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SYNTHESIS OF 9-(3-AZIDO-2,3-DIDEOXY-β-D-ERYTHRO-PENTOFURANOSYL)-2,6-DIAMINOPURINE (AzddDAP)

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Abstract

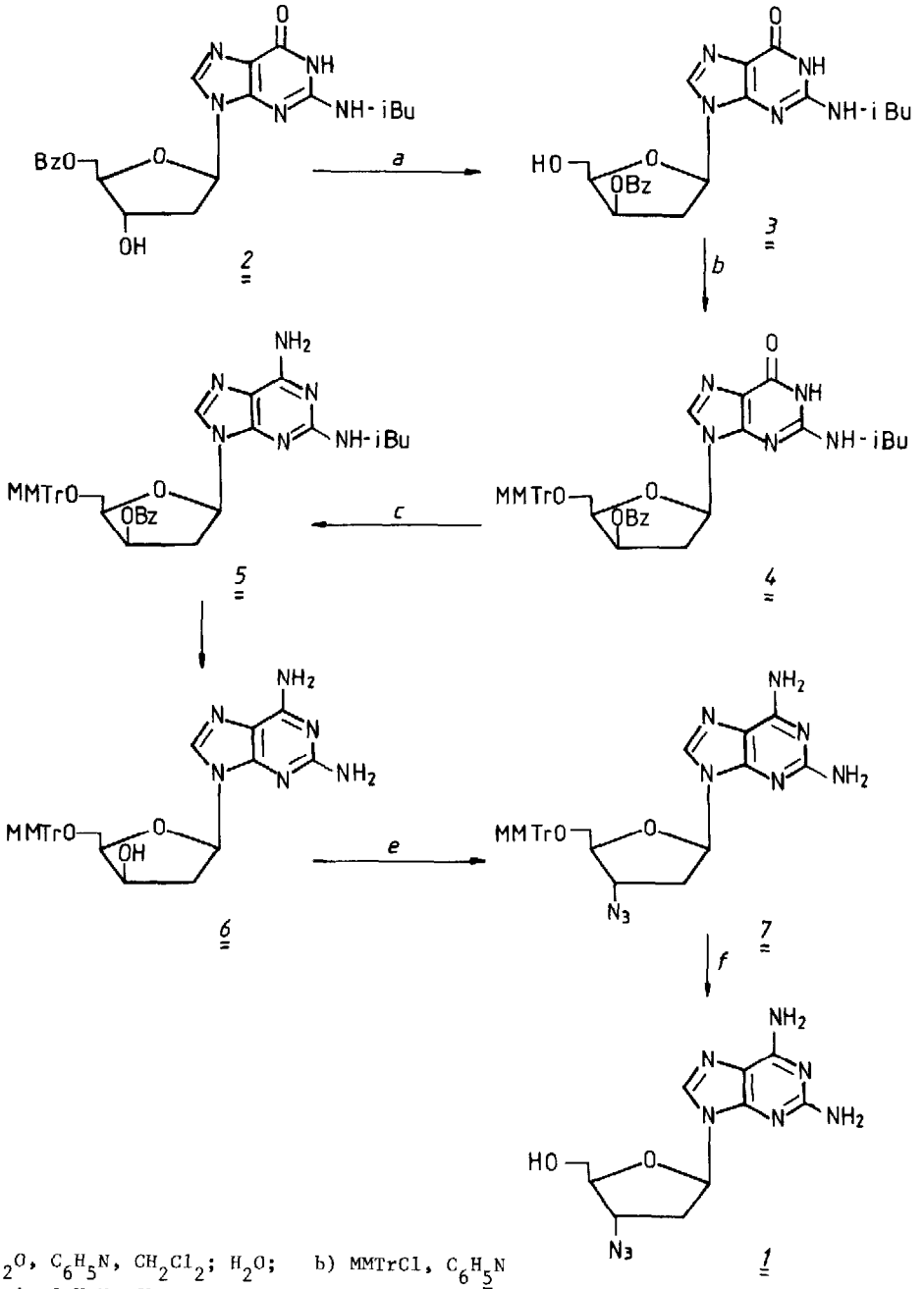
A new synthesis of AzddDAP is described starting from 2'-deoxyguanosine. The reaction scheme makes use of trifluoromethanesulfonic anhydride for inversion of the configuration at the 3'-position as well as for the introduction of the 6-amino group.

AzddDAP (1) can be considered as a promising anti-AIDS compound. At 0.3 μM a 50 % protection of MT-4 cells against the cytopathic effect of HIV was obtained, while only at a concentration of 45 μM the viability of normal uninfected MT-4 cells was reduced by 50 %. This means a therapeutic index of 150[1].

The synthesis of this compound, starting from natural guanosine, presents problems for the inversion of the configuration at the 3'-position and for the conversion of the lactam function of the base into an amidine group. The product has been synthesized previously by a transglycosylation procedure in low yields[2] and by a laborious route starting from guanosine[3]. Here we describe a simplified procedure, starting from 2'-deoxyguanosine.

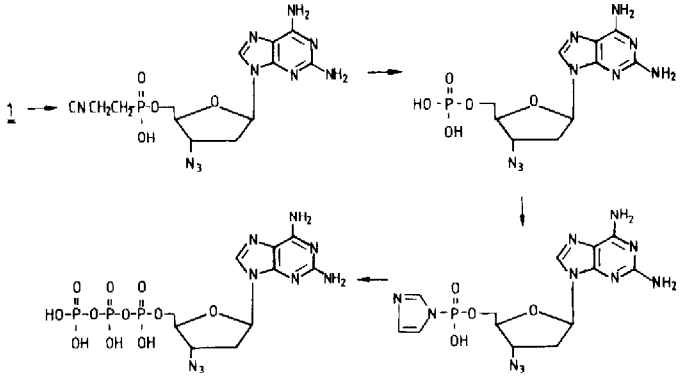
Treatment of N^2-isobutyryl-5'-O-benzoyl-2'-deoxyguanosine[4] with 1.5 equivalents of trifluoromethanesulfonic anhydride in dichloromethane (10 ml/mmol) containing 10 % of anhydrous pyridine, at 0°C for 30 minutes was followed by the addition of H_2O (1 ml) and a further stirring for 7 h at room temperature. TLC ($CHCl_3$-MeOH 90:10) of the reaction mixture revealed four compounds. After workup, N^2-isobutyryl-9-(3-O-benzoyl-2-deoxy-β-D-threo-pentofuranosyl)guanine (2) was obtained as the main reaction product (56 % yield). At low temperature (0°) the reaction of the anhydride with the amide function of the guanine base is negligible. This inversion of the configuration at the 3'-position can be explained by assuming a cyclic hemi-orthoester as the intermediate. The latter can be formed by the attack of the 5'-O-carbonyl group on the activated 3'-position. Cleavage of this intermediate preferentially yields the 3'-O-benzoate as the primary alcohol is the better leaving group.

The 5'-hydroxyl function of 3 was protected with a monomethoxytrityl group in 90 % yield (2 equivalents of monomethoxytrityl chloride in pyridine at room temperature for 2 days, column chromatography: $CHCl_3$-MeOH 99:1).



a) $(CF_3SO_2)_2O$, C_6H_5N, CH_2Cl_2; H_2O; b) MMTrCl, C_6H_5N
c) $(CF_3SO_2)_2O$, C_6H_5N, CH_2Cl_2; NH_3, $C_4H_8O_2$; d) MeO^-, MeOH
e) ϕ_3P, LiN_3, CBr_4, DMF; f) 80 % HOAc-H_2O

Different methods have been described for the modification of the 6-position of guanosine[5-7]. We made use of the good leaving capability of the triflate group to perform this conversion. A solution of 4 in a mixture of CH_2Cl_2-pyridine (20:5) (10 ml/mmol) was treated with 1.5 equivalents of trifluoromethanesulfonic anhydride. Therefore, the anhydride was added as a 10 % solution in dichloromethane at low temperature (-30°C) and the mixture was warmed up to room temperature and stirred further for 1 1/2 h. TLC ($CHCl_3$-MeOH 95:5) revealed two compounds: one with a higher mobility than the starting material, which is presumed to be the 6-O-triflate and one which remains near the start position and which we believe to be the N-(purin-6-yl)pyridinium salt. Both compounds were transferred to 5 by pouring the reaction mixture into a saturated solution of ammonia in dioxane and stirring the solution overnight (TLC: $CHCl_3$-MeOH 95:5 Rf 0.55). Some 3'-O-debenzoylation also took place as a side reaction. Both acyl groups of 5 were removed with methanolate in methanol at 60°C (10 h). The reaction was worked up by neutralizing with Dowex 50WX-8 (H^+), filtration and column chromatography ($CHCl_3$-MeOH 96:4). The total yield for the conversion of 4 into 6 is 69 %. The use of a mixture of triphenylphosphine-carbon tetrabromide-lithium azide (3-3-30 equivalents) in dimethylformamide at room temperature overnight allowed the one step conversion of 6 into 7, which was isolated after column chromatography ($CHCl_3$-MeOH 95:5) in 60 % yield. The purification of this compound was somewhat obscured by the presence of a minor side compound with similar mobility on TLC, which we assumed to be the 3'-bromo-derivative. The monomethoxytrityl group was removed with 80 % of aqueous acetic acid for 4 h at room temperature and the title compound was isolated as crystalline material in 78 % yield[8].



For metabolic studies, AzddDAP was further converted into the mono- and triphosphate as depicted in Scheme 2. The monophosphate was synthesized by reaction of 1 with 2-cyanoethyl phosphate and dicyclohexylcarbodiimide in pyridine[9,10] followed by removal of the cyanoethyl

protecting group with lithium hydroxide[9]. Purification was carried out on a DEAE-cellulose column with a linear gradient of triethylammonium bicarbonate (0 - 0.2 M). The reaction of 1 with cyanoethyl phosphate was monitored by TLC on cellulose (i-propanol-NH_3-H_2O 60:30:10). The monophosphate was converted into its sodium salt by passing through an Amberlite IRC 50 (Na^+) column. The method of Hoard and Ott[11] was used to transfer the monophosphate into a triphosphate. The excess of 1,1'-carbonyldiimidazole was not decomposed before addition of the pyrophosphate. The reaction mixture was purified on a DEAE-cellulose column (diethylammonium bicarbonate 0 - 0.5 M) and the triphosphate was converted into its sodium salt by passing through an Amberlite IRC 50 (Na^+) column.

Acknowledgment

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8. mp (MeOH): 221°C (dec); MS m/e 291 (M^+); UV (H_2O): λ_{max} 280 nm (ε 11300), 256 nm (ε 10700). UV (0.1N HCl) λ_{max} 290 nm (ε 11200), 252 nm (ε 13300). IR (KBr): 2100 cm^{-1}.(N_3). ^1H NMR (DMSO-d_6) δ :2.22-2.58 (m, H-2'); 2.68-3.04 (m, H-2"); 3.62 (m, H-5', H-5"); 3.90 (brq, H-4'); 4.59 (m, H-3'); 5.32 (brt, 5'-OH); 5.78 (brs, NH_2); 6.12 (t, J=7.0 Hz, H-1'); 6.73 (brs, NH_2); 7.91 (s, H-8)ppm. Elem. anal.: calculated (C: 41.24, H: 4.50, N: 43.28), found (C: 41.31, H: 4.69, N: 42.93).
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