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SYNTHESIS OF ADENINE NUCLEOSIDES RELATED TO SINEFUNGIN

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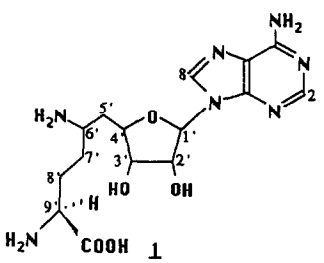
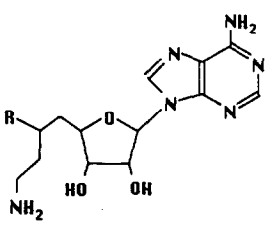
Summary : The extended adenine nucleosides **2a-b** and **3** have been prepared from D-ribose by a reasonably short sequence using the suitably functionalized intermediate **6**.

Sinefungin **1** a fermentation product isolated from *Streptomyces griseolus* [1] and *S. incarnatus* [2] has been shown to be active against fungi [1,2], viruses [3], parasites [4] and tumors *in vitro* [5]. The compound however provokes nephreotoxicity in dogs and goats which precludes its clinical uses. Research efforts are directed towards the elucidation of the cellular target [3,6] of sinefungin and to prepare structurally related active analogues with reduced toxicity. In this respect there is a constant need to synthesize new molecules related to **1** to determine the structural elements which influence its biological activity.

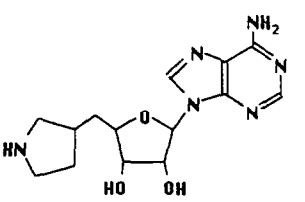
This is now possible on the basis of the various elegant synthetic strategies which have been worked out by several groups for sinefungin **1** and other chain extended nucleosides [7] . The main chemical problem in this area is to find an efficient method to introduce a chain at the relatively chemically inert C-5 position of ribose. One solution to this problem makes use of the readily accessible Horner-Wittig reagent **4** [8]. When the latter is combined with an appropriate aldehyde it gives rise to an intermediate which can serve as a precursor for a variety of extended adenosine derivatives.



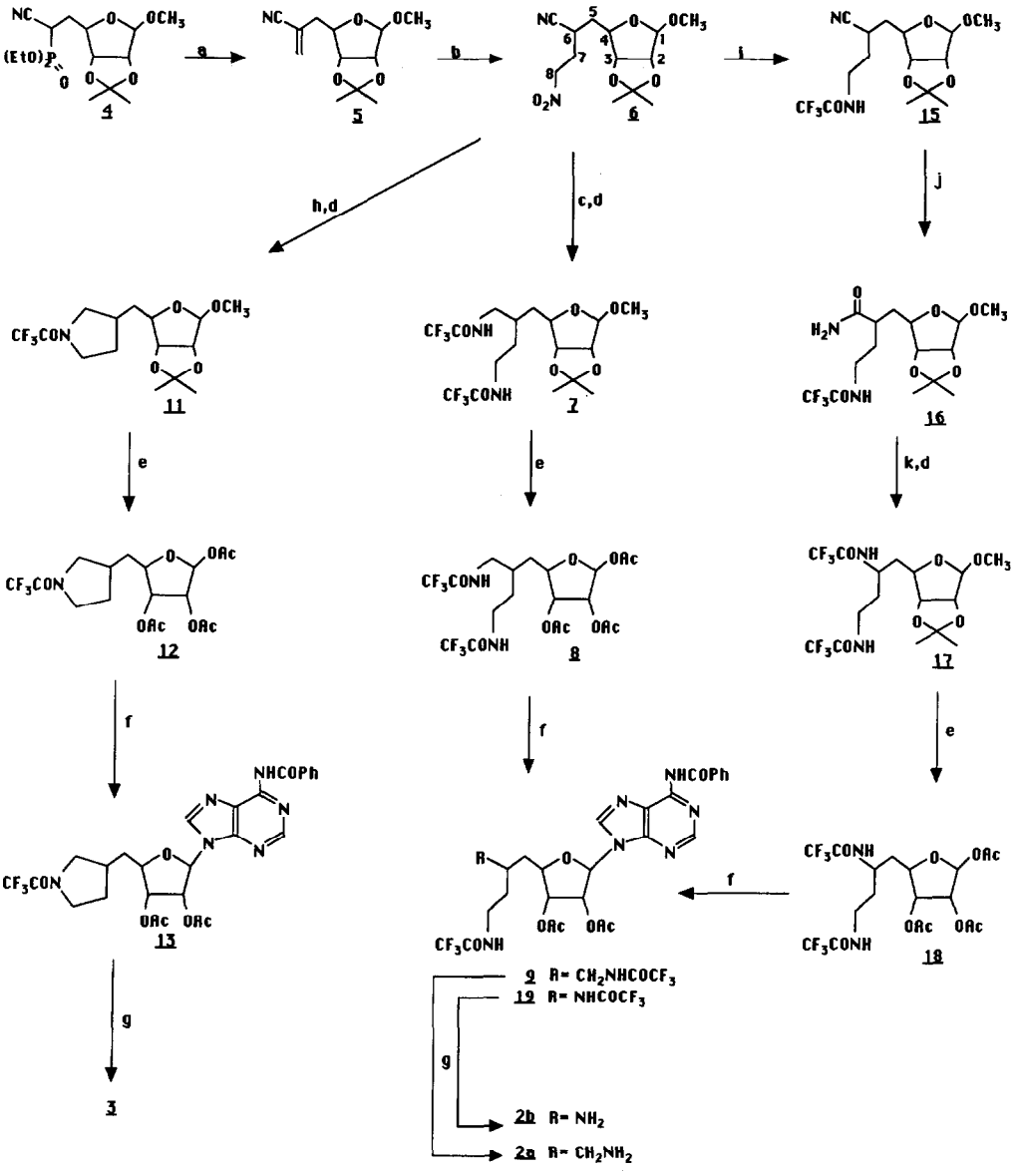
1



2a R=CH_2NH_2
2b R=NH_2



3


4
5
6
15
11
7
16
12
8
17
13
18
9 R= CH2NHCOCF3
19 R= NHCOCF3
2b R= NH2
2a R= CH2NH2
3
a
b
c,d
h,d
i
j
e
k,d
f
g

Scheme

Herein we describe a new development of this strategy which resulted in the synthesis of compounds **2a** , **2b** and **3** in acceptable yields. These compounds might hopefully interfer in the polyamine biosynthesis and/ or be selective inhibitors of some methylases in various cell types.

The synthesis of our target nucleosides **2a**, **2b** and **3** commenced with the preparation of their common intermediate **6** which was obtained in two steps from **4**[8]. Reaction of the latter with paraformaldehyde produced the unsaturated nitrile **5** (m.p. 40-41°C).which after addition of nitromethane[9] gave two saturated nitriles **6** (m.p.91-92°C).These compounds which are epimers at C-6 are separable by column chromatography[10]. To obtain the appropriate precursor of the targeted nucleosides we had to devise a suitable procedure to reduce simultaneously or chemoselectively the cyano- and nitro functionalities of compound **6**. Thus hydrogenation[11] (under 5 atm.) of **6** in the presence of activated PtO_2 resulted in the formation of a diamino derivative which , after treatment with ethyl trifluoroacetate[12] was isolated as the N^6,N^9-ditrifluoroacetamide **7**.This compound was hydrolysed and peracetylated to give **8**. For the adenylation reaction the best results were obtained by treating **8** with N^6,N^9-*bis* trimethylsilyl-N^6-benzoyladenine in refluxing 1,2-dichloroethane containing trimethylsilyltriflate[13]. Under these conditions the protected nucleoside **9** was isolated in 34 % yield. Complete removal of the different acyl protecting groups was accomplished by treatment with a methanolic solution of ammonia.

For the selective reduction of the 8-nitro function of **6** to amine we addressed to hydrogenation using palladium on carbon as the catalyst[14]. When normal grade methanol was used as solvent two compounds **11** and **15** were isolated after trifluoroacetylation of the reaction mixture[15]. Their relative proportions varied from one experiment to the other. Finally, by employing methanol:acetic acid (9:1) the pyrrolidine **11** was obtained in 68% yield after N-trifluoroacetylation. It is presumed that in acidic medium the intermediate imine is protonated and finally intercepted by the newly formed amine at the end of the chain. Subsequent transformation of **11** to give the corresponding nucleoside **3** was effected in the same way as in the case of compound **2a**. Alternatively,when the hydrogenation of **6** was carried out in absolute methanol we obtained, after trifluoroacetylation[12], the protected derivative **15** in satisfactory yield. The best reaction conditions for the nitrile-amide conversion to give **16** were those which call for the use of potassium superoxide [16]. Treatment of **16** with (bis (trifuoroacetoxy) iodo)benzene[17] and protection[12] of the resulting amine led to the N^6,N^8-ditrifluoroacetamido derivative **18**. By following the route previously indicated for **2a** and **3** we have obtained the nucleoside **2b**.

In conclusion,this work describes an efficient procedure to obtain three chain extended nucleoside derivatives the synthesis of which was inspired by considering the structure of sinefungin **1**.

Schemel. Reagents,conditions and yields : a $(CH_2O)_n$, $Mg(OMe)_2$, MeOH, room temp., 4h, 85%; (b) nitromethane, potassium *tert* butylate, room temp., 4h, 70 % (*R* and *S* epimers at C-6 in 1/1 ratio) ; (c) H_2, 5atm., PtO_2, absolute EtOH, room temp., 4h, not isolated ; (d) ethyl trifluoroacetate, NEt_3, 0°C, 70-75 % (from **6**) ; (e) trifluoroacetic acid : H_2O (1:2), room temp., 16h, then acetic anhydride, pyridine, room temp., 16h,70-80 %; (f) N^6benzoylN^6N^9trimethylsilyladenine, trimethylsilyltriflate, 1,2-dichloroethane, reflux,16h,34-40 % ; (g) 32% NH_4OH : MeOH (1:1), room temp., 16h, 70-85%; (h) H_2,3.5 atm., 10 % Pd/C, MeOH : acetic acid (9:1), room temp., 4h, not isolated then (d), 68 % (from **6**) ; (i) H_2,3.5 atm., 10% Pd/C, absolute EtOH, room temp., 4h, not isolated then (d), 70% (from **6**) ; (j) KO_2,dimethyl sulfoxide, room temp., 18h then ethyl acetate then ethyl trifluoroacetate ,58% ; (k) $PhI(OCOCF_3)_2$,N,N-dimethylformamide:H_2O (1:1), room temp., 3.5h, then (d) 79% (from **16**).

References

(1) R.L.HAMILL and R.NAGARAJAN,US Patent 1978,4 087 603.
(2) J.FLORENT,J.LUNEL and D.MANCY,US Patent 1980,4 189 349.
(3) C.S.G.PUGH,andR.T.BORCHARDT,Biochemistry,1982,21,1535 ; M.VEDEL,F.LAWRENCE,M.ROBERT-GERO and E.LEDERER, Res.Commun.,1978,85,371.
(4) U.BACHRAH,L.F.SCHNUR,J.EL- ON,C.L.GREENBLATT,E.PEARLMAN, M.ROBERT-GERO,and E.LEDERER,FEBS Lett.,1980,121,287.
(5) R.J.SUHADOLNIK, "Nucleosides as Biological Probes",Wiley,New York,N.Y.,1979 p 19-23.
(6) J.K.COWARD, "Design of Enzyme Inhibitors as Drugs", eds M.SANDLER and J.SMITH,Oxford Press, London, 1988, chapter 21 ; R.W.FULLER, and R.NAGARAJAN, Biochem.Pharmacol., 1978,, 27,1981.
(7) For syntheses of **1** see : M.P.MAGUIRE, P.L. FELDMAN, and H. RAPOPORT, J.Org.Chem., 1990, 55,948 ; J.G. BUCHANAN, A. FLINN, P.H. MUNDILL, and R.H. WIGTHAM, Nucleosides Nucleotides, 1986, 5, 313 ; M. GEZE, P.BLANCHARD, J.-L.FOURREY, and M.ROBERT-GERO, J.Am.Chem.Soc., 1983, 105, 7638 ; G.A. MOCK, and J.G. MOFFATT, Nucleic Acids Res., 1982, 10, 6223. For syntheses of chain extended nucleosides see : J. FIANDOR, M.T. GARCIA-LOPEZ, and F. De las HERAS, Nucleosides Nucleotides, 1989, 8, 1325 and references cited therein ; N. DODIC, M. GEZE, P. BLANCHARD, J.-L. FOURREY, and M. ROBERT-GERO, Nucleosides Nucleotides, 1985, 4, 275 ; A.R. MOORMAN, T. MARTIN, and R.T. BORCHARDT, Carbohydr. Res., 1983, 113, 233 ; J.W. LYGA, and J.A. SECRIST III, J.Org.Chem., 1983, 48, 1982.
(8) A. HAMPTON, T. SASAKI, and B. PAUL, J.Am.Chem.Soc., 1973, 95, 4404.
(9) A. OSTASZYNSKI, J. WIELGAT, and T. URBANSKI, Tetrahedron, 1969, 25, 1929.
(10) The (*S*) configuration at C-6 was given to the more polar isomer (silica gel TLC, ether : pentane, 2:3) of compound (**6**) by X-ray crystallography (Dr.J.Guilhem,to be published).
(11) J.A.SECRIST III, and M.W.LOGUE, J. Org. Chem., 1972, 37, 335.
(12) T.J.CURPHEY, J.Org.Chem., 1979, 44, 2805.
(13) H. VORBRUGGEN, K. KROLKIEWICZ, and B. BENNUA, Chem.Ber., 1981, 114, 1234.
(14) P.N. RYLANDER, "HydrogenationMethods", AcademicPress, London, 1985, chapter 8.
(15) For related cyclization reactions see : J.B. HESTER Jr., J.Org.Chem., 1964, 29, 1158 ; G.N. WALKER, J.Med.Chem., 1965, 8, 583.
(16) N. KORNBLUM, and S. SINGRAM, J.Org.Chem., 1979, 44, 4727
(17) G.M. LOUDON, A.S. RADHAKRISHNA, M.R. ALMOND, J.G. BLODGETT, and R.H. BOUTIN, J.Org.Chem., 1984, 49, 4277 ; R.H. BOUTIN, and G.M. LOUDON, Ibid., 1984, 49, 4277.

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