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PREPARATION OF CARBOCYCLIC PHOSPHONATE NUCLEOSIDES

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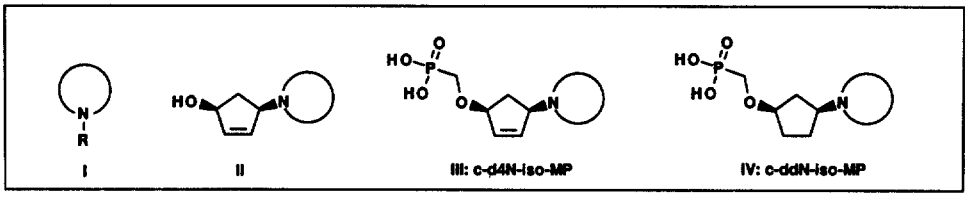
Abstract: *A versatile and high-yielding synthesis of racemic carbocyclic phosphonate nucleosides of adenine, hypoxanthine, guanine, cytosine, uracil, and thymine has been developed. These newly prepared compounds are isosteric (and isoelectronic) with (carbo)cyclic 2',3'-dideoxy- and 2',3'-dideoxy-2',3'-didehydronucleoside monophosphates.*

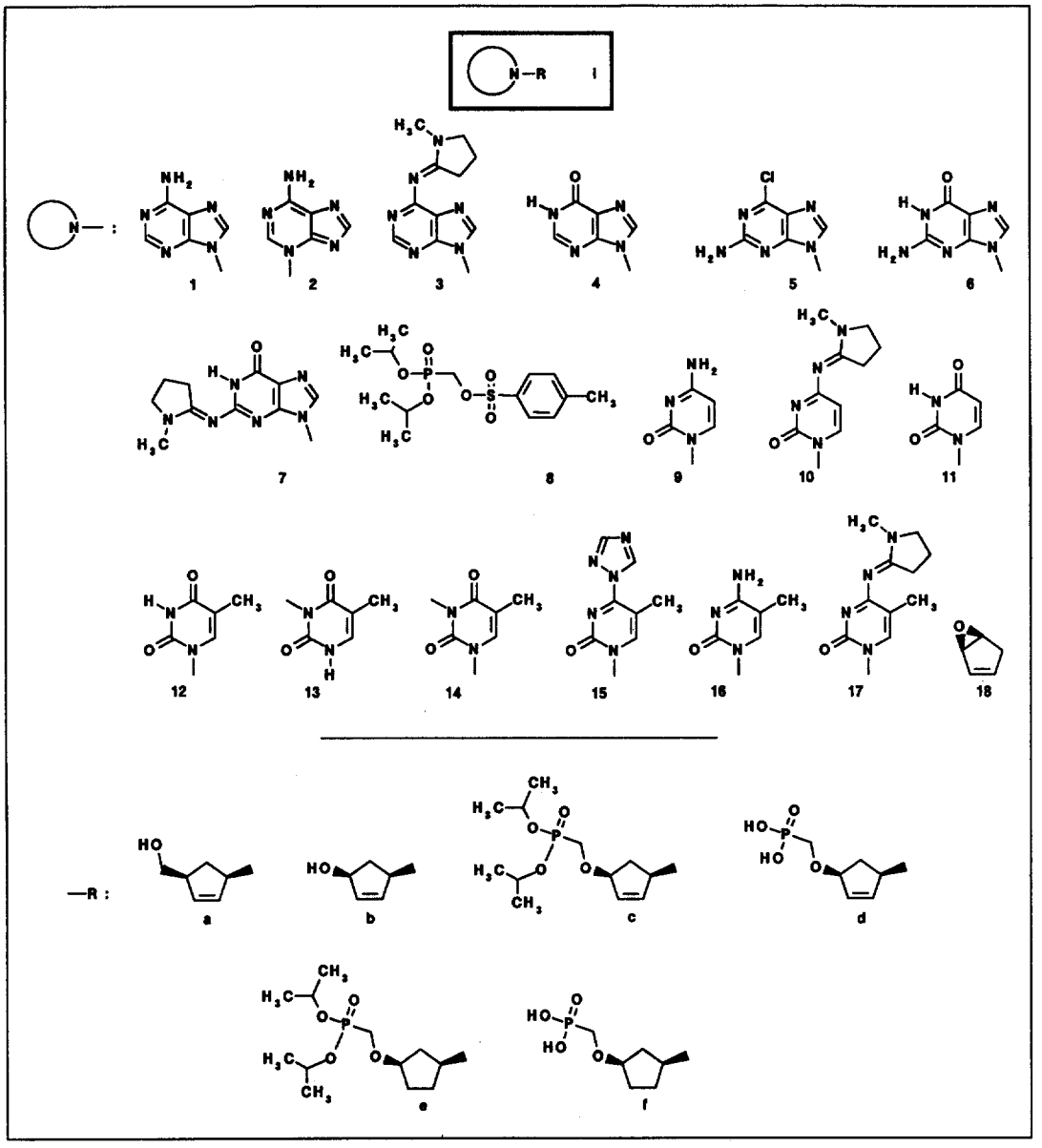
Dideoxynucleosides like 3'-azido-3'-deoxythymidine (zidovudine) and 2',3'-dideoxyinosine (didanosine) are currently the only licensed drugs for the anti-HIV treatment of AIDS patients[1]. Members of the dideoxy class of compounds, however, are perceived to have a number of disadvantages, including toxicity and lability of the glycosidic bond to acidic or enzymic catalysis[2]. In an attempt to overcome some of these drawbacks, dideoxy- and dideoxy-didehydronucleoside analogues in which the tetrahydrofuran ring has been replaced by a cyclopentane or cyclopentene ring have been described. The most prominent compound in this series is "carbovir" **6a**[3], the carbocyclic analogue of 2',3'-dideoxy-2',3'-didehydroguanosine. Carbovir, like the other nucleoside analogues, is thought to act via its anabolically formed triphosphate as an inhibitor of the HIV reverse transcriptase (HIV-RT) [3].

We (and others[4]) set out to synthesize carbocyclic phosphonate nucleosides of the general structures III and IV. These hydrolytically stable carbocyclic analogues are unique in that the P-O-C5´-bond of nucleoside monophosphates is exchanged for a P-C-O5´-bond affording a carbocyclic phosphonate nucleoside thus representing isosteric (and isoelectronic) analogues of nucleoside monophosphates of the (carbo)ddN- and (carbo)d4N-type.

In this communication we wish to report on the syntheses of the unsaturated (c-d4N-iso-MP) and saturated (c-ddN-iso-MP) racemic carbocyclic phosphonates of adenine, hypoxanthine, guanine, cytosine, uracil, and thymine. The preparation of the key intermediate of the general formula II looked quite straightforward in the light of Trost's synthesis of aristeromycin[5], where he was able to add 3,4-epoxycyclopentene 18 to adenine in a 1,4-regio- and 1,4-cis-stereocontrolled manner using a Pd(0)-based catalyst. We hoped to be able to expand the scope of this reaction to the synthesis of carbocyclic nucleotide analogues of type I by using other nucleobases or suitable precursors.



I II III: c-d4N-iso-MP IV: c-ddN-iso-MP



We first repeated the addition of 18 to adenine (adenine, THF/DMSO, $Pd[P(OiPr)_3]_4$, 18, 0°C-->r.t., 8 h). As with the normal course of alkylation of adenine, and contrary to the published results[5], we isolated two isomeric products (ratio 7:2) which turned out to be the N9-isomer 1b (major) and N3-isomer 2b (minor), the structures of which were confirmed by uv and nmr spectroscopy[6]. Protection of 1b (DMF-diethyl acetal, dichloromethane, r.t., 98%) as the exocyclic amidine derivative 3b, followed by reaction of the sodium salt (NaH, DMF, r.t.) of the allylic alcohol 3b with diisopropyl *p*-tolylsulfonyloxymethanephosphonate 8[7] (24 h, r.t., 54%) yielded the phosphonate ester 3c which was first deprotected (aq. ammonia, Δ, 8 h, 98% 1c) and then subjected to reaction with bromotrimethylsilane[8] (TMS-Br) (DMF, TMS-Br, r.t., 3 h; then:

acetone/water, 65%) giving the unsaturated carbocyclic phosphonic acid **1d** (c-d4A-iso-MP). Hydrogenation of **1c** (Pd/C (10%), H_2, iPrOH, 91%) yielded the saturated ester **1e** which was transformed to the phosphonic acid **1f** (c-ddA-iso-MP) as described for **1d**. Thus, in a 6 or 7 step synthesis, respectively, starting with cyclopentadiene and adenine, the preparation of carbocyclic adenine phosphonate nucleosides was achieved.

Essentially the same sequence of reaction steps (with some modifications) was applicable to all other carbocyclic phosphonate nucleosides prepared:

Most easily, the c-d4I-iso-MP **4d** and c-ddI-iso-MP **4f** compounds were prepared by reaction of **1c** and **1e** with sodium nitrite in a mixture of acetic acid/1N HCl/water at r.t. (yields: 80 - 86%), followed by phosphonate ester cleavage.

The guanine derivatives **6d** and **6f** could not be prepared directly, because guanine itself did not react with **18** and the Pd(0)-based catalyst; presumably because of the extremely low solubility of guanine in the THF/DMSO system used. A chemical equivalent, however, 2-amino-6-chloropurine, reacted smoothly using the standard reaction conditions giving exclusively the desired N9-substituted 1,4-cis-regioisomer **5b** in 66% yield. Treatment of **5b** with 2N HCl at 70°C for 2 h yielded the guanine derivative **6b** which after protection of the amino functionality (giving **7b**) was reacted with **8** to give the protected phosphonate ester **7c** in 64% yield. Deprotection (yielding **6c**) and phosphonate ester cleavage performed as above gave c-d4G-iso-MP **6d**; and deprotection (**6c**), hydrogenation of the cyclopentene double bond (**6e**) followed by phosphonate ester cleavage gave c-ddG-iso-MP **6f**.

Having achieved the syntheses of the purine nucleotide analogues we turned our attention to the pyrimidine series. No problems were accounted for in the syntheses of the cytosine derivatives c-d4C-iso-MP **9d** (**9b** --> **10b** --> **10c** --> **9c** --> **9d**) and c-ddC-iso-MP **9f** (**9c** --> **9e** --> **9f**). The uracil congeners c-d4U-iso-MP **11d** and c-ddU-iso-MP **11f** were prepared by the reaction of the respective cytosine phosphonate esters with sodium nitrite in acetic acid/1N hydrochloric acid/water mixture as were the hypoxanthine derivatives prepared from the respective adenine precursors.

Several trials were needed to find the best way to prepare the thymine derivatives: When thymine was used directly, three products were isolated in low yield: About 1% of the desired N1-adduct **12b** besides 3% of the N3-adduct **13b** and 37% of a diasteromeric mixture of the N1,N3-bis-adduct **14b**. Finally, similar to the preparation of the cytosine/uracil pair of compounds, we tried the detour *via* the 5-methylcytosine derivative. As we had the impression that the known methods for the preparation of 5-methylcytosine were too lengthy to perform[9] we tried a method that up to now was applied only to N1-substituted uracils or thymines: We reacted thymine with phosphorus oxychloride or better with diphenyl phosphorochloridate ($POCl(OPh)_2$), 1,2,4-triazole and NEt_3 in dry acetonitrile and isolated (after mild alkaline hydrolysis of the bis-adducts that were also formed) the corresponding triazole derivative **15** (R=H) in 49% yield. The triazole group at C4 in 5-methyl-4-(1,2,4-triazol-1-yl)-pyrimidine-2(1H)-one was susceptible to nucleophilic displacement reactions and gave 5-methylcytosine on reaction with concentrated aqueous ammonia in 79% yield. This compound added to **18** in the usual way giving the 1,4-cis-disubstituted cyclopentene derivative **16b** in 48% yield. Protection of the amino function (**17b**), reaction with **8** (**17c**), ammonolysis of the exocyclic amidine (**16c**) followed by hydroxy-deamination with sodium nitrite in acetic acid/hydrochloric acid mixture (**12c**) and subsequent phosphonate ester cleavage gave the carbocyclic phosphonate nucleoside c-d4T-iso-MP **12d**. Catalytic hydrogenation of the respective precursor (**12c**) yielded, after phosphonate ester cleavage with TMS-Br, the saturated derivative c-ddT-iso-MP **12f**[10].

In summary, we successfully devised a method for the preparation of carbocyclic phosphonate nucleosides of adenine, hypoxanthine, guanine, cytosine, uracil, and thymine as hydrolytically stable compounds isosteric (and isoelectronic) with (carbo)cyclic 2',3'-dideoxy- and 2',3'-dideoxy-2',3'-didehydronucleoside monophosphates. The easy to perform syntheses proceed in high yield and require only 6 - 9 steps starting with cyclopentadiene and the respective purine or pyrimidine base. A

complete description of our investigations in this series will be discussed in a forthcoming full paper.

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[6] All new compounds gave satisfactory spectroscopic and analytical results. 1b: white, crystalline solid; m.p. 178-179°C (from iPrOH); λ_{max} (pH7, H_2O)/nm: 262 (log ε=4.18); δ_H (270 MHz, d_6-DMSO: 8.14 (s,1H), 8.07 (s,1H), 7.20 (s,2H), 6.19 (dt,1H), 5.98 (dq,1H), 5.51 (dd,1H), 5.44 (m,1H), 4.72 (m,1H), 2.89 (dp,1H), 1.74 (dt,1H); δ_C (68MHz, d_6-DMSO): 156.01 (C6), 152.16 (C2), 148.83 (C4), 139.28 (C8 or C3'), 139.24 (C3'or C8), 130.68 (C2'), 119.01 (C5), 73.74 (C1'), 57.12 (C4'), 41.10 (C5'); $C_{10}H_{11}N_5O$ requires C 55.30, H 5.07, N 32.26; found: C 55.12, H 5.29, N 32.30; 2b: white, crystalline solid, m.p. 270-276°C (from iPrOH); λ_{max} (pH7, H_2O)/nm: 274 (log ε=4.14); δ_H (270 MHz, d_6-DMSO): 8.31 (s,1H), 7.93 (s,2H), 7.74 (s,1H), 6.63 (d,1H), 6.25 (m,1H), 5.97 (dd,1H), 5.61 (d,1H), 4.70 (t,1H), 2.92 (p,1H), 1.92 (dt,1H); δ_C (68 MHz, d_6-DMSO): 155.08 (C6), 151.55 (C2), 148.58 (C4), 124.42 (C8), 140.38 (C3'), 129.61(C2'), 120.56 (C5), 74.18 (C1'), 64.06 (C4'), 39.51 (C5'); $C_{10}H_{11}N_5O$ requires C 55.30, H 5.07, N 32.26; found: C 55.21, H 5.22, N 32.18.

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[10] 16b: To a mixture of 1.6 mol% of $Pd[P(OiPr)_3]_4$[5] and 50 g (0.4 mol) of 5-methylcytosine in 200 mL of dry THF and 200 mL of dry DMSO is added a solution of 49.2 g (0.6 mol) of 18[11] dissolved in 100 mL of THF at 5°C (1.5 h) and stirred at r.t. for 3 d. The solvent was evaporated and the residue was stirred with 300 mL of a 2N Na_2CO_3-solution. The precipitate was washed with H_2O and acetone and yielded 29.8 g (36%) **16b** with m.p. 241-245°C. Chromatography (SiO_2, CH_2Cl_2/MeOH 9/1) of the mother liquors afforded another 9.9 g of **16b**, the total yield thus being 48%. 17b: The reaction of 20.2 g (0.1 mol) of **16b** with 77 mL of N-methyl-2,2-diethoxypyrrolidine in 350 mL of dry pyridine at r.t. yielded 23.3 g (83%) **17b** with m.p. 143-145°C. 16c: Reaction of the anion of **17b** [23.9 g (83 mmol) **17b**, 400 mL of dry DMF, 5.23 g (124 mmol) of a 55% suspension of NaH in mineral oil, 5°C] with 43.5 g (124 mmol) 8 yielded **17c** which, without further purification, was suspended in conc. aqueous ammonia and heated to reflux (4 h) while ammonia gas was bubbled through. Chromatography (SiO_2, CH_2Cl_2/MeOH 9/1) yielded 17.31 g (54.2%) of **16c** (oil) as the hemitosylate. 12c: To a mixture of 20.7 g of $NaNO_2$ in 250 mL of H_2O, 25 mL of acetic acid, and 50 mL of 1N HCl was added 19.25 g (41mmol) **16c**. The resulting mixture was stirred at r.t. for 4 h, neutralized by adding solid Na_2CO_3, and evaporated to dryness. The residue was extracted several times with hot acetone. Chromatography (SiO_2, CH_2Cl_2/MeOH 9/1) of the acetone extracts afforded 10.84 g (68.7%) **12c** with m.p. 117-118°C. 12e: A solution of 4.63 g (12 mmol) of **12c** in 100 mL of iPrOH containing 0.5 g Pd/C(10%) was hydrogenated at r.t., and yielded, after chromatography (SiO_2, CH_2Cl_2/MeOH 9/1) 4.64 g (99.7%) **12e**. 12f: A solution of 3.49 g (9 mmol) of **12e** in 40 mL of dry DMF was treated with 13.1 mL of TMS-Br at r.t. for 4 h. The reaction mixture was evaporated and the residue was dissolved in 6.4 mL of H_2O; then 175 mL of acetone were added and the mixture was put into the freezer for several hours. The precipitate was collected, washed with acetone and recrystallized from ethanol giving colourless crystals of 1-[(1RS,4SR)-4-phosphonylmethoxy-cyclopent-1-yl]thymine **12f** as the hydrate with m.p. 123-125°C (1.84 g (67%)). δ_H (270 MHz, D_2O): 7.71 (d,1H), 4.99 (m,1H), 4.15 (m,1H), 3.73 (m,2H), 2.40 (m,1H), 2.10 (m,2H), 1.90 (s,3H), 1.78 (m,3H); $C_{11}H_{17}N_2O_6P$ x H_2O requires C41.00, H 5.90, N 8.70 P 9.63; found: C 40.8, H 5.9, N 8.6, P 9.4.

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