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SYNTHESIS OF FURO[3,2-d]PYRIMIDINE NUCLEOSIDES: A NOVEL C-NUCLEOSIDE ISOSTERE OF ADENOSINE[1]

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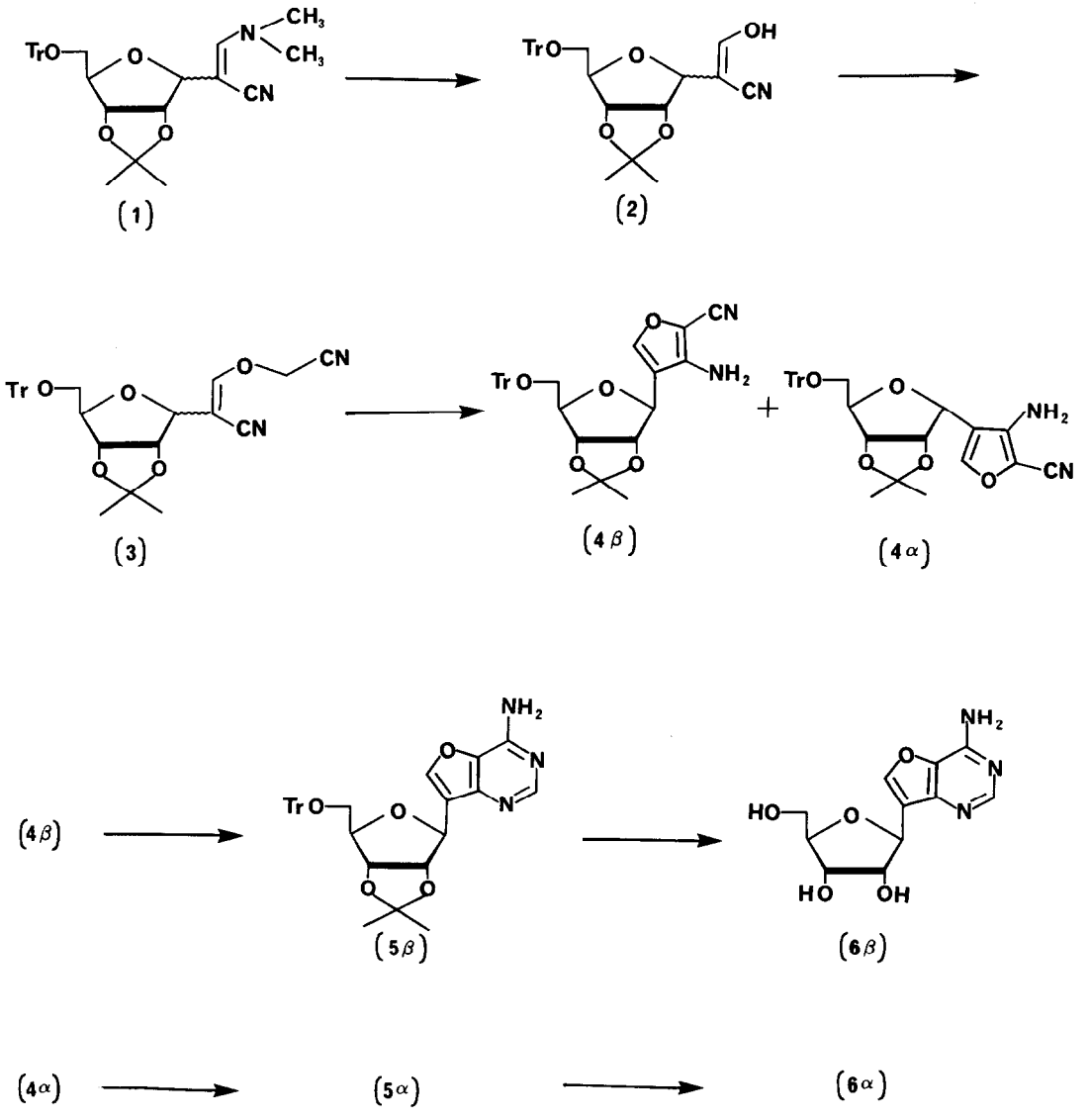
Abstract: The synthesis of 4-amino-7-(β-D-ribofuranosyl)-furo[3,2-d]pyrimidine, a new C-nucleoside analog of adenosine, is described. It involves base-catalyzed cyclization of the 2-(ribofuranosyl)-2-cyano ethers **3** to afford the ribosyl-3-amino-2-cyanofurans **4α** and **4β**, followed by a two step conversion into the desired furo[3,2-d]pyrimidine system.

Previous studies in this laboratory have led to the synthesis of a number of purine-like C-nucleosides in which modifications are restricted to the site of the original purine imidazole ring[2]. Many of these compounds, for example the 7-(β-D-ribofuranosyl)-pyrrolo[3,2-d]pyrimidine nucleosides[2a,b,e], are close analogs of naturally-occurring purines, and it is perhaps not too surprising that they show a variety of biological activities. For example, 9-deazaadenosine is extremely cytotoxic towards several lines of mouse and human tumor cells[3] and 9-deazainosine is an effective inhibitor of the growth of certain pathogenic protozoa[4]. What is surprising, however, is the fact that the more highly modified thieno[3,2-d]pyrimidine C-nucleosides show a similar spectrum of activities[3a,4a]. In fact, the thieno[3,2-d]pyrimidine isostere of adenosine behaves as a purine antimetabolite[3a], and it ranks amongst the most highly cytotoxic purine-like compounds known, with ID_{50} values in the nanomolar range[3d]. In view of these results, it is clearly of interest to determine the extent to which these C-nucleosides can be modified before they are no longer recognized biochemically as purines. To this end, we describe here the synthesis of 4-amino-7-(β-D-ribofuranosyl)furo[3,2-d]pyrimidine (**6**, fig 1).

The furo[3,2-d]pyrimidine ring system has not been studied extensively, and the few examples that have been reported are all 6-substituted compounds. Moreover, the known synthetic approaches, namely the Hofmann reaction of furan-2,3-dicarboxamides[5] and thermal rearrangements of 5-propynyloxy pyrimidines[6], were not suitable for our present needs. We have therefore developed a new approach to furo[3,2-d]pyrimidines that starts with the 3-dimethylaminoacrylonitrile **1**, a versatile intermediate that has been used in the synthesis of oxazinomycin[8] and a variety of purine-like C-nucleosides[2]. The controlled hydrolysis of enamine **1** under mild conditions in a two-phase system ($CF_3COOH/H_2O/CH_2Cl_2$, 20 ° for 5 hr.) affords the blocked 2-(D-ribofuranosy)-2-formylacetonitrile **2** in excellent yield. Conversion of **2** into the cyano ether **3** was achieved by treating the mixed isomers with chloroacetonitrile (2.5 eq.) in dry DMF in the presence of potassium fluoride and 18-crown-6 (20°, 20 hr)[7]. The α,β/cis-trans

Figure 1



isomers of **3** are separable by silica gel flash chromatography (benzene-EtOH, 9:1), but the mixed isomers were used for the subsequent steps.

Based on our earlier studies on the synthesis of pyrroles and thiophenes, we envisaged that **3** would readily undergo base-catalyzed cyclization to **4**. In practice, the cyclization proved to be difficult, and conditions that were satisfactory in the earlier cases (such as NaOEt / EtOH, 20° or DBN/THF, 80°) were ineffective with **3**, as were the bases KOtBu/THF 20°, and n-BuLi/THF, -70°. However, using a large excess of the strong base LDA (5 eq. in THF, 2hr, -70°) does promote cyclization of **3**, and the 3-amino-2-cyanofuran C-nucleosides **4** was obtained as an α,β mixture, albeit in moderate (35%) yield. Separation of the anomers (β/α = 1.3) by silica gel column chromatography, and treatment of each with formamidine acetate (8 eq.) in boiling EtOH for 48hr. then affords the 4-aminofuro[3,2-d]pyrimidine-C-nucleoside **5α** and **5β**, each in 80% yield.

A number of NMR criteria were used to determine the anomeric configurations of the C-nucleosides **4** and **5**[9,10]. Thus the relative chemical shifts of the anomeric protons, the multiplicities of the H-4' signals, and the Δδ values of the isopropylidene groups were all consistent with the empirical rules derived from studies with both C- and N-nucleosides[8,11,12]. Further, the chemical shifts of the isopropylidene methyl carbon atoms in each anomer of **4** and **5** are in excellent agreement with previous reports [11,13] that the methyl signals of 2',3'-O-isopropylidene-β-C-nucleosides appear at 25.5 ± 0.2 and 27.5 ± 0.2ppm, whereas they appear at 24.9 ± 0.3 and 26.3 ± 0.2 ppm in the α series. These observations further confirm that no epimerization occurred during the conversion of **4α** into **5α**, or of **4β** into **5β**.

Treatment of **5β** with 6% HCl/MeOH at 25° for 1 hr, followed by precipitation with ether, affords the unblocked furo[3,2-d]pyrimidine C-nucleoside (**6β**), as its hydrochloride salt in 80% yield. An analytically-pure sample was obtained after recrystallization from MeOH/CCl_4: mp 150-152°C; ^{1}H-NMR (DMSO-d_6), δ 3.64 (m, H-5'a,b); 3.91-4.07 (m, H-2',3' and 4'); 4.91 (m, H-1', broadened by virtual coupling); 8.57(s, H-6); 8.68 (s, H-2); 9.26(bs, NH_2, ex D_2O). Similar unblocking of **5α** affords **6α** as a hygroscopic solid; ^{1}H-NMR (DMSO-d_6), δ 3.4-3.7 (8-line m, H-5'a,b); 4.26-4.05(m, H-2',3' and 4'); 5.19 (d, $J_{1',2}$ = 2.5Hz.); 8.44 (s, H-6); 8.64 (s, H-2) and 9.22 (bs, NH_2 ex D_2O). The final product **6β** was obtained from **1** in 10% overall yield.

Preliminary studies indicate that **6β** is only ten fold less active than its pyrrolo- and thieno[3,2-d]pyrimidine congeners, with ID_{50} values of 1.7 and 0.68 X 10^{-8}M against mouse L1210 and P815 cells *in vitro*, respectively. Further studies with this ring system are in progress.

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References and Notes:

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7. Rather specific conditions appear to be required: **3** was not observed when **2** was treated with $ClCH_2CN$ in the presence of NaH, or CH_2Cl_2/aq $NaOH/nBu_4NHSO_4$, or $n\text{-}Bu_2SnO$.

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9. a)**4β** ^1H NMR ($CDCl_3$): δ 1.36 and 1.57 (2s, $C(CH_3)_2$); 3.31 and 3.42 (7-line m, H-5'a,b);4.18 (m,H-4'); 4.53-4.79 (overlapping m, H-1',2' and 3'); 7.18-7.44 (m, trityl and H-5);4.16 (bs, NH_2, ex D_2O); $J_{4',5'a} = J_{4',5'b} = 4.2$; $J_{3',4'}=4.0$; $J_{5'gem} = 11$ Hz.

b)**4α** ($CDCl_3$): δ1.34 and 1.49 (2s, $C(CH_3)_2$); 3.35 and 3.24(7-line m, H5'a,b); 4.29 (pseudotriplet,H-3'); 4.78 (d, H-3'); 4.88 (dd, H-2'); 5.12 (d, H-1'); 7.48-7.22 (m, trityl and H-5); 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

10. a) **5β** ^1H-NMR ($CDCl_3$): δ1.37 and 1.61 (2s, $C(CH_3)_2$); 3.30 and 3.26 (m, H-5'a,b); 4.34 (m, H-4'); 4.76 (dd, H-3'); 5.11 (dd, H-2'); 5.25 (dd, H-1'); 7.18-7.58 (m, trityl); 7.73 (d, H-6); 8.45 (s, H-2);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.

b) **5α**($CDCl_3$): δ 1.30 and 1.45 (2s, $C(CH_3)_2$); 3.25 (pseudo-d, 5'a,b):4.36(pseudo-t, H-4'); 4.77 (d,H-3'); 4.90 (dd, H-2'); 5.40 (dd, H-1');7.2-7.5 (m, trityl); 7.90 (d, H-6); 8.44 (s, H-2); ~5.4 (bs, NH_2, ex D_2O); $J_{1',2'} = 3.6$; $J_{1',6} = 1.0$; $J_{2',3'} = 6.2$; $J_{3',4'} < 0.5$; $J_{4',5'a} = J_{4',5'b}= 5.0$; $J_{5'gem} = 10.2$Hz.

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