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Synthesis of 2-Amino-9-(3'-Azido-2',3'-Dideoxy-Beta-D-Erythro-Pentofuranosyl)-6-Methoxy-9H-Purine (AzddMAP) and AzddGuo

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Abstract: *A novel synthesis of AzddMAP and AzddGuo is described starting from 1, 2-O-isopropylidene-alpha-D-xylofuranose. The key step in this synthesis involves the replacement of a diphenyl carbamoyl protecting group in the purine 6-position by methanol.*

In 1987 Hartmann, Hunsmann, and Eckstein (1) reported that 3'-azido-2',3'-dideoxyguanosine, AzddGuo, inhibits the replication of human immunodeficiency virus in vitro. Eckstein et al. (2, 3) have reported that AzddGuo has a 50% effective antiviral dose against HIV in the range of 1.4 to 1.7 micromolar. Furthermore, the authors have also reported that AzddGuo has a selectivity index ranging from 140 to 171 (2, 3). Given these facts, AzddGuo warranted further investigation as a potential agent for the treatment of AIDS. Therefore, our goal was to develop a facile synthesis that would allow for the synthesis of large quantities of AzddGuo.

The nucleoside derivative AzddGuo was first synthesized by F. Eckstein and M. Imazawa (4) in 1978 using a *trans*-glycosylation procedure. The authors reacted silylated N^2-palmitoylguanine and 3'-azido-3'-deoxy-5'-O-acetylthymidine with trimethylsilyl trifluoromethanesulfonate. This procedure suffers from the fact that *N*7 isomers and *N*9 isomers, as well as alpha anomers and beta anomers, are generated. Herdewijn et al. (5) have synthesized AzddGuo from guanosine. Herdewijn's synthesis involves the treatment of 2'-O-tosylguanosine with excess lithium triethylborohydride to generate 9-(2'-deoxy-beta-D-threo-pentofuranosyl)guanine. From this intermediate, AzddGuo was synthesized in three additional steps.

This article reports on the novel and efficient syntheses of AzddMAP and AzddGuo from a carbohydrate precursor. The compound AzddMAP is active against both HIV-1 and HIV-2 in vitro with 50% effective antiviral doses of 5.6 and 5.5 μM, respectively (6).

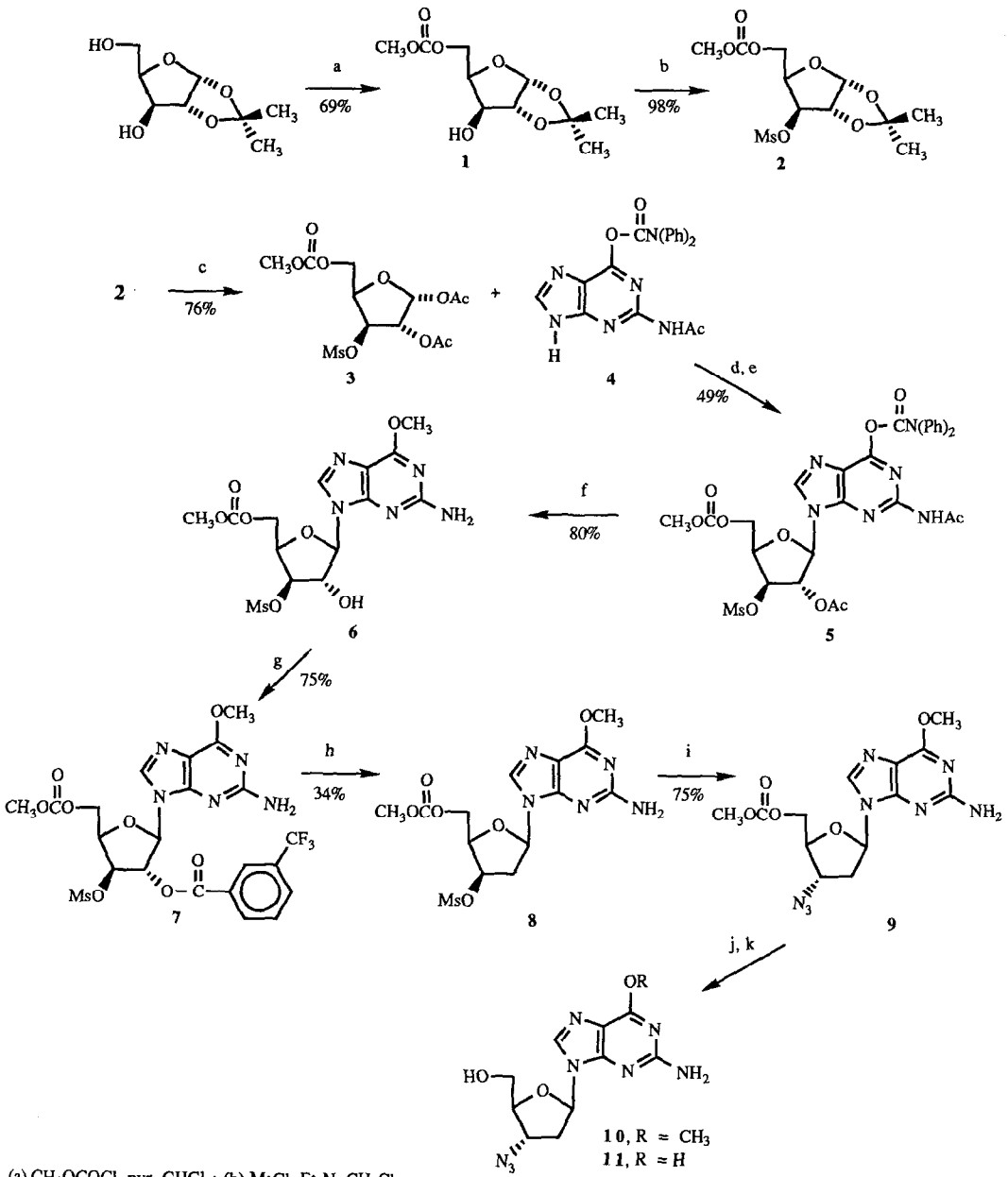
Chemistry

Starting from commercially available 1,2-O-isopropylidene-alpha-D-xylofuranose, 1,2-O-isopropylidene-5-O-methoxycarbonyl-D-xylofuranose **1** was synthesized according to the method of Baker (7) using methyl chloroformate, pyridine, and chloroform in a 69% yield. Compound **1** was combined with 1.25 equivalents of dry triethylamine in dry dichloromethane (1.8 mL/mmol). The solution was cooled to an internal temperature of 0 °C and 1.25 equivalents of methanesulfonyl chloride was added at such a rate that the internal temperature did not rise above +25 °C. Stirring was continued at ambient temperature for 1.5 h followed by stirring at 4 °C for 16 h. After aqueous workup, mesylate **2** was purified on a flash chromatography column and isolated in a 98% yield. The mesylate **2** (7) was combined with acetic anhydride (0.57 mL/mmol) and cooled in an ice bath. Glacial acetic acid (4.13 mL/mmol) was added followed by the dropwise addition of concentrated sulfuric acid (0.23 mL/mmol) over a 30 min period. Stirring was continued at room temperature for an additional 16 h. After aqueous workup, the diacetate **3** (7) was purified on a flash chromatography column. The product, an oil, was obtained in a 76% yield (Scheme 1).

There are many methods available for the synthesis of purine nucleosides. We desired an efficient method that would minimize the production of the *N*-7 isomer. Robins (8) has recently reported on the regioselective coupling of bis-trimethylsilylated 2-*N*-acetyl-6-O-diphenylcarbamoylguanine **4** with acetylated pentofuranoses as a convenient route to *N*-9 guanine products. In addition, Robins reported that *N*-7 guanine products were not detected. We therefore converted **4** to the corresponding TMS-derivative using *N*,O-bis(trimethylsilyl)acetamide (BSA) in 1,2-dichloroethane and treated this derivative with **3** in the presence of a stoichiometric amount of trimethylsilyl triflate in anhydrous toluene at 80 °C for 2 h followed by stirring at ambient temperature overnight. The reaction was quenched with saturated sodium bicarbonate and extracted with ethyl acetate. The product was purified on a Waters Prep LC/System 500A, which was eluted with chloroform : methanol (99:1, v:v). The product, nucleoside **5**, was isolated as a yellow foam in a 49% yield.

We had planned on selectively deprotecting the 2'-alcohol using methanolic HCl generated in situ from methanol and acetyl chloride. Nucleoside derivative **5** was combined with a methanolic hydrogen chloride solution (10.5 mL/mmol), which was prepared by cautiously adding acetyl chloride (4 mL) dropwise to methanol (125 mL). This solution stirred at ambient temperature for 18 h and was then neutralized by adding solid sodium bicarbonate. The product was purified on a flash chromatography column, which was eluted with chloroform : methanol (98:2, 97:3 followed by 96:4, v:v). Derivative **6** was isolated as an off- white foam in an 80% yield. To our knowledge this is the first direct displacement of a diphenyl carbamoyl moiety by a primary alcohol in the nucleoside literature. Our preliminary results suggest that other alcohols and perhaps thiols will behave similarly. Initially, alcohol **6** was treated with DMAP (2 equivalents) and phenyl chlorothionocarbonate (1.2 equivalents) in dry acetonitrile and dichloromethane (15 mL/mmol, 50:50, v:v) according to the method of Robins (9). Upon aqueous workup and purification, the phenyl thionocarbonate ester was isolated in a 40% yield. Because of this low yield, other deoxygenation procedures were considered. Using the method of Saito (10), the alcohol **6** was converted to the *m*-trifluorobenzoate in a 75% yield. The alcohol **6** was combined with dry dichloromethane (4 mL/mmol) and triethylamine (1.5 equivalents). The solution was cooled in an ice bath and 3-(trifluoromethyl)benzoyl chloride (1.5 equivalents) was then added dropwise. Finally, DMAP (0.45 equivalents) was added. Stirring was continued in the ice bath for an additional 30 min followed by stirring at

SCHEME I



(a) CH_3OCOCl, pyr, $CHCl_3$; (b) MsCl, Et_3N, CH_2Cl_2;
(c) HOAc, Ac_2O, H_2SO_4; (d) BSA, $ClCH_2CH_2Cl$, 80 °C;
(e) TMS triflate, toluene, 80 °C; (f) MeOH, CH_3COCl;
(g) Et_3N, CH_2Cl_2, DMAP, 3-(trifluoromethyl)benzoyl chloride;
(h) MCZ (10:1, v:v), i-propanol : H_2O, hv; (i) LiN_3, DMF, 100 °C;
(j) NaOMe, MeOH; k) ADA

room temperature for 2 h. After aqueous workup and purification on a silica gel flash chromatography column, the product was obtained as a yellow foam. The ester **7** and *N*-methylcarbazole (MCZ) were dissolved in isopropanol-water (10:1, v:v), and the solution purged with nitrogen. The solution was then irradiated in the presence of a Schott glass filter for 4.4 h using a Hanovia Ace apparatus. The 2'-deoxygenated nucleoside **8** was isolated in a 34% yield (11). The mesylate **8** was reacted with lithium azide in anhydrous dimethylformamide at 100 °C and the 5' alcohol was deprotected using sodium methoxide in methanol. To achieve our goal, AzddMAP was treated with bovine adenosine deaminase (ADA). The product AzddGuo was identical to authentic material (4). The yield over these three steps was 32%. Target compound **11** (12) was isolated in an overall yield of 2.7%.

We have achieved a novel synthesis of both AzddMAP and AzddGuo from a carbohydrate precursor. This carbohydrate precursor **3** allows for the selective deblocking and deoxygenation of nucleoside derivative **6.** In addition, the mesylate remains intact throughout the synthesis and allows for the facile generation of **9**. The regioselective coupling of bis-trimethylsilylated 2-*N*-acetyl-6-O-diphenylcarbamoylguanine with diacetate **3** generates exclusively the desired beta *N*-9 guanine product. This method eliminates the tedious separation of isomers generated by the *trans*-glycosylation procedure. Furthermore, this synthesis demonstrates the first direct displacement of a diphenyl carbamoyl moiety by a primary alcohol. Our preliminary results suggest that it will be possible to generate other anologues using this methodology. Finally, AzddMAP is active against both HIV-1 and HIV-2 in vitro.

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11. This yield was not optimized.
12. 200 MHz 1H NMR (DMSO-d_6) δ: 8.07, (s, 1H, 8H), 6.47, (br s, 2H, NH2), 6.15, (t, J = 6.5 Hz, 1H, 1'H), 5.12, (br t, 5'OH), 4.68-4.5, (m, 1H, 3'H), 3.94, (s, 3H, OCH3), 3.94-3.8, (m, 1H, 4'H), 3.55, (m, 2H, 5'H, 5"H), 2.91-2.75 and 2.5-2.35, (2m, 2H, 2'H, 2"H).
    High resolution EIMS: calc. mass $C_{11}H_{14}N_8O_3$ 306.1189, obs. mass $C_{11}H_{14}N_8O_3$ 306.1181.
    HPLC analysis: K' = 2 on a PRP-1 column eluted at a flow rate of 1 mL/min with MeOH : H_2O (70:30, v:v).

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