining the furo[3,4-d]pyrimidine system.

EXPERIMENTAL SECTION

Melting points were determined on an Electrothermal digital melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were

run on a Varian XL-200 spectrometer. ^1H NMR chemical shifts were measured relative to internal tetramethylsilane (TMS); ^{13}C NMR chemical shifts were measured relative to the solvent absorbance except when D_2O was used as the solvent, in which case dioxane was included as the internal standard. Microanalyses were performed by M.H.W. Laboratories, Phoenix, Az. Thin layer chromatography (TLC) was performed on 250 μm silica gel GH plates (Analtech, Inc.), 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 500 μm, 20 x 20 cm silica gel plates (Analtech, Inc.), and the products were visualized by short-wave UV light. Preparative column chromatography was performed by standard techniques on Merck Silica gel 60 (70-230 mesh ASTM) or by flash chromatographic techniques on Merck silica gel 60 (230-400 mesh ASTM). The UV spectra were obtained on a Gilford Response II spectrophotometer. Mass spectra were obtained on a Finnigan MAT 90 Mass Spectrometer using glycerol, glycerol/thioglycerol or DMSO matrix.

Methyl 5-(2,3,5-tri-O-benzoyl-β-(and α)D-ribofuranosyl)-4-(formylamino)thiophene-3-carboxylate (7b and 7a). A mixture of **5** (16.9 g, 91.3 mmol), **6** (22.24 g, 44.1 mmol) and dry 1,2-dichloroethane (150 mL) was brought to reflux under a N_2 atmosphere. To this solution was added freshly distilled $SnCl_4$ (22.97 g, 88.2 mmol) and the mixture was refluxed for 4 h. Upon cooling to room temperature, the mixture was diluted with CH_2Cl_2 (300 mL) and stirred vigorously with 10% (w/v) aq. $NaHCO_3$ (200 mL) for 20 min. The mixture was filtered through Celite and the layers separated. The organic layer was washed once with brine and dried (Na_2SO_4). Removal of the solvent gave a residue which was dissolved in toluene (40 mL) and purified by flash chromatography using toluene-ethyl acetate (95:5) to obtain unreacted **5** (13.21 g, 78%). Elution with toluene-ethyl acetate (89:11) gave **7b** [6.21 g, 50% based on amount of **5** reacted (Lit.[6] yield 30%).

^1H NMR ($CDCl_3$) : δ 3.86 (s, 3H, $COOCH_3$), 4.60 (dd, 1H, H-5', $J_{5',4'}$ = 4 Hz, $J_{5',5''}$ = 12 Hz), 4.72 (m, 1H, H-4'), 4.84 (dd, 1H, H-5'', $J_{5'',4'}$ = 4 Hz), 5.70 (m, 2H, H-3'and H-2'), 6.12 (d, 1H, H-1', $J_{1',2'}$ = 4 Hz), 7.10 - 8.24 (m, 16H, Ph and H-5), 8.60 (br s, 1H, NHCHO), 9.15 (br s, 1H, NHCHO, exch. with D_2O).

Anal. Calcd for $C_{33}H_{27}NO_{10}S$: C, 62.95; H, 4.32; N, 2.23; S, 5.09. Found : C, 62.85; H, 4.25; N, 2.14; S, 5.15.

Compound **7a** was eluted next with toluene-ethyl acetate (87:13). Rechromatography using toluene-ethyl acetate (9:1) afforded **7a** (1.39 g, 10% based on amount of **5** consumed, Lit.[6] yield 13%, β/α = 4.4).

^{1}H NMR ($CDCl_3$) : δ 3.82 (s, 3H, $COOCH_3$), 4.50 - 4.90 (m, 3H, H-4', H-5', H-5''), 5.94 (dd, 1H, H-3', J = 5 Hz, 7 Hz), 6.11 (d, 1H, H-1', $J_{1',2'}$ = 3 Hz), 6.27 (t, 1H, H-2'), 7.16 - 8.20 (m, 16H, Ph and H-5), 8.26 (d, 1H, NHC<u>H</u>O, $J_{CH,NH}$ = 1 Hz), 9.14 (br s, 1H, N<u>H</u>CHO, exch. with D_2O).

Anal. Calcd for $C_{33}H_{27}NO_{10}S$: C, 62.95; H, 4.32; N, 2.23; S, 5.09. Found : C, 62.72; H, 4.34; N, 2.16; S, 5.21.

7-(2,3,5-Tri-<u>O</u>-benzoyl-β-(and α-)D-ribofuranosyl)thieno[3,4-<u>d</u>]pyrimidin-4(3H)-one (9b and 9a). A mixture of **7b** (1.00 g, 1.6 mmol), aq. methanolic hydrochloric acid (15% v/v conc. HCl in MeOH, 50 mL) and $CHCl_3$ (12.5 mL) was stirred at 25°C for 1.5 h. The solvents were removed under reduced pressure and the residual traces of hydrochloric acid were removed by entrainment with three small portions of methanol. A final entrainment with diethyl ether gave crude **8** as a light yellow colored foam.

A mixture of **8** (as obtained above), formamidine acetate (1.66g, 16.0 mmol), triethylamine (0.16 g, 1.6 mmol), and absolute ethanol (25 mL) was refluxed for 7 h with protection from moisture. The solvent was removed under reduced pressure and the residue triturated with ice-water to yield a solid which was filtered off and dried (0.87 g). This was dissolved in $CHCl_3$ (1.5 mL) and purified by flash chromatography using $CHCl_3$-MeOH (0.5% → 1.3% of MeOH). Compound **9b** was obtained as a yellow foam (0.42 g, 44%).

^{1}H NMR ($CDCl_3$): δ 4.65 (dd, 1H, H-5', $J_{5',4'}$ = 4 Hz, $J_{5',5''}$ = 12 Hz), 4.75 (app q, 1H, H-4'), 4.89 (dd, 1H, H-5'', $J_{5'',4'}$ = 3 Hz), 5.90 - 6.09 (m, 3H, H-1', H-2', H-3'), 7.20 - 8.26 (m, 17H, Ph, H-2, H-5), 9.72 (br s, 1H, CONH, exch. with D_2O); ^{13}C NMR ($CDCl_3$) : δ 64.1 (C-5'), [72.8, 76.4, 76.7 and 80.9 (sugar carbons)], 126.0 - 134.0 (thienopyrimidine and Ph carbons), 142.2 (C-2), 146.0, 159.3 (C-4), [165.3, 165.5 and 166.3 (C=O)].

Anal. Calcd for $C_{32}H_{24}N_2O_8S$: C, 64.42; H, 4.06; N, 4.70. Found : C, 64.19; H, 4.33; N, 4.68.

Compound **9a** was eluted next (0.23g, 24%); ^{1}H NMR ($CDCl_3$) : δ 4.57 - 4.94 (m, 3H, H-4', H-5', H-5''), 6.02 (dd, 1H, H-3', J = 4 Hz and 8 Hz), 6.20 (t, 1H, H-2'), 6.43 (d, 1H, H-1', $J_{1',2'}$ = 3 Hz), 7.20 - 8.30 (m, 17H, H-2, H-5, Ph), 9.67 (br s, 1H, CONH exch. with D_2O); ^{13}C NMR ($CDCl_3$) : δ 64.4 (C-5'), [73.6, 73.9, 75.4 and 77.9 (sugar carbons)], 125.4 - 135.0 (thienopyrimidine and phenyl carbons), 142.1 (C-2), 145.7, 159.2 (C-4), [165.0, 165.3 and 166.3 (C=O)].

Anal. Calcd for $C_{32}H_{24}N_2O_8S$: C, 64.42; H, 4.06; N, 4.70. Found : C, 64.26; H, 4.21; N, 4.68.

7-β-D-Ribofuranosylthieno[3,4-d]pyrimidine-4(3H)-one (10b). A mixture of **9b** (2.20 g, 3.7 mmol) and sodium methoxide (25 wt% solution in methanol, 3.96 g, 18.3 mmol) in absolute methanol (100 mL) was stirred at 25°C for 10 min. The solution was rendered neutral with Amberlite IRC-50 (H^+) ion-exchange resin and filtered. The filtrate was evaporated under reduced pressure and the residue diluted with water. The aqueous solution was extracted with diethyl ether (x4) and evaporated under reduced pressure to give **10b** as a crystalline solid (0.90 g, 86%). An analytical sample was obtained by crystallization from methanol. Mp 210-212°C. ^1H NMR (D_2O) : δ 3.84 (m, 2H, H-5', H-5''), 4.00 - 4.46 (m, 3H, H-2', H-3', H-4'), 5.48 (d, 1H, H-1', $J_{1',2'}$ = 7 Hz), 7.87 (s, 1H, H-2), 8.39 (s, 1H, H-5). UV λ_{max} (H_2O): 213.0, 237.5, 244.5 (sh), 315.5; λ_{max} (0.1 N NaOH) : 249.0, 326.0; λ_{max} (0.1 N HCl): 211.5, 238.5, 244.0, 316.0.

Anal. Calcd for $C_{11}H_{12}N_2O_5S$: C, 46.48; H, 4.22; N, 9.86; S, 11.27. Found : C, 46.23; H, 4.43; N, 9.68; S, 11.18.

7-α-D-Ribofuranosylthieno[3,4-d]pyrimidin-4(3H)-one (10a). A mixture of **9a** (0.20 g, 0.34 mmol) and sodium methoxide (25 wt% solution in methanol, 0.36 g, 1.7 mmol) in absolute methanol (10 mL) was stirred at 25°C for 15 min. The solution was rendered neutral with Amberlite IRC-50 (H^+) ion-exchange resin and filtered . The filtrate was evaporated under reduced pressure and the residue was thoroughly washed with diethyl ether by repeated trituration followed by decantation to yield **10a** (0.087 g, 92%). An analytical sample was obtained by crystallization from water, mp 235-238°dec. ^1H NMR (DMSO-d_6) : δ 3.20 - 4.30 (m, 5H, H-2', H-3', H-4', H-5', H-5''), 4.75 (t, 1H, 5'-OH, J = 5 Hz exch. with D_2O), 4.98 (d, 1H, OH, J = 8 Hz exch. with D_2O), 5.25 (d, 1H, OH, J = 4 Hz, exch. with D_2O), 5.71 (app d, 1H, H-1', J = 2 Hz), 7.76 (br s, 1H, H-2), 8.41(s, 1H, H-5), 11.63(br s, 1H, CONH).

Anal. Calcd for $C_{11}H_{12}N_2O_5S$: C, 46.47; H, 4.26; N, 9.85. Found : C, 46.39; H, 4.38; N, 9.86.

Methyl 4-[(N-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl))formylamino]-thiophene-3-carboxylate (11). A mixture of **5** (4.0 g, 21.6 mmol), **6** (21.80 g, 43.2 mmol), Et_2AlCl (1.0 M solution in hexanes, 43.2 mL, 43.2 mmol) and dry 1,2-dichloroethane (100 mL) was refluxed for 4 h and

worked up as for **7b** and **7a**. The viscous oil obtained after evaporation of the organic layer was dissolved in toluene (25 mL) and purified by flash chromatography. Unreacted **5** was eluted with toluene (1.27g, 32%). Elution with toluene-ethyl acetate (97.5:2.5) gave mixed fractions containing **11** and an unidentified product derived from **6**. These were pooled, evaporated (10.80 g) and rechromatographed eluting with hexane-ethyl acetate (5:2). There was obtained 5.40 g (58.3%) of **11** as a colorless foam; ^{1}H NMR ($CDCl_3$)[12] : δ 3.49 (s, 3H, CH_3), 4.30 - 4.70 (m, 3H), 5.20 - 5.70 (m, 2H), 5.94 (d, 0.4H, J = 7 Hz), 6.70(d, 0.6H, J = 8 Hz), 7.10 - 8.20 (m, 17H, H-2, H-5 and Ph), 8.24 (s, 0.6H), 8.50 (s, 0.4H); ^{13}C NMR ($CDCl_3$)[12] : δ 51.5 and 51.7 ($COOCH_3$), 64.1 and 64.2 (C-5'), [(71.4, 70.4), 79.6, 80.0 and 90.0 (sugar carbons)], 126.0 - 136.0 (thiophene and Ph carbons), 163.2 and 163.9 (N-CHO), [165.2, 165.5 and 166.0 (C=O)].

Anal. Calcd for $C_{33}H_{27}NO_{10}S$: C, 62.95; H, 4.29; N, 2.22. Found : C, 62.92; H, 4.37; N, 2.21.

Methyl 4-[(N-(2,3-O-isopropylidene-β-D-ribofuranosyl))formylamino]-thiophene-3-carboxylate (13). A mixture of **12** (0.14 g, 0.44 mmol), acetone (7mL) and p-toluenesulfonic acid monohydrate (5 mg) was stirred at 25°C for 2.5 h at which time another portion of p-toluenesulfonic acid monohydrate (10 mg) was added. The stirring was continued for an additional 3 h. Solid $NaHCO_3$ was added and the mixture stirred for 20 min. The solid was removed by filtration and thoroughly washed with acetone. The filtrate was evaporated under reduced pressure and the residue purified by preparative TLC (3 plates) using CH_2Cl_2-MeOH (96:4) as the developing agent. Pure **13** was extracted with the same solvent mixture (0.132 g, 84%); ^{1}H NMR ($CDCl_3$)[12] : δ [(1.30, 1.34), (1.52, 1.58) two sets of two s, 6H, $C(CH_3)_2$], 2.76 (m, 1H, 5'-OH exch. with D_2O), 3.52 - 4.56 (m, 6H, $COOCH_3$, H-5', H-5'', H-4'), 4.81 (dd, 1H, H-3' or H-2', J ≈ 4 Hz, 6 Hz), 5.01 (dd, 1H, H-2' or H-3', J ≈ 4 Hz, 6 Hz), 5.51 (d, 1H, H-1'), 7.40 (d, 1H, H-5, J = 4 Hz), 8.15 (d, 1H, H-2, J = 4 Hz), 8.21 and 8.43 (two s, 1H, N-CHO); ^{13}C NMR ($CDCl_3$)[12] : δ 25.4 and 27.3 [$C(\underline{C}H_3)_2$], 52.1 and 52.3 ($COO\underline{C}H_3$), 62.4 and 62.7 (C-5'), 114.0 and 114.7 [$\underline{C}(CH_3)_2$], 125.3 and 125.6 (C-5), 129.8 (C-4), 133.2 and 134.2 (C-2), 137.1 (C-3), 162.5 ($\underline{C}OOCH_3$), 163.1 and 163.3 (-N-$\underline{C}$HO).

Anal. Calcd for $C_{15}H_{19}NO_7S$: C, 50.41; H, 5.36; N, 3.92; S, 8.97. Found : C, 50.49; H, 5.37; N, 3.93; S, 9.10.

1-β-D-Ribofuranosylthieno[3,4-d]pyrimidin-4(1H)-one (14). A solution of **11** (1.0 g, 15.9 mmol) in saturated methanolic ammonia (saturated at 0°C, 80 mL) was stirred in a stainless steel bomb in an oil bath heated at 75°C. After heating for 8 h, the solution was stirred at ambient temperature for 7 h. The solvent was removed under reduced pressure and the residual traces of NH_3 were removed by entrainment with methanol. Finally, the residue was triturated with cold methanol to yield a colorless solid that was collected by filtration, washed with two small portions of cold methanol and once with diethyl ether, and dried to give **14** (0.086 g, 19%, mp 202-203°dec).

^1H NMR (DMSO-d_6) : δ 3.60 - 3.92 (m, 2H, H-5', H-5''), 4.01 (app q, 1H, H-4'), 4.11 (dd, 1H, H-3', changes to t with D_2O), 4.31 (dd, 1H, H-2') 5.26 (d, 1H, OH, J = 5 Hz, exch. with D_2O), 5.32 (t, 1H, 5'-OH, J = 5 Hz, exch. with D_2O), 5.61 (d, 1H, OH, J = 6 Hz, exch. with D_2O), 5.67 (d, 1H, H-1', J = 6 Hz), 7.87 (d, 1H, H-7, J = 3 Hz), 8.46 (d, 1H, H-5, J = 3 Hz), 8.59 (br s, 1H, H-2); ^{13}C NMR (DMSO-d_6) : δ 60.3 (C-5'), [69.2, 72.4, 85.5 and 93.4 (sugar carbons)], [108.7, 129.0 (C-5, C-7)], [125.7, 136.0 (C-4a, C-7a)]; UV λ_{max} (H_2O) : 276.5, 324.5; FAB MS (+) : m/z 285 (M+1, calcd 285).

Anal. Calcd for $C_{11}H_{12}N_2O_5S$: C, 46.47; H, 4.26; N, 9.85; S, 11.28. Found : C, 46.70; H, 4.40; N, 10.04; S, 11.40.

The filtrate obtained above was evaporated under reduced pressure and the residue was purified on a Chromatotron® (2 mm plate). Compound **12** was eluted with CH_2Cl_2-MeOH (95:5) and obtained as a hygroscopic semi-solid (0.21 g, 41%); ^1H NMR (D_2O)[12] : δ 3.00 - 4.32 (m, 8H, CH_3, H-2', H-3', H-4', H-5' and H-5''), 5.58 (d, 0.8H, H-1', $J_{1',2'}$ = 4 Hz), 6.00 (d, 0.2H, H-1', $J_{1',2'}$ = 3 Hz), 7.60 and 7.69 (two br overlapping s, 1H, H-5), 8.20 - 8.72 (m, 2H, N-CHO and H-2); ^{13}C NMR ($CDCl_3$)[12] : δ 52.6 ($COO\underline{C}H_3$), 62.8 and 63 (C-5'), 126.4 and 127.2 (C-5), 133.9 and 134.2 (C-2), 163.1 ($\underline{C}OOCH_3$), 163.8 (NHCHO).

Anal. Calcd for $C_{12}H_{15}NO_7S$: C, 45.42; H, 4.77; N, 4.41; S, 10.11. Found : C, 45.45; H, 4.87; N, 4.45; S, 9.96.

4-[(N-(β-D-Ribofuranosyl))formylamino]thiophene-3-carboxamide (16). A mixture of **14** (0.08 g, 0.28 mmol) and distilled water (8 mL) was stirred at ambient temperature for 23 h. TLC (CH_2Cl_2-MeOH, 5:1) indicated complete disappearance of **14** (R_f = 0.30) and the appearance of a new UV absorbing spot with R_f = 0.24. The mixture was clarified by filtration and the filtrate was freeze-dried for 48 h to yield **16** as a colorless solid (0.082 g, ≈ 100%).

^{1}H NMR (DMSO-d_6)[12] : δ 3.20 - 3.96 (m, H-2', H-3', H-4', H5', H-5''), 4.72 (two overlapping t, 1H, 5'-OH, exch. with D_2O), 4.93 and 5.07 (two d, 1H, OH, exch, with D_2O), 5.26 and 5.67 (two d, 1H, OH, exch. with D_2O), 5.38 and 5.86 (two d, 1H, H-1'), 7.45 and 7.81 (two br s, 2H, $CONH_2$, exch. with D_2O), 7.49 and 7.69 (two d, 1H, H-5), 7.99 and 8.08 (two d, 1H, H-2), 8.14 and 8.41 (two s, 1H, -N-CHO); ^{13}C NMR (DMSO-d_6)[12] : δ 61.7 (C-5'), 125.1 and 127 (C-5), 128.8 (C-2), 131.3 (C-4), 133.3 and 134.5 (C-3), 163.4 and 164.1 (-N-CHO), 164.5 and 165.0 ($CONH_2$); λ_{max} (H_2O): 203.0, 240.0 (sh); FAB MS (+) : m/z 303 (M+1, calcd 303).

Anal. Calcd for $C_{11}H_{14}N_2O_6S$: C, 43.70; H, 4.67; N, 9.27; S, 10.61. Found : C, 43.53; H, 4.72; N, 9.16; S, 10.50.

Methyl 5-(2,3,5-tri-O-benzoyl-β-(and α-)D-ribofuranosyl)-4-(formylamino)furan-3-carboxylate (20b and 20a). A mixture of **19**[16] (8.64 g, 51.1 mmol), **6** (12.89 g, 25.6 mmol) and dry 1,2-dichloroethane (150 mL) was brought to reflux under a N_2 atmosphere. To this was added freshly distilled $SnCl_4$ (13.31 g, 51.1 mmol) and the mixture was refluxed for 4 h. Upon cooling to room temperature, the mixture was diluted with CH_2Cl_2 (250 mL) and stirred vigorously with 10% (w/v) aq. $NaHCO_3$ (200 mL) for 20 min. The mixture was filtered through Celite and the layers separated. The organic layer was washed once with brine and dried (Na_2SO_4). Removal of the solvent gave a residue which was dissolved in toluene (25 mL) and purified by flash chromatography using toluene-ethyl acetate (95:5) to obtain unreacted **19** (2.80 g, 32.4%). Elution with toluene-ethyl acetate (89:11) gave **20b** (3.63 g, 17% based on amount of **19** consumed).

^{1}H NMR ($CDCl_3$) : δ 3.85 (s, 3H, $COOCH_3$), 4.56 (dd, 1H, H-5', $J_{5',4'}$ = 4 Hz, $J_{5',5''}$ = 12 Hz), 4.69 (m, 1H, H-4'), 4.81 (dd, 1H, H-5'', $J_{5'',4'}$ = 3 Hz), 5.92 (t, 1H, H-3'), 6.01 (t, 1H, H-2', J = 5 Hz), 6.20 (d, 1H, H-1', $J_{1',2'}$ = 5 Hz), 7.00 - 8.40 (m, 17H, H-5, NHCHO and Ph), 8.67 (s, 1H, NHCHO, exch. with D_2O); ^{13}C NMR ($CDCl_3$)[12] : δ 51.9 ($COOCH_3$), 63.9 (C-5'), [112.2, 121.0, 114.1 (C-2, C-3, C-4)], 128.0-135 (Ph C), 147.2 and 147.8 (C-5), 158.1 (NHCHO), 163.9 ($COOCH_3$), [165.3, 165.5 and 166.2 (C=O)].

Anal. Calcd for $C_{33}H_{27}NO_{11}$: C, 64.60; H, 4.44; N, 2.28. Found : C, 64.56; H, 4.51; N, 2.25.

Compound **20a** was eluted next with toluene-ethyl acetate (86:14). Rechromatography using toluene-ethyl acetate (85:15) afforded pure **20a** (0.38 g, 1.8% based on amount of **19** consumed, β/α = 9.4); ^{1}H NMR

($CDCl_3$) : δ 3.83 (s, 3H, $COOCH_3$), 4.60 (dd, 1H, H-5', $J_{5',4'}$ = 4 Hz, $J_{5',5''}$ = 12 Hz), 4.75 (dd, 1H, H-5'', $J_{5'',4'}$ = 4 Hz), 4.87 (m, 1H, H-4'), 5.89 (dd, 1H, H-3' or H-2', J = 5 Hz and 7 Hz), 6.24 (m, 2H, H-1' and H-2' or H-3'), 7.20 - 8.20 (m, 16H, H-5 and Ph), 8.27 (s, 1H, NH-CHO), 8.53 (br s, 1H, NHCHO, exch. with D_2O); ^{13}C NMR ($CDCl_3$) : δ 51.7 ($COOCH_3$), 64.3 (C-5'), [73.0, 73.5, 75.6 and 78.4 (sugar carbons)], [112.1, 120.3, 140.5 (C-2, C-3, C-4)], 147.0 (C-5), 158.2 (NHCHO), 163.7 ($COOCH_3$), [164.9, 165.2 and 166.2 (C=O)].

Anal. Calcd for $C_{33}H_{27}NO_{11}$: C, 64.60; H, 4.44; N, 2.28. Found : C, 64.56; H, 4.51; N,2.25.

Methyl 5-(2,3-O-isopropylidene-β-D-ribofuranosyl)-4-(formylamino)-furan-3-carboxylate (22b). A mixture of **21b** (0.155 g, 0.52 mmol), acetone (8 mL) and p-toluenesulfonic acid monohydrate (17 mg) was stirred at 25°C for 3 h at which time another portion of p-toluenesulfonic acid monohydrate (10 mg) was added. The stirring was continued for an additional 1 h. Solid $NaHCO_3$ was added and the mixture was stirred for 15 min. The solid was removed by filtration and thoroughly washed with acetone. The filtrate was evaporated under reduced pressure and the residue was purified by preparative TLC (5 plates) using CH_2Cl_2-MeOH (96:4) as the developing agent. Pure **22b** was extracted with the same solvent mixture (0.08 g, 46%); ^1H NMR ($CDCl_3$) : δ 1.31 and 1.55 [two s, 6H, $C(CH_3)_2$], 2.39 (br s, 1H, H-5'), 3.50 - 4.40 (m, 6H, $COOCH_3$, H-5', H-5'', H-4'), 4.60 - 5.10 (m, 2H, H-2', H-3'), 5.56 (d, 1H, H-1', $J_{1',2'}$ = 5 Hz), 7.80 - 8.70 (m, 3H, H-5, NHCHO); ^{13}C NMR[12] ($CDCl_3$) δ [(25.4, 25.6), 27.5 $C(CH_3)_2$], 52.0 ($COOCH_3$), 62.5, 62.6 (C-5'), 147.0 and 147.5 (C-5), 158.2 (NHCHO), 163.8 ($COOCH_3$).

Anal. Calcd for $C_{15}H_{19}NO_8$: C, 52.78; H, 5.61; N, 4.10. Found : C, 52.78; H, 5.77; N, 4.10.

4-(Formylamino)-5-(β-D-ribofuranosyl)furan-3-carboxamide (23b). A solution of **20b** (0.50 g, 0.82 mmol) in saturated methanolic ammonia (saturated at 0°C, 40 mL) was stirred in a stainless-steel bomb at 25°C for 22 h. The solvent was removed under reduced pressure and the residual traces of ammonia were removed by entrainment with methanol. The residue was purified by preparative TLC (5 plates) using CH_2Cl_2-MeOH, 5:1 as the developing agent. The plates were developed twice. Two major bands were observed under UV light (R_f = 0.11 and 0.46). Each was extracted with methanol.

The more polar compound was isolated as a light yellow solid and identified as **23b** (0.039 g, 16%); ^1H NMR (D_2O) : δ 3.77 (8-line m, 2H,

H-5' and H-5''), 4.05 (app q, 1H, H-4'), 4.29(t, 1H, H-3'), 4.47 (t, 1H, H-2', J = 6 Hz), 4.92 (d, 1H, H-1', $J_{1',2'}$ = 6 Hz), 8.11 (s, 1H, H-5), 8.31 (s, 1H, NHCHO); ^{13}C NMR (D_2O)[12] : δ 62.5 (C-5'), 119.2 and 146.7 (furan C), 146.7 (C-5), 164.8 and 168.1 (NHCHO); FAB MS (+) : m/z 287 (M+1, calcd 287).

Anal. Calcd for $C_{11}H_{14}N_2O_7$. 0.4 H_2O : C, 45.02; H, 5.08; N, 9.55. Found : C, 45.38; H, 5.27; N, 9.15.

The less polar compound was isolated as a colorless, hygroscopic semi-solid and identified as **21b** (0.113 g, 46%); ^{1}H NMR (D_2O) : δ 3.60-3.98 (m, 5H, CH_3, H-5' and H-5''), 4.05 (app q, 1H, H-4'), 4.29 (t, 1H, H-3'), 4.47 (t, 1H, H-2', J = 6 Hz), 4.94 (d, 1H, H-1', $J_{1',2'}$ = 6 Hz), 8.24 (s, 1H, H-5), 8.32 (s, 1H, NHCHO).

4-(Formylamino)-5-(α-D-ribofuranosyl)furan-3-carboxamide (23a). A solution of **20a** (0.525 g, 0.86 mmol) in saturated methanolic ammonia (saturated at 0°C, 40 mL) was stirred in a stainless-steel bomb at 25°C for 23 h. The reaction mixture was worked-up and the product purified exactly as for **23b** to yield **23a** (0.025 g, 9.7%, R_f = 0.10); ^{1}H NMR (D_2O) : δ 3.88 (m, 2H, H-5', H-5''), 4.16 (m, 1H, H-4'), 4.22 (m, 2H, H-2' H-3'), 5.22 (d, 1H, H-1', $J_{1',2'}$ = 3 Hz), 8.11 (s, 1H, H-5), 8.27 (s, 1H, NHCHO); FAB MS (+) : m/z 287 (M+1, calcd 287).

Anal. Calcd for $C_{11}H_{14}N_2O_7$. 0.75 H_2O : C, 44.08; H, 5.21; N, 9.35. Found : C, 44.35; H, 5.35; N, 8.71.

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18. Similar ^{13}C NMR criteria were used to establish the site of glycosylation of the thiophene C-nucleosides. In addition to chemical shift considerations, analysis of the two- and three bond couplings of all the thiophene carbons in the N-acetyl nucleoside corresponding to deblocked **7b** revealed unambiguously that the sugar is located on the carbon adjacent to the amide function (Unpublished results).

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