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Synthesis of a New Exocyclic Amino Carbocyclic Nucleoside with Potential Antiviral Activity.

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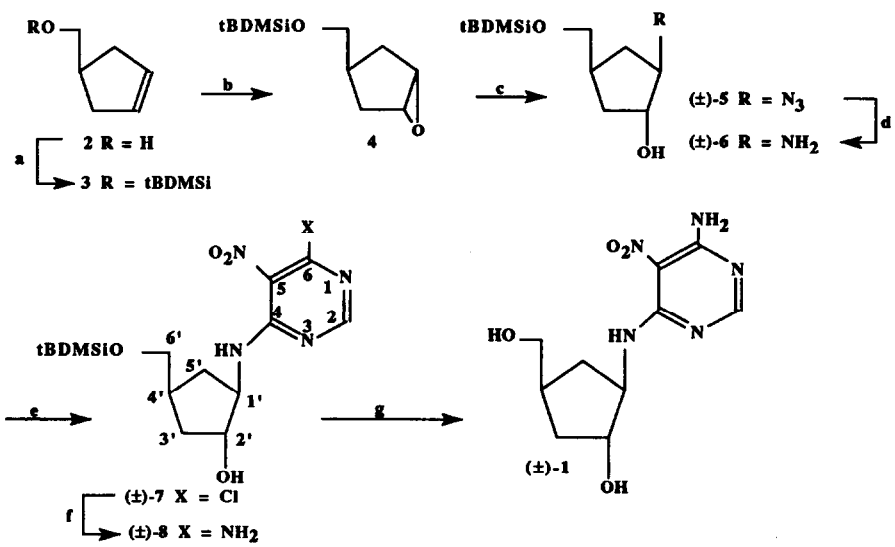
Abstract : *The total synthesis of a new exocyclic amino carbocyclic nucleoside, (±)-(1), (±)-1'-(β)-[4-(6-amino-5-nitro)pyrimidine]-amino-2'-(α)-hydroxy-4'-hydroxymethylcyclopentane has been accomplished. 1-Hydroxymethyl-3-cyclopentene has been converted into a carbocyclic nucleoside in six steps.*

Carbocyclic nucleosides are compounds structurally related to nucleosides in which the furanose oxygen atom has been replaced by a methylene group. Consistent with the absence of a glycosidic structure, carbocyclic analogs are resistant to cleavage by hydrolases which attack the glycosyl bond of nucleosides [1-2]. For about ten years, several carbocyclic purine or pyrimidine nucleosides have been shown to have a biological interest[3-7] against HSV 1 & 2 for instance. The aristeromycin[8] and the neplanocin[9,10] show activity against human cytomegalovirus. More recently, Carbovir[11,12], C-2',3'-dideoxy-2',3'-didehydroguanosine, displays potent activity against HIV, which is comparable to that of AZT.

As part of a continuing program of synthesis of carbocyclic nucleosides and derivatives that may exhibit potential antiviral activity, the synthesis of 1, (see scheme 1), a derivative of a biologically active nucleoside[13-15], with the same heterocycle moiety, was performed.



a) : tBDMSi-Cl, Py., 0°C; b) : mCPBA, CH_2Cl_2 reflux; c) : NaN_3, NH_4Cl, H_2O/EtOH;
d) : H_2, Pd/C 10%; e) : 4,6-dichloro-5-nitro-pyrimidine, Et_3N, Et_2O; f) : NH_3, MeOH; g) : NH_4F, MeOH.

Scheme 1

The 1-hydroxymethyl-3-cyclopentene was obtained acording to the literature [16]. The key step of our synthesis (see scheme 1) was the formation of the epoxide **4** [16-18]. Only the *anti* isomer must be used in the course of synthetic studies of carbocyclic analogues. In a preceding paper [19], we have shown that the use of *tert*-butyldimethylsilyl ether as a 5'-hydroxyl protecting group favored the formation of the *anti* isomer.

The sequence of reactions leading to **1** was as follows (see scheme 1) : the treatment of the hydroxy-alkene **2** with *tert*-butyldimethylsilyl chloride gave **3** in 84%yield. The reaction of **3** with 3-chloroperbenzoic acid led to the epoxides *anti*-**4** and *syn*-**4'** in a 8.2:1 ratio of anti:syn isomers.

The *anti* opening of the epoxide ring of compound **4** with azide ion gave the azidoalcohol **5** (43%). Reduction of the azido group was performed by a catalytic hydrogenation (H_2, Pd/C 10%) and gave **6** quantitatively. The reaction of the amine **6** with 4,6-dichloro-5-nitropyrimidine gave **7** (51%) and the substitution of the aromatic chlorine in **7** with methanolic ammonia gave **8** (76%).

The deprotection of **8** was performed by addition of a solution of NH_4F/MeOH [20] and gave the target compound **1** [21,22] in 72% yield. It is interesting to note that **1** could be directly obtained, with low yield, during the deprotection of **7** with a solution of NH_4F/MeOH; in fact, the ammonia released during this reaction could substitute the chlorine.

The modified coupling procedure [13] led quickly, with good yields and regioselectively to product (±)-**7** and (±)-**8** which are key synthons in the synthesis of new carbocyclic 3'-deoxy-purine-ribonucleosides.

The biological properties of (±)-**1** will be detailed elsewhere.

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21. Selected spectroscopic data for (±)-**1** : *^{1}H NMR δ (DMSO-D6) 9.26 (d, 1H, J =7.40 Hz, NH), 8.58 (s, 2H, NH_2), 7.97 (s, 1H, C_2-H_{base}), 4.92 (d, 1H, J = 4.28 Hz, 2'-OH), 4.75 (t, 1H, J = 4.84 Hz, 3'-OH), 4.42 (q, 1H, J = 4.5 Hz, $C_{1'}$-H), 3.95 (q, 1H, J = 4.5 Hz, $C_{2'}$-H), 3.41 (d, 2H, J = 8.1 Hz, $C_{6'}$-H_2), 2.24 (m, 2H, $C_{4'}$-H, $C_{5'}$-H_β), 1.67 (m, 2H, $C_{3'}$-H_2), 1.32 (m, 1H, $C_{5'}$-H_α). ^{13}C NMR (DEPT) δ (DMSO-D6) 160.9 (C_2 base), 77.2 ($C_{1'}$), 65.8 ($C_{6'}$), 60.8 ($C_{2'}$), 38.2 ($C_{4'}$), 36.2 ($C_{3'}$), 34.1 ($C_{5'}$). MS (M^+) 270, 252, 234, 165, 157. Anal. ($C_{10}H_{15}N_5O_4$) calcd : C 44.61, H 5.62, N 26.01; Found : C 44.58, H 5.57, N 25.96.*
22. All new compounds (**1-8**) were purified by column chromatography or HPLC and product structures were determined by infrared, high resolution ms, 200 MHz ^{1}H NMR and ^{13}C NMR.

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