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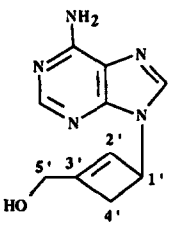
An Efficient Synthesis of 9-[(1-Hydroxymethyl)-cyclobut-1-ene-3-yl] adenine and 1-(Adenin-9-yl)-3-methylidene-but-1-ene-4-ol Via Regiospecific Addition of Phenyl selenenyl bromide to the Alkene Precursor.

Tawfik Gharbaoui*, Michel Legraverend and Emile Bisagni.
Laboratoire de synthèse organique, associé au CNRS, Institut Curie-Biologie, Bâtiments 110-112, Centre Universitaire, 91405 Orsay France

Abstract: Phenylselenenyl bromide permits the efficient synthesis, in two steps, under mild conditions and in good yield of the allylic bromide 8 from 6-chloro-9-(3-methylidene-1-cyclobutyl) purine 4. Depending on the temperature, 9-[(1-hydroxymethyl)-cyclobut-1-ene-3-yl] adenine 1 and 1-(adenin-9-yl)-3-methylidene-but-1-ene-4-ol 2 were then specifically obtained in two steps.

Several nucleoside analogs such as d4T[1], carbovir[2], neplanocin A[3] and adenallene[4], bearing an unsaturated carbocyclic or acyclic chain display potent antiviral activities. Furthermore, two carbocyclic analogs of oxetanocin A and oxetanocin G have been shown to be broad spectrum antiviral agents against herpes viruses and HIV-1[5].



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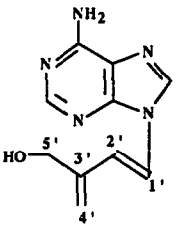

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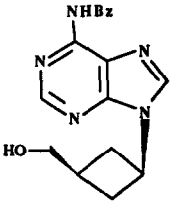

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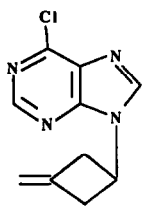
These data made cyclobutenyl and butadienyl derivatives of purine bases such as **1** and **2** interesting target molecules.

The first synthesis of compound **1** has been recently reported in five steps and 3.6 % overall yield [6] starting from the alcohol 3[7] in an unspecific manner. Furthermore, the reported melting point was in disagreement with the one observed independently in our laboratory. Therefore we report herein our efficient route to compounds **1** and **2** starting from the easily prepared 6-chloro-9-(3-methylidene-1-cyclobutyl) purine precursor 4[8].

Several routes may be attempted toward allylic alcohol **1**, including the base-promoted rearrangement of epoxide **5**[9] or an elimination step from 1,2-alkanediol **6**[10]. However they proved to be of no synthetic interest.



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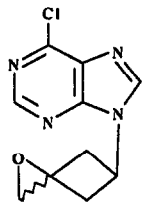

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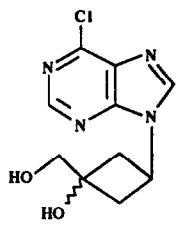

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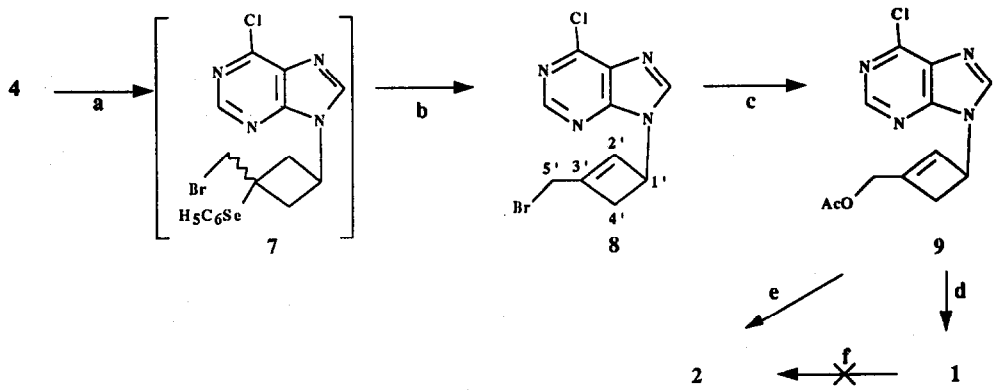
Compound **4**[8] was treated with phenylselenenyl bromide in CH_2Cl_2 affording the β-bromo selenide **7**[11] corresponding to the anti-Markovnikov adduct according to the ^1H NMR spectrum of the mixture. Furthermore, "one pot" oxidation-elimination of unpurified intermediate **7** proceeded smoothly with H_2O_2 in THF to give the allylic bromide **8**[12]. Substitution of the bromine atom of compound **8** by an acetoxy group was performed in ethanol at 40°C with anhydrous potassium acetate affording the allylic acetoxy compound **9**[13] in 54% yield.



Reagent: a: $BrSeC_6H_5$, CH_2Cl_2, -78°C, 30 min. b: H_2O_2 (30%), THF, -78°C to 35°C, 2h (78%). c: KOAc, EtOH, 40°C, 24h (54%). d: liq.NH_3/EtOH (1/3), 40°C, 24h (85%). e: liq.NH_3/EtOH (1/3), 70°C, 24h (100%). f: boiling MeOH, 1h

Treatment of **9** in a solution of ethanol / liq. ammonia: 3 / 1 above 60°C gave quantitatively a yellow solid which recrystallized in methanol affording a pure compound with a melting point of 220°C. The proton NMR spectrum showed chemical shifts of two protons $H_{1'}$ (δ 7.42) and $H_{2'}$ (δ 7.41) split with a trans coupling constant (J = 15 Hz) and two protons of methylene group at $H_{4'}$(δ 5.35 and 5.26) which corresponded to the butadienyl derivative **2**[14].

Finally, the synthesis of the cyclobutenyl derivative **1** was achieved by treatment of compound **9** in a solution of ethanol / liq. ammonia: 3 / 1 at 40°C thus avoiding the cyclobutene opening. The presence of a cyclobutenyl system was confirmed by the UV spectrum and the particular chemical shifts of $H_{4'a}$ and $H_{4'b}$ in the ^1H NMR as described by Maruyama et al[6].

Opening of the cyclobutene ring was observed in **8** when the temperature rose above 40°C. In contrast, compound **1** remained stable in boiling methanol. These data emphasize the important effects of 6-(withdrawing or donating) subtituent of the purine on the stability of this type of substituted cyclobutene. The differences between the melting points of **1** (135°C) and **2** (220°C) as well as their ^1H NMR and UV spectra allow their unambiguous identification. The melting point reported by Maruyama et al[6] for compound **1** (250°C) is therefore striking.

Whereas compound **1** has been claimed to be a potent antiviral agent (no data)[6], our preliminary experiments on HIV-1 with **1** and **2** showed no activity. Further investigation on other viruses are under way. Extension of the strategy reported here is currently developped in order to access to nucleoside analogs bearing different natural bases.

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11 6-Chloro-9-[(1-bromomethyl-1-phenylselenenyl)-cyclobutane-3-yll purine **7**: To a solution of 2.03 g (8.6 mmol) of phenylselenenyl bromide in 50 ml of methylene chloride, stirred in dry ice-acetone bath was added a solution of 1.9 g (8.61 mmol) of **4** in 50 ml of methylene chloride. After being stirred for 30 min, the solvent was concentrated and a brownish oil was obtained.**^{1}H NMR** (200 MHz, $CDCl_3$, δ ppm) of the mixture of the cis / trans isomers: 8.75, 8.7 (1H, 2s, H_2 purine); 8.3, 8.2 (1H, 2s, H_8 purine); 7.7-7.5 (2H, m, m-C_6H_5Se); 7.4-7.2 (3H, m, o,p-C_6H_5Se); 5.5, 5.25 (1H, 2q, $H_{1'}$); 3.9, 3.75 (2H, 2s, $H_{5'}$); 3.45-3.3, 3.25-3 (4H, 2m, $H_{2'4'}$).

12 6-Chloro-9-[(1-bromomethyl)-cyclobut-1-ene-3-yll purine **8**: The mixture **7** was dissolved in 100 ml of THF and stirred in dry ice-acetone bath. The solution was then treated with 2.2 ml (18.92 mmol) of 30% hydrogen peroxide. The temperature was allowed to rise to 35°C in 2 h. Usual work-up and separation by silica gel column chromatography (AcOEt / heptane: 2 / 1) gave a colorless oil which crystallized at room temperature. The white solid was washed twice with a mixture of ether / pentane: 1 / 9 to afford 2 g of allylic bromide **8** (78%). **^{1}H NMR** (200 MHz, $CDCl_3$, δ ppm): 8.75 (1H, s, H_2 purine); 8.2 (1H, s, H_8 purine); 6.3 (1H, s, $H_{2'}$); 5.55 (1H, m, $H_{1'}$); 4 (2H, s, $H_{5'}$); 3.3 (1H, dd, J= 4 Hz, J= 13.7 Hz, $H_{4'a}$); 2.75 (1H, d, J= 13.7 Hz, $H_{4'b}$).**MS (IC)**: MH^+(299, 301, 303).**m.p.**: 55°C.

13 6-Chloro-9-[(1-acetoxymethyl)-cyclobut-1-ene-3-yll purine **9**: A solution of 1 g (3.3 mmol) of **8** in 50 ml of ethanol was stirred in presence of 0.5 g (5.1 mmol) of KOAc at 40°C for 24 h. Removal of the solvent left a white solid which was treated in the same manner as described above. 0.5 g of allylic acetoxy compound **9** (54%) was isolated as a white solid. **^{1}H NMR**(200 MHz, $CDCl_3$, δ ppm): 8.73 (1H, s, H_2 purine); 8.18 (1H, s, H_8 purine); 6.23 (1H, s, $H_{2'}$); 5.55 (1H, m, $H_{1'}$); 4.75 (2H, s, $H_{5'}$); 3.3 (1H, dd, J= 4.3 Hz, J= 14 Hz, $H_{4'a}$); 2.6 (1H, d, J= 14 Hz, $H_{4'b}$); 2.13 (3H, s, CH_3CO).**MS (IC)**: MH^+(279, 281).**m.p.**: 88°C.

14 1-(Adenine-9-yl)-3-methylidene-but-1-ene-4-ol **2**: A 150 ml stainless steel autoclave was charged with a solution of 0.298 g (1.07 mmol) of **9** in 50 ml ethanol / liquide ammonia (3 / 1) and heated at 70°C for 24 h. After cooling to room temperature the bomb was opened and the solution was concentrated to afford a yellow solid. After recrystallization in methanol, 0.23 g of **2** (100%) was isolated as a yellow solid. **^{1}H NMR** (200 MHz, DMSO d6, δ ppm): 8.55 (1H, s, H_2 purine); 8.25 (1H, s, H_8 purine); 7.42 (1H, d, J= 15 Hz, $H_{1'}$); 7.41 (2H, br s, NH_2); 7.31 (1H, d, J= 15 Hz, $H_{2'}$); 5.35, 5.26 (2H, 2s, $H_{4'}$); 5.10 (1H, t, J= 5.4 Hz, OH); 4.25 (2H, d, J= 5.4 Hz, $H_{5'}$).**MS (IC)**: MH^+(218).**UV**: λ max (MeOH) 254 nm. **m.p.**: 220°C. **Anal.**Calcd for $C_{10}H_{11}N_5O$: C (55.29), H (5.10), N (32.24), O (7.36). Found: C (55.19), H (5.21), N (32.11), O (7.65).

15 9-[(1-Hydroxymethyl)-cyclobut-1-ene-3-yll adenine **1**: 150 ml stainless steel autoclave was charged with a solution of 0.3 g (1.08 mmol) of **9** in 70 ml ethanol / liquide ammonia (3 / 1) and heated at 40°C for 24 h. After cooling to room temperature and removal of the solvent, the solid was dissolved in water and extracted by methylene chloride. The organic layer was dried over $MgSO_4$ and evaporated at 30°C to give 0.199 g of **1** (85%) as yellow solid. **^{1}H NMR** (200 MHz, DMSO d6, δ ppm): 8.17 (1H, s, H_2 purine); 8.14 (1H, s, H_8 purine); 7.27 (2H, br s, NH_2); 6.20 (1H, s, $H_{2'}$); 5.30 (1H, m, $H_{1'}$); 5.03 (1H, br s, OH); 4.08 (2H, s, $H_{5'}$); 3.47 (1H, dd, J= 4 Hz, J= 13.3 Hz, $H_{4'a}$); 2.66 (1H, d, J= 13.3 Hz, $H_{4'b}$).**MS (IC)**: MH^+(218).**UV**: λ max (MeOH) 261 nm. **m.p.**: 135°C. **Anal.** Calcd for $C_{10}H_{11}N_5O.1/4\ H_2O$: C (54.17), H (5.23), N (31.58), O (9.02). Found: C (53.79), H (5.53), N (31.26), O (9.41).

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