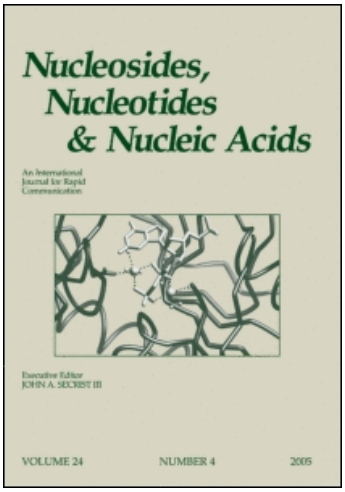

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SYNTHESIS OF *CIS*-DISUBSTITUTED CYCLOBUTENYL NUCLEOSIDE ANALOGUES

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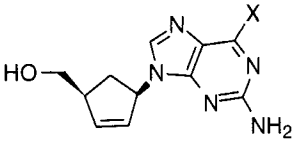
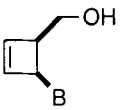
Abstract: *cis*-Disubstituted cyclobutene nucleosides analogues were prepared by a linear synthesis starting from *cis*-cyclobutene dicarboxylic anhydride. This strategy involved mild reaction conditions with intent to restrict the thermal electrocyclic ring opening into (*Z*,*E*)-dienes.

Unsaturated nucleosides such as carbovir[1] **1** or its prodrug[2] **2** display potent antiviral activity. This prompted us to synthesize norderivatives. This was also a challenge with regard to the easy thermal ring opening of such compounds.



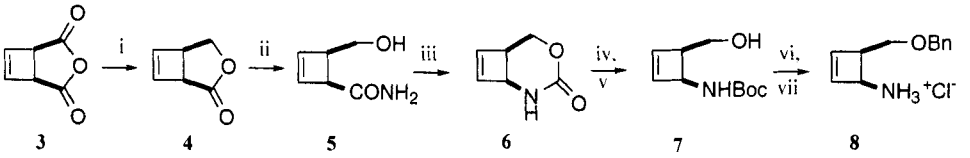


1 carbovir X = OH
2 1592U89 X = NH(cyclopropyl)

B = adenine, hypoxanthine, 4,6-diamino-5-nitropyrimidine, guanine

We firstly prepared the carbocyclic amine intermediate and then built the base moiety around the amino group.[3] The starting material of this synthesis was cyclobutene anhydride **3**.[4] Introduction of the nitrogen group from the cyclobutene hemiester by Curtius or Hofmann reactions failed. On the other hand, treatment of the bicyclic lactone

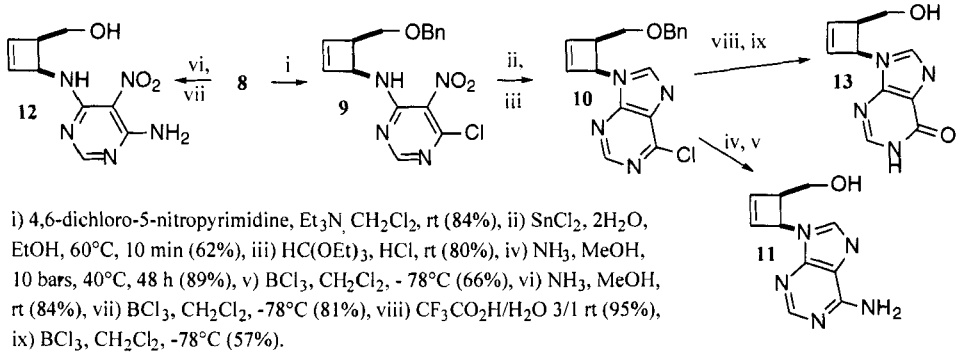
4 with ammonia provided hydroxyamide **5** which was submitted to Hofmann degradation with bis(acetoxy)iodobenzene. The resulting bicyclic carbamate was submitted to *t*-butoxycarbonylation followed by basic cleavage.



3 **4** **5** **6** **7** **8**

i) $NaBH_4$ (79%), ii) NH_3, MeOH, rt (93%), iii) $PhI(OAc)_2$, MeOH, KOH, -5°C to rt (87%), iv) Boc_2O, Et_3N, 4-DMAP, THF, rt (95%), v) LiOH, MeOH/H_2O 1/1, -10°C (100%), vi) BnBr, nBu_4NI, NaH, THF, -15°C to 5°C (79%), vii) 3M HCl/MeOH, -5°C to 15°C (89%).

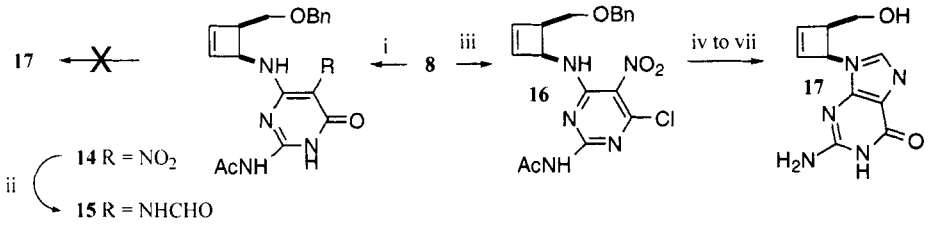
When the corresponding hydrochloride was reacted with 4,6-dichloro-5-nitropyrimidine, substitution occurred at room temperature although it has been usually reported in refluxing ethanol or dioxane. Thermal ring opening was thus avoided. So it was with the other steps that involved classical reactions. Adenine derivative **11** was thus obtained in 12 steps and 15% overall yield from anhydride **3**.



i) 4,6-dichloro-5-nitropyrimidine, Et_3N, CH_2Cl_2, rt (84%), ii) $SnCl_2$, $2H_2O$, EtOH, 60°C, 10 min (62%), iii) $HC(OEt)_3$, HCl, rt (80%), iv) NH_3, MeOH, 10 bars, 40°C, 48 h (89%), v) BCl_3, CH_2Cl_2, - 78°C (66%), vi) NH_3, MeOH, rt (84%), vii) BCl_3, CH_2Cl_2, -78°C (81%), viii) CF_3CO_2H/H_2O 3/1 rt (95%), ix) BCl_3, CH_2Cl_2, -78°C (57%).

Other nucleoside analogues **12**, **13** and norcarbovir **17** with different bases were also prepared. In the course of the synthesis of **17**, we were pleased to observe that *N*-acetyl-6-chloro-3,4-dihydro-5-nitro-4-oxopyrimidine, which was obtained according to Temple *et al*,[5] reacted with hydrochloride **8** in mild conditions (1h, rt, CH_2Cl_2, instead of refluxing DMF or EtOH as usual). Unfortunately, reduction with $SnCl_2$ gave bad results, and

formamide **15**, obtained by reaction with Zn/HCO_2H together with more than 20% of dienic compounds, did not lead to the guanine derivative. We then decided to use a nitropyrimidine, as in the previous synthesis, and we could obtain small amounts of **17**.[6] However several steps didn't work well, or produced mixtures of compounds which were not easily separated, so that we intend to consider new strategies in the near future.



i) *N*-acetyl-6-chloro-3,4-dihydro-5-nitro-4-oxopyrimidine, Et_3N, CH_2Cl_2, rt (83%), ii) Zn, HCO_2H, iii) *N*-acetyl-4, dichloro-5-nitropyrimidine, Et_3N, CH_2Cl_2, rt, iv) $SnCl_2,2H_2O$, EtOH, 60°C, 15 min (37%), v) $HC(OEt)_3$, HCl, rt, vi) CF_3CO_2H/H_2O 3/1, rt (26%) vii) BCl_3, CH_2Cl_2, -78°C (67%).

Cyclobutene nucleoside analogues **11**, **12** and **13** did not show any significant activity against HIV-1 or-2 (CEM-4 cells) and cancer (KB cells), compound **17** has not been evaluated and the phosphorylated derivatives have not been prepared to date.

Finally we could prepare the first cyclobutene nucleosides unsubstituted at the vinylic position when choosing suitable reagents and experimental conditions to restrict the easy thermal ring opening[7] of cyclobutene intermediates.

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6. Characterization data of **9-[2'-((benzyloxy)methyl)cyclobut-3'-enyl]guanine (16)**: ^{1}H NMR (DMSO-d_6): 10.55 (broad s, 1H, NH); 7.61 (s, 1H, H_8); 7.23 (m, 3H, Ph); 6.98 (m, 2H, Ph); 6.47 (m, 3H, NH_2, $H_{3'}$ or $H_{4'}$); 6.41 (d, 1H, H_4 or H_3); 5.35 (d, 1H, $H_{1'}$, $J_{1'-2'}$ = 4.0 Hz); 4.14 (d (AB system), 1H, benzylic, J = 11.8 Hz); 3.96 (d (AB system), 1H, benzylic, J = 11.8 Hz); 3.47 (m, 1H, $H_{2'}$); 3.41 (d (AB system), 1H, CH_2O, J = 9.6, 5.1Hz); 3.18 (d (AB system), 1H, CH_2O, J = 9.6, 8.8 Hz). FAB-MS: 324 $[M+H]^+$. Characterization data of **9-[2'-((hydroxy)methyl)cyclobut-3'-enyl]guanine (17)**: ^{1}H NMR (DMSO-d_6): 11.01 (broad s, 1H, NH); 7.72 (s, 1H, H_8); 6.90 (m, 2H, NH_2); 6.52 (d (AB system), 1H, $H_{3'}$ or $H_{4'}$, $J_{3'-4'}$ = 2.5 Hz); 6.40 (d (AB system), 1H, $H_{4'}$ or $H_{3'}$, $J_{4'-3'}$ = 2.5 Hz); 5.25 (d, 1H, $H_{1'}$, $J_{1'-2'}$ = 3.4 Hz); 4.44 (t, 1H, OH, J = 5.2 Hz); 3.29 (m, 1H, $H_{2'}$); 3.21 (dd, 1H, CH_2O, J = 10.8, 6.4 Hz); 3.13 (dd, 1H, CH_2O, J = 10.8, 7.4 Hz). ^{13}C NMR (DMSO-d_6): 156.47, 154.04, 151.14 and 115.95 (quat. C of base); 143.12 (C_8); 136.07 and 134.25 ($C_{3'}$ and $C_{4'}$); 60.37 (CH_2O); 54.23 ($C_{1'}$); 51.12 ($C_{2'}$).

7. For a paper on ring opening of cyclobutene bearing nitrogen substituents see Gourdel-Martin, M.-E.; Huet, F. *Tetrahedron Lett.* **1996**, *37*, 7745-7748.