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Synthesis of Novel Nucleoside: 2'-deoxyuridine-3',5'-di(4,4'-dimethoxy-5, 6, 5', 6'-dimethylenedioxybiphenyl-2-methoxy carbonyl 2'-carboxylate)

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Abstract: Hepatitis B Virus (HBV) belongs to the family of hepadnaviridae which comprises several animal viruses, including human HBV, woodchuck hepatitis (WHV), ground squirrel hepatitis virus (GSHV) and duck hepatitis B virus (DHBV). These viruses share common features such as the genome organization, mode of replication and similar tropism for hepatocytes[1]. 2'-deoxyuridine-substituted biphenyl carboxylate was synthesized as anti-hepatitis B agents. The structure was confirmed by UV, ^{1}HNMR spectrum and elementary analysis.

Keywords: 2'-Deoxyuridine biphenyl carboxylate; biphenyl; 2'-deoxyuridine.

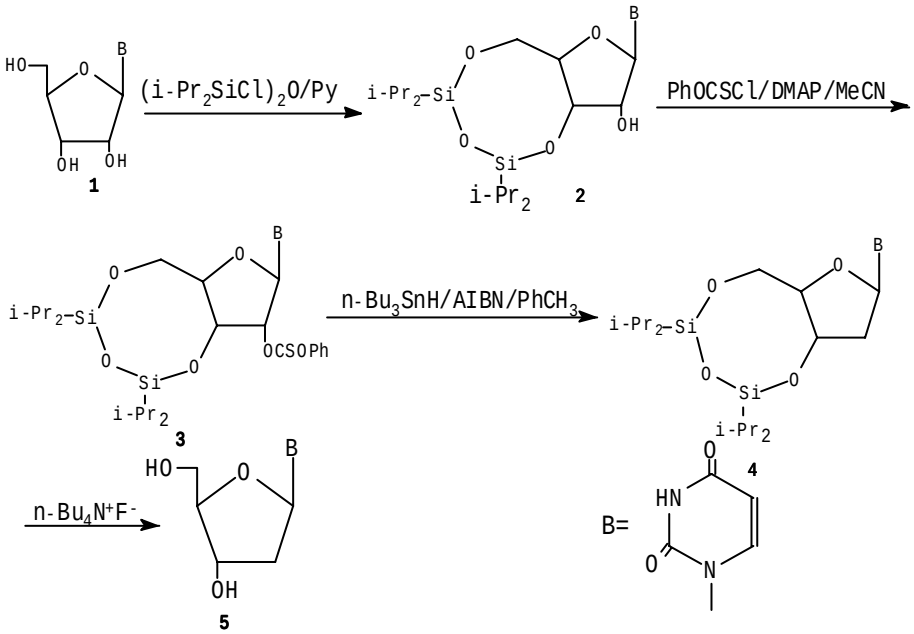
A number of nucleosides have been reported to be anti-hepatitis B virus agents[2], although none of them have yet been proved to be clinically usefull. In addition, dimethyl dicarboxylate biphenyl (DDB) is a widely used anti-hepatitic drug with high effect in lowering SGPT and considerable low toxicity[3]. In view of the discovery that several nucleosides with the D-configuration and analogues of the biphenyl dicarboxylate are selective antiviral agents, it was of interest to synthesize nucleoside derivatives as potential antiviral agents.

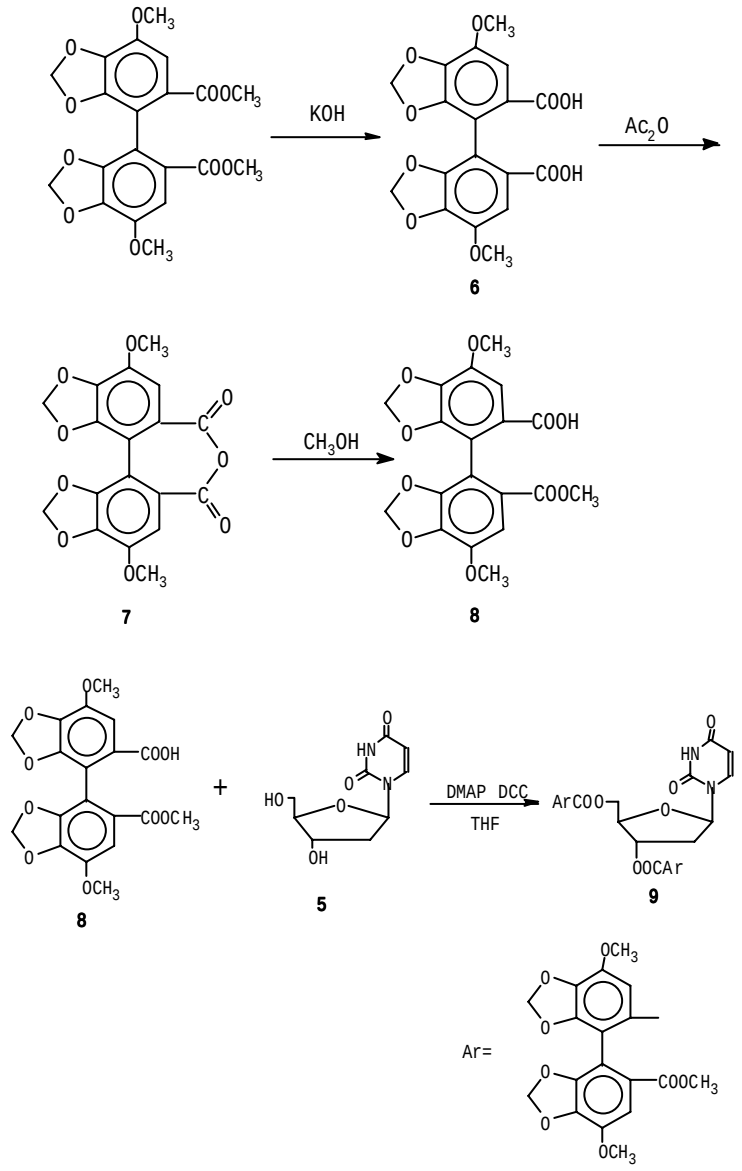
Recently, the carbocyclic analogue of 2'-deoxyguanosine (2'-CDG) is the first nucleoside which was reported to exhibit potent inhibition to HBV replication[4]. In 2.2.15 cells, 2'-CDG showed a 50% inhibition to HBV DNA polymerase activity at 5 ng/ml, whereas at 25 ng/ml, the complete disappearance of HBV replication was observed. In the hepG2 cells, 2'-CDG was found to be converted to its triphosphate, which can be efficiently incorporated into HBV DNA, although the exact enzymes responsible for its phosphorylation were not clear. The triphosphate of 2'-CDG is a competitive inhibitor of dGTP for both HBV DNA polymerase and eukaryatic DNA polymerase δ and the Ki of 2'-CDGTP for the viral enzyme is 6 times lower than the latter enzyme[5]. 2'-CDG was also reported to induce a prolonged inhibition to DHBV DNA synthesis in primary duck hepatocyte cultures and in the liver[6]. However, 2'-CDG was found to be toxic with a 50% inhibition of cell growth (HepG2 2.2.15cells) at 32μM[7]. Therefore, it is not suitable for the long-term usage in humans. With this information, it was of interest to explore whether we could achieve an enhancement of delivery of nucleosides to the HBV by using the nucleoside and dimethyl dicarboxylate biphenyl prodrugs.

First, we synthesized the 2'-deoxyuridine from the uridine **(Scheme 1)**. The protection of **1** with 1,3-dichloro-1,1,3,3-tetraisopropyl-1,3-disiloxane in the presence of dry pyridine gave **2** in quantitative yield **(Scheme 1)**. Subsequent reaction of **2** with phenyl chlorothionoformate in the presence of DMAP led to the 2'-Phenoxythiocarbonyl ester **3** in 42% yield. This compound was then deoxygenated by treating with tri-n-butyltin hydride and a catalytic amount of 2,2'-azobisisobutyronitrile (AIBN). The product after purification by flash column chromatography gave a desired 2'-deoxyribonucleoside **4** in 50% yield. Removal of the disiloxane protecting group was easily achieved by treatment with 2 molar equivalent of tetrabutylammonium fluoride in tetrahydrofuran for 20 min at room temperature. This afforded 2'-deoxyuridine **5**[7] in quantitative yield. The intermediate 4,4'-dimethoxy-5,6,5',6'-dimethylenedioxy-2-methoxycarbonyl-2'-carboxyl biphenyl (compound **8**)[8] was prepared from the α-DDB. with aqueous KOH solution, α-DDB was saponified to dicarboxyl biphenyl **6**, the latter gives **7** with acetic anhydride. Compound **8** was given by refluxing **7** in CH_3OH for 6 h.

The synthesis of 2'-deoxyuridine-biphenyl carboxylate was accomplished from the key intermediate **8** according to the method by Yasuhisa Kuroda[9] **(Scheme 1)**.

Scheme 1.





Compound **9** was prepared by treating 4,4'-dimethoxy-5,6,5',6'-dimethylenedioxy-2-methoxycarbonyl-2'-carboxylbiphenyl with 2'-deoxyuridine in THF at room temperature and then refluxing. After purification by silica gel column chromatography (EtOAc：CH_2Cl_2=1：1) and then recrystallized from methanol to afford **9** in 25% yield. mp:148-150℃,$[\alpha]_D^{20}$ -40.4 (c=0.25, $CHCl_3$), UV (CH_3OH) λ max 230.5 nm, 275.5 nm, ^{1}HNMR (DMSO-d_6) δ 2.10 (2H, q), 3.56 (6H, s), 3.59 (2H, m), 3.85 (12H, s), 4.10～4.30 (2H, m), 5.60 (1H, d), 5.91～6.01 (8H, d), 6.04 (1H, d), 7.18～7.40 (4H, m),

7.5 (1H, q), 11.36 (1H, s). Anal. Calcd for $C_{47}H_{40}O_{23}N_2 \cdot 3CH_3OH$: C, 54.75; H, 4.04; N, 2.55; Found: C, 54.96; H, 4.01; N, 2.65.

In summary, the synthesis of other pyrimidine and purine nucleosides as well as the biological evaluations of the synthesized compounds are in progress in our laboratory.

References and Notes

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7. Compound **5**: m. p.: 167-169℃, ^{1}HNMR δ 7.86 (1H, d), 6.17 (1H, t), 5.64 (1H, d), 5.25 (1H, d), 5.01 (1H, t), 4.23 (1H, d), 3.78 (1H, d), 3.60 (1H, d), 3.59 (2H, m), 2.09 (2H, m), 11.29 (1H, s).
8. Compound **8**: m. p.: 226-228℃, ^{1}HNMR δ 3.97 (6H, s), 6.00 (2H, s), 5.96 (2H, d), 7.37 (1H, s), 7.45 (1H, s), 3.67 (3H, s).
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