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Synthesis of N^6-Cyclopropyl-2,6-diamino-9 β -D-arabinofuranosyl-purine

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Abstract: Synthesis of N^6-cyclopropyl-2,6-diamino-9 β -D-arabinofuranosyl-purine has been accomplished by treatment silylated 2-amino-6-chloro-purine **4** with 2,3,5-tri-O-benzyl- β -D-arabinofuranosyl chloride **3** in the presence of molecular sieves, followed by reaction with cyclopropylamine and debenzyl reaction to give the β -anomeric nucleoside. The structures of all products were confirmed by UV, ^{1}H-NMR and elemental analysis.

Keywords: Cyclopropylamine; arabinofuranose; purnie.

Recently, various classes of nucleosides have been synthesized and evaluated as potential anti-HIV and anti-HBV agents. From these efforts several nucleosides were discovered as promising anti-HIV agents, among which AZT, ddI, ddC and d_4T[1-4] are being used as clinically effective anti-HIV drugs. Furthermore, several other nucleosides[3-8] are currently being studied preclinically as well as clinically as anti-HIV and anti-HBV agents. Among these classes of nucleosides, carbovir[9] and its 6-cyclopropylamino-purine analogue[10] are the most interesting compounds, and the latter is currently undergoing clinical trials as anti-HIV agent. In addition, several interesting D-nucleosides mentioned above have been recently discovered as potent anti-HIV and anti-HBV agents. Therefore, it was of interest to synthesize D-nucleosides as potential anti-virus agents. As part of our ongoing research work, we now report here the synthesis of N^6-cyclopropylamino nucleoside.

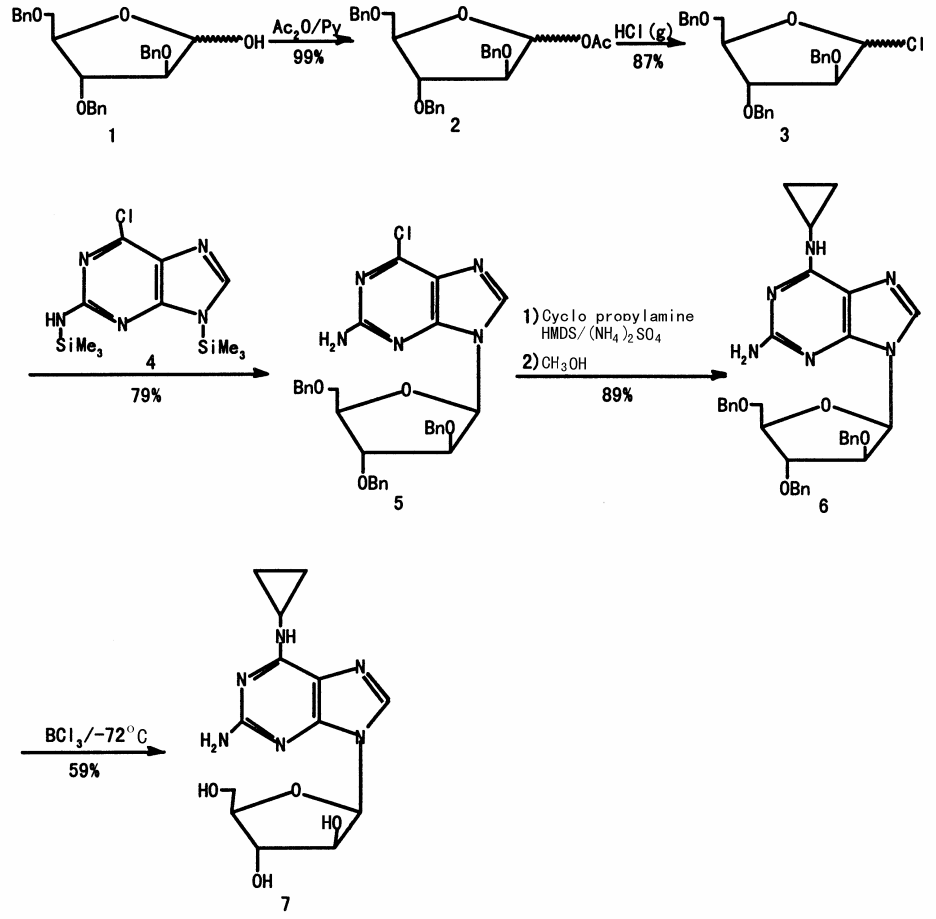
For the synthesis of N^6-cyclopropylamino nucleoside, we utilized the general strategy that we have developed for the synthesis of β -D-nucleosides (**scheme 1**).

A solution of 2,3,5-Tri-O-benzyl-D-arabino-furanose **1** in dry pyridine and acetic anhydride was stirred at room temperature for 4h. The solution was concentrated with toluene and to give a syrup **2**, which was used as such in the next step.

Syrup **2** was dissolved in anhydrous dichloromethane and the solution was colded to 0℃.The solution is kept for 3h at 0℃ while dry hydrogen chloride gas is slowly bubbled through the solution in order to maintain saturation. The solvent is then

removed in *vacuo*, and the residue is coevaporated with dry xylene. The syrup was dried in *vacuo* to give compound **3**, which was used as such in the next setp.

Scheme 1



2-amino-6-chloropurine was heated at reflux in hexamethyldisilazane in the presence of ammonium sulfate until a clear solution was obtained. The solvent was then removed at reduced pressure to leave a white solid which was silylated 2-amino-6-chloropurine **4**. To a suspension of this solid in 1,2-dichloroethane was added molecular sieves (4Å) and a solution of **3** in 1,2-dichloroethane. The mixture was stirred at room temperature for seven days. Dichloromethane was added and the solution was filtered through Celite. The filtrate was washed successively with aqueous sodium carbonate and saturated salt solution and then dried over sodium sulfate. Removal of the solvent left a dark yellow solid, which was flash chromatographed on

silica gel using hexane-ethyl acetate. The products was obtained, after evaporation of the appropriate fractions, as a white foam **5** in 67% yield based on starting material **1**[11].

Purine derivative **6** was prepared in 89% yield by treating compound **5** with cyclopropylamine in the presence of methanol[12]. A solution of **6** in dichloromethane was added slowly to the 1M BCl_3 solution in dichloromethane colled at -72℃ (dry ice-actone). After a total reaction of 6h, the cooling bath was removed, and the solvent and BCl_3 gas were removed in *vacuo*. The residue was dissoloved in cold dichloromethane and the solution evaporated to dryness until a white solid was obtained. 5% sodium hydrogen carbonate solution of cold was added to adjust the pH to 7. The mixture was diluted with ethanol, heated to boiling, filtered through Celite, and the filtrate allowed to stand overnight at room temperature. It was then chilled, and the solid was collected by filtration, which was washed with cold water successively and dried in *vacuo* to give compound **7** in 59% yield[13].

The anti-virus evaluation of the synthesized nucleoside is in progress and will be reported elsewhere.

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11 Compound **5**: white foam, UV (CH_3OH) λ_{max} 248 nm, 310 nm; ^{1}H-NMR ($CDCl_3$) δ 3.65 (2H, d), 4.22 (3H, m), 4.57 (6H, d), 5.03 (2H, bs, exchangeable in D_2O), 6.30 (1H, d), 6.93 (2H, m), 7.31 (13H, m), 8.12 (1H, s). Anal. calcd for $C_{31}H_{30}O_4N_5Cl \cdot 0.2CH_3OH$: C, 64.78; H, 5.37; N, 12.11; Found: C, 64.93; H, 5.21; N, 11.98.

12 Compound **6**: yellowish syrup: $[\alpha]_D^{28}$ +72.2 (c 0.51, CH_3OH), UV (CH_3OH) λ_{max} 284 nm, 268 nm, 209 nm; ^{1}H-NMR ($CDCl_3$) δ 0.62 (2H, s), 0.84 (2H, d), 2.18 (1H, s, exchangeable in D_2O), 2.99 (1H, s), 3.65 (2H, d), 4.22 (3H, m), 4.53 (4H, m), 4.56 (2H, s),

5.79 (2H, s, exchangeable in D_2O), 6.33 (1H, s), 7.01 (2H, m), 7.25 (13H, m), 7.85 (1H, s). Anal. Calcd for $C_{34}H_{36}O_4N_6 \cdot 0.6CH_3OH$: C, 67.91; H, 6.32; N, 13.73; Found: C, 67.58; H, 6.01; N, 13.48.

13 Compound **7**: m.p.: 228-230℃, UV (H_2O)λ_{max}306, 245 nm, 228 nm, ^{1}H-NMR (DMSO-d_6): δ0.63（2H, s), 0.81 (2H, d), 2.26 (2H, m), 2.80 (1H, bs, exchangeable in D_2O), 3.64 (2H, q), 3.77 (1H, m), 4.09 (2H, d), 5.06 (1H, s, exchangeable in D_2O), 5.64 (1H, s, exchangeable in D_2O), 6.16 (1H, d), 6.50 (2H, bs, exchangeable in D_2O), 8.56 (1H, s), FAB MS (m/z) 323 (M+1), Anal.Calcd for $C_{13}H_{18}O_4N_6 \cdot 0.2CH_3OH$: C, 48.23; H, 5.76; N, 25.57; Found: C, 48.40; H, 5.70; N, 25.38

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