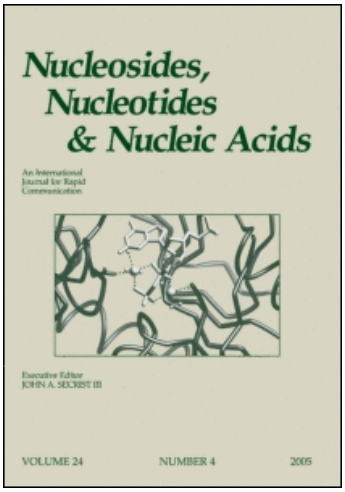

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Zhimeng Wu[a]; Shaoman Zhou[a]; Jiri Zemlicka[a]
[a] Developmental Therapeutics Program, Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, Michigan, USA

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STEREOSELECTIVE APPROACH TO THE *Z*-ISOMERS OF METHYLENECYCLOPROPANE ANALOGUES OF NUCLEOSIDES: A NEW SYNTHESIS OF ANTIVIRAL SYNGUANOL

Zhimeng Wu, Shaoman Zhou, and Jiri Zemlicka

Developmental Therapeutics Program, Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, Michigan, USA

□ *Stereoselective synthesis of antiviral synguanol (**1**) is described. Reaction of 6-benzyloxy-2-(dimethylaminomethyleneamino)purine (**10**) with ethyl (cis,trans)-2-chloro-2-(chloromethyl) cyclopropane-1-carboxylate (**2c**) under the conditions of alkylation-elimination gave (Z)-6-benzyloxy-2-formylamino-9-[(2-carbethoxycyclopropylidene)methyl]purine (**11**) but no E,N^9-isomer. Minor amounts of (Z)-6-benzyloxy-2-formylamino-7-[(2-carbethoxy-cyclopropylidene)methyl]purine (**13**) were also obtained. Hydrolysis of compounds **11** and **13** in 80% acetic acid afforded (Z)-9-[2-(carbethoxycyclopropylidene)methyl]guanine (**14**) and (Z)-7-[2-(carbethoxy-cyclopropylidene)methyl]guanine (**15**). Reduction of **14** furnished synguanol (**1**). Reaction of N^4-acetylcytosine (**7**) with ester **2c** led to (Z,E)-1-(2-carbethoxycyclopropylidenemethyl)cytosine (**8**, Z/E ratio 6.1:1). Basicity of purine base, lower reactivity of alkylation intermediates as well as interaction of the purine N^3 or cytosine O^2 atoms with the carbonyl group of ester moiety seem to be essential for the observed high stereoselectivity of the alkylation-elimination. The Z-selectivity is interpreted in terms of E1cB mechanism leading to a transitory "cyclic" cyclopropenes which undergo a cyclopropene-methylenecyclopropane rearrangement.*

Keywords Methylenecyclopropanes; nucleoside analogues; alkylation-elimination; *Z*-stereoselectivity; antivirals; synguanol

INTRODUCTION

Methylenecyclopropane analogues of nucleosides have received much attention owing to their significant antiviral effects.[1–3] This biological activity resides in the Z-isomers of purine derivatives whereas the *E*-isomers and pyrimidines are effective only in a few instances. In the

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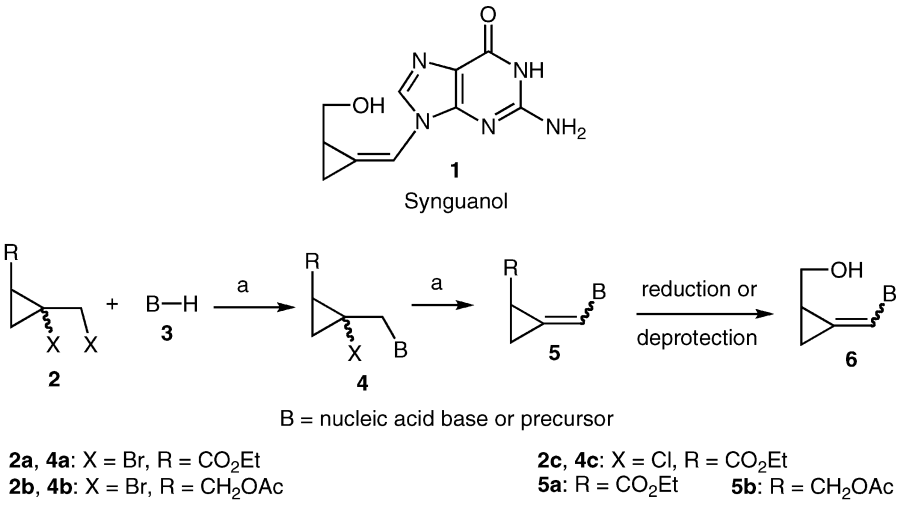
Address correspondence to Jiri Zemlicka, Barbara Ann Karmanos Cancer Institute, 110 E. Warren Ave., Detroit, MI, 48201-1379, USA. E-mail: zemlicka@karmanos.org



a. Base, DMF, Δ.

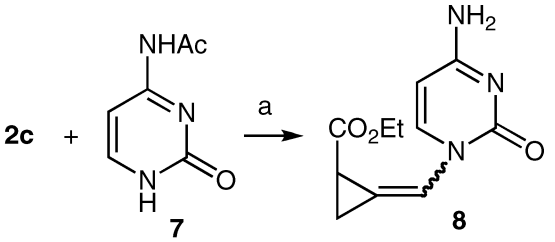
SCHEME 1 Synthesis of methylenecyclopropane analogues by alkylation-elimination.

first generation series, the *Z*-isomer synguanol (**1**) is among the most potent. It is active in vivo against human and murine cytomegalovirus (HCMV and MCMV).[4] Synthesis of methylenecyclopropane analogues of nucleosides is based on alkylation-elimination[5–8] method (Scheme 1). The reaction of dibromocyclopropanes **2a** or **2b** and nucleic acid bases or appropriate precursors **3** is usually carried out under base catalysis at an elevated temperature in DMF. Under these conditions, the products of alkylation **4a** or **4b** are not usually isolated but they are converted *in situ* to *Z*- and *E*-isomeric mixtures of methylenecyclopropanes **5a** or **5b**. After reduction[5,6] (**5a**) or deacetylation[7] (**5b**), the *Z*- and *E*-isomers of **6** are separated by chromatography. Difficult isomer separation coupled with the fact that a considerable amount of intermediates **4a** or **4b** is converted to *E*-isomers of very limited use constitutes a drawback of this protocol. Selective synthesis of the Z-isomers of purine methylenecyclopropanes **6** can therefore be of a significant value. An example of such a procedure, synthesis of synguanol (**1**), is described in this communication.

RESULTS AND DISCUSSION

Synthesis

Alkylation-elimination procedure with esters **2a** gave a somewhat improved Z/E ratio (2:1)[5,6] over that employing reagents **2b** (1:1 or 1:2).[7,8] We have now found that this ratio was significantly increased by

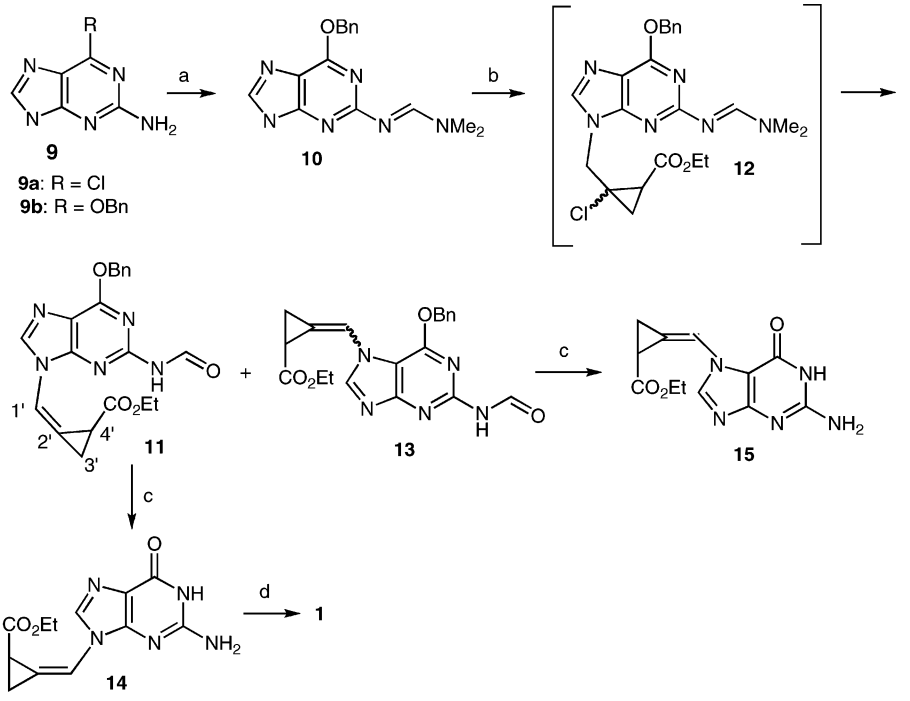


a. K_2CO_3/Cs_2CO_3, DMF, Δ.

SCHEME 2 Stereoselective alkylation-elimination of N^4-acetylcytosine (**7**) with ester **2c**.

using dichloro ester **2c** in the reaction with N^4-acetylcytosine (**7**) employing K_2CO_3/Cs_2CO_3 as a base in DMF at 100–105°C to give ester **8** (*Z/E* 6.1:1, 56% yield, Scheme 2). Compound[9] **2c** was obtained in 65% yield by addition of ethyl diazoacetate on 2,3-dichloro-1-propene catalyzed by $Rh_2(OAc)_4$ using the previously described[5] protocol for the corresponding dibromo derivative[6] **2a**. It should be noted that reaction of **7** with dibromo ester **2a** under similar conditions (K_2CO_3, DMF, 100°C) gave 47% yield of the ester[6] **9** (Et = Me) with the *Z*/E ratio of only 2.3:1. As indicated above, purine *Z*-methylenecyclopropanes are in the center of our current interest. In contrast to dibromo ester[5] **2a**, reaction of dichloro ester **2c** with 2-amino-6-chloropurine (**9a**) led to a mixture of products even after a prolonged reaction time. We have reasoned that lower reactivity of **2c** may be offset by employing a more basic nucleobase precursor.

To increase the basicity of a purine base, we turned our attention to N-dimethylaminomethylene derivatives of purine bases.[10] The 2-amino-6-benzyloxypurine (**9b**) was converted to N-dimethylaminomethylene compound **10** using N,N-dimethylformamide dimethyl acetal in DMF[10] (85%, Scheme 3). Alkylation-elimination of **10** with dichloro ester **2c** in DMF (K_2CO_3, 110–115°C, 40 hours) followed by chromatography gave the *Z*,N^9-isomer of N-formylmethylenecyclopropane **11** (via intermediary chloro ester **12**) in 41–47% yield. The Z,N^7-isomer ***Z*-13** (3.4%) and unresolved mixture of *Z*,N^7- and *E*,N^7-isomers ***E, Z*-13** (8.6%) were also obtained. The *E*-isomer of **11** was not detected. As expected,[11] the long-wavelength UV maximum of the N^7-isomer ***Z*-13a** was bathochromically shifted relative to that of N^9-isomer **11**. Likewise, the chemical shifts of **11** and ***Z*-13** /($\delta H_8(N^9) < \delta H_8(N^7)$ and $C_8(N^9) < C_8(N^7)$/ reflected the pattern of other purine methylenecyclopropanes[11] and they were in line with N^7- and N^9-alkylpurines.[12] The strong NOE enhancements between the $H_{4'}$- H_8 (5.81%) and $H_{1'}$- $H_{3'}$ (3.37%) of ***Z*-13** provided final support for the *Z*,N^7 isomeric structure while they ruled out the *Z*,N^3- or *E*,N^3-isomers.



a. $Me_2NCH(OMe)_2$, DMF. b. **2c**, K_2CO_3, DMF, Δ. c. 50-80% AcOH, Δ.

d. DIBALH, THF, 0 °C.

SCHEME 3 Stereoselective synthesis of synguanol (**1**).

A smooth transformation of the N-dimethylaminomethylene group into N-formyl function is surprising. In a study of hydrolysis of N-dimethylaminomethylene derivatives of nucleosides[13] at different pH values, the N-formyl intermediates have not been detected. Treatment of **11** with 80% acetic acid at 75–85°C resulted in removal of the both N-formyl and O-benzyl groups to give guanine methylenecyclopropane ester (**14**, 85%). A similar hydrolysis of the *Z*,N^7-isomer ***Z*-13** furnished ester **15** in 71% yield. The UV_{max} and H_8 (C_8) chemical shifts patterns of **14** and **15** corresponded to those observed for compounds **11** and ***Z*-13**. Reduction of **14** with DIBALH in THF furnished synguanol (**1**, 79%).

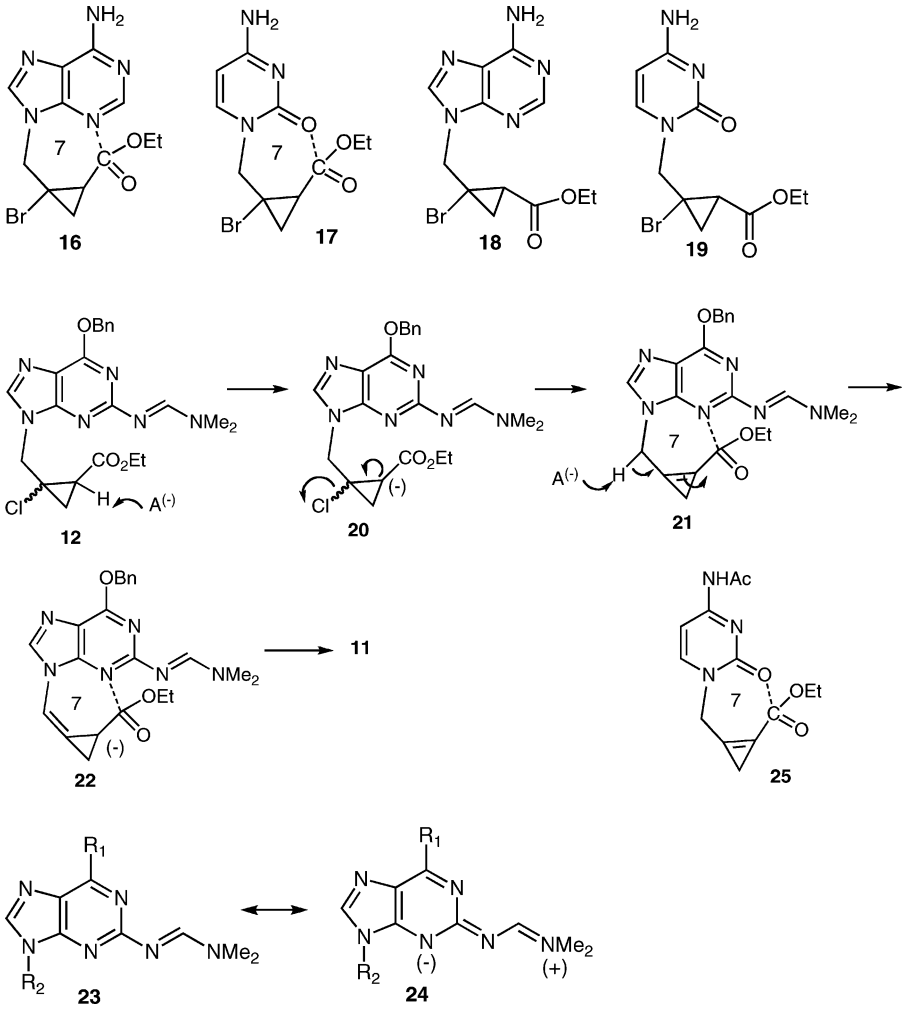
Reaction Course

Two sites of proton abstraction and two mechanisms of elimination can be considered to explain the reaction course observed in the β-elimination of halide (Br or Cl) from the *Z(trans)*- and *E(cis)* intermediates **4a-4c**. The E2 mechanism initiated by a proton abstraction at the methylene group

adjacent to a heterocyclic base can lead to a direct formation of both *Z*- and *E*-methylenecyclopropane isomers **5a–5c**. Depending on the base used, the *E(cis)*-isomeric esters **4a** (B = adenine) gave the Z,E isomers of **5a** (B = adenine) in the ratios[5] of 1.5–2.5:1 whereas the *Z(trans)*-isomers **4a** (B = adenine) led to ratios 0.5–1.5:1. It is important to note that a preponderance of the *Z*-isomers **5a** (B = adenine) may possibly be explained by an interaction of the carbonyl group with the N^3 of purine ring in a *syn* conformation (structure **16**). A similar structure **17**, with the carbethoxy function interacting with the 2-keto group of cytosine of the *E(cis)*-isomer **4a** (B = cytosine), can also be visualized whereas in the *Z(trans)*-isomers **4a** (B = adenine or cytosine) such a seven-membered "cyclic" arrangement is not possible (structures **18** and **19**). Interestingly, the IR spectra provided an evidence for such an interaction in the *E(cis)*-isomer **16** (ν_{CO} 1745 cm^{-1}) as opposed to the *Z(trans)*-isomer **18** (ν_{CO} 1725 cm^{-1}).[5]

In an alternate E1cB mechanism (Scheme 4), proton abstraction by a base $A^{(-)}$ at the cyclopropane carbon attached to the ester moiety of **12** can generate carbanion **20** from both *Z*- and *E*-isomers of **12**. The elimination of chloride leads then to the cyclopropene intermediate **21** with a *cis* arrangement of the heterocyclic portion and carbethoxy group. Because of an increased rigidity of **21** and necessary *cis*-configuration of the cyclopropene moiety, interaction between the carbonyl group of the ester function and the N^3 can be stronger than that observed in the *Z*-isomer[5] **16**. This "cyclic" arrangement (seven-membered "ring") of the cyclopropene **21** may then facilitate a subsequent cyclopropene-methylenecyclopropane rearrangement[14] to form preferentially a *Z*-methylenecyclopropane system of **11** via carbanion **22**. Similar rearrangement was observed in methylenedifluorocyclopropane series of purine nucleoside analogues.[15] In this instance, a thermodynamically controlled mixture of *Z*- and *E*-isomers and difluorocyclopropene analogue related to the proposed intermediate **21** was obtained. It is likely that the N^3- CO (ester) interaction will be strengthened in the presence of more basic heterocycles. The N-dimethylaminomethylene group can increase the electron density at the N^3 of purine ring (structures **23** and **24**). In a similar fashion, intermediate **25** may explain high *Z*-selectivity in the formation of ester **8**. Interestingly, in this case, the N-acetyl function which decreases the basicity of the cytosine ring does not significantly interfere with the *Z*-stereoselectivity of the process.

Difference between the degree of stereoselectivity of β-elimination of bromo and chloro substituted derivatives **4a** and **4c** is more difficult to explain. A mechanistic dichotomy at two different reaction sites, E2 for bromides at a methylene group carrying the nucleic acid base and E1cB for chlorides at cyclopropane CH α to the carbethoxy group, may be invoked. Although bromides appear to be better leaving groups than chlorides for both nucleophilic substitution and β-elimination,[16] kinetic studies of



SCHEME 4 Proposed mechanism of stereoselective alkylation-elimination.

β-elimination in systems with different leaving groups including bromide and chlorides are not clear-cut. In some cases, the chlorides preferred E1cB mechanisms[17]whereas bromides followed E2 but in other[18] no definite conclusion was possible. Nevertheless, in these instances, only a single possible reaction site was present in the molecule.

EXPERIMENTAL SECTION

General Methods

The UV spectra were measured in ethanol and NMR spectra were determined at 300 or 400 MHz (^{1}H) and 75 or 100 MHz (^{13}C) in CD_3SOCD_3

unless stated otherwise. Mass spectra were determined in electron-impact (EI-MS), chemical ionization (CI-MS, 2-methylpropane) or electrospray ionization (ESI-MS, methanol-NaCl) mode. Thin-layer chromatography (TLC) was performed on Analtech aluminum foils coated with silica gel F254. For acronyms of common reagents, solvents and protecting groups see *J. Org. Chem.* **2006**, *71*, 28A-29A.

Starting Materials

2-Amino-6-benzyloxypurine (**9b**) was prepared as described.[19]

Ethyl (*cis,trans*)-2-Chloro-2-(chloromethyl)cyclopropane-1-carboxylate (2c). A solution of ethyl diazoacetate (11.4 g, 0.1 mol) in CH_2Cl_2 (10 mL) was added into a stirred mixture of 2,3-dichloro-1-propene (15.9 mL, 10.17 mol) and $Rh_2(OAc)_4$ (11.5 mg, 0.025 mmol) in CH_2Cl_2 (2 mL) with the aid of a syringe pump at a rate of 1 mL/h at room temperature. The solvent and unreacted alkene were distilled off and trapped at −78°C. The water (50 mL) was added to the residue followed by a solution of $KMnO_4$ (15 g) in water (60 mL) with external ice-cooling and stirring. The stirring was continued for 2 hours and excess of $KMnO_4$ was removed by addition of solid $Na_2S_2O_3$. The mixture was extracted with ethyl ether (3 × 25 mL), the organic phase was washed successively with saturated $NaHCO_3$, water and brine. It was dried ($MgSO_4$) and the solvent was evaporated to give compound **2c** as a yellow oil (12.8 g, 65%). ^{1}H NMR ($CDCl_3$) δ 1.29 (two overlapped t, 3H, J = 7.2 Hz, CH_3), 1.51 (dd, J = 9.3, 6.9 Hz), 1.71 (d, J = 8.1 Hz), 1.85 (t, J = 6.9 Hz, total 2H, H_3), 2.18 (dd, J = 9.3, 6.9 Hz), 2.35 (t, J = 8.3 Hz, 1H, H_1), 3.76, 3.80 (AB, J = 12.3 Hz), 3.97, 4.08 (AB, J = 11.9 Hz, 2H, CH_2Cl), 4.20 (two overlapped q, J = 7.2 Hz, CH_2 of Et). ^{13}C NMR 14.3, 14.5 (CH_3), 20.6, 24.6 (C_3), 27.9, 30.1 (C_1), 47.0, 48.7 (C_2), 48.8, 51.9 (CH_2Cl), 61.7, 61.8 (CH_2 of Et), 168.1, 169.7 (C=O). EI-MS 196, 198 (M, 2.5, 1.8), 133 (100.0), HRMS calcd for $C_7H_{10}{}^{35}Cl_2O_2$ 196.0058, found 196.0052. CI-MS (2-methylpropane) 197, 199 (M + H, 100.0, 64.0).

(*Z,E*)-1-(2-Carbethoxycyclopropylidenemethyl)cytosine (8). A mixture of N^4-acetylcytosine (**7**, 1.53 g, 10 mmol), dichloro ester **2c** (2.2 g, 11 mmol), K_2CO_3 (4.14 g, 30 mmol) and Cs_2CO_3 (9.75 g, 30 mmol) was heated in DMF (50 mL) with stirring at 100–105°C for 7 hours. The reaction mixture was cooled to 80°C, ethanol (15 mL) was added and the stirring was continued for 1 hour. The solvents were evaporated in vacuo and the crude product was chromatographed on a silica gel column in CH_2Cl_2-MeOH (40:1 to 20:1) and then in CH_2Cl_2-MeOH (40:1) to give the *Z,E*-isomers (**8**, 1.31 g, 56%, ratio 6.1:1). ^{1}H NMR corresponded to compound[6] **8** (Et = Me) except the *Z/E* ratio. ^{1}H NMR δ 1.11–1.23 (m, 3H, CH_3), 1.79, 1.72 (t and m, *Z*-isomer), 2.03, 1.94 (2m, total 2H, $H_{3'}$, *E*-isomer), 2.76, 2.43 (2m, 1H, $H_{4'}$), 4.08 (m, 2H, CH_2 of Et), 5.81 (d, J = 7.2 Hz, 2H, H_5,), 7.37 (s, 1H, $H_{1'}$), 7.41 (s, 2H, NH_2), 7.65, 7.95, (2d, 1H, J = 7.6 Hz, *Z*- and *E*-isomer, ratio 6.1:1,

H_6), ^{13}C NMR (*Z*-isomer) 9.3 ($C_{3'}$), 14.7 (CH_3), 18.8 ($C_{4'}$), 61.4 (CH_2 of Et), 109.3, 116.7 ($C_{1'}$, $C_{2'}$), 96.1, 140.5, 154.4, 166.1 (cytosine), 171.0 (C=O, ester).

6-Benzyloxy-2-(dimethylaminomethyleneamino)purine (10). A mixture of 2-amino-6-benzyloxypurine (**9b**, 5.6 g, 23 mmol) and N,N-dimethylformamide dimethyl acetal (9.0 mL, 66.7 mmol) in DMF (100 mL) was stirred at 40°C for 16 hours. The solvent was evaporated in vacuo and the crude product was crystallized from EtOAc (40 mL) to give compound **10** (5.79 g, 85%) as a white solid, mp 244–245°C. UV λ_{max} 293 nm (ε 26,400), 233 (ε 14,200), 202 (ε 23,800). ^{1}H NMR δ 2.99, 3.10 (2s, 6H, CH_3), 5.54 (s, 2H, CH_2 of Bn), 7.31–7.40 (m, 3H), 7.47 (d, 2H, $J = 8.0$ Hz, Ph), 8.01 (s, 1H, H_8), 8.57 (s, 1H, N^2=CH), 12.74 (bs, 1H, NH). ^{13}C NMR 35.2, 41.0 (CH_3), 67.7 (CH_2 of Bn), 128.6, 128.9, 129.1, 137.7 (Ph), 140.5, 142.9, 155.4, 158.6, 160.0, 162.3 (purine, N^2=CH). EI-MS 296 (M, 5.2), 93 (100.0). HRMS calcd M 296.1386, found 296.1383. Anal. Calcd for $C_{15}H_{16}N_6O$: C, 60.80; H, 5.44; N, 28.36. Found: C, 60.81; H, 5.55; N, 28.20.

(*Z*)-6-Benzyloxy-2-formylamino-9-[(2-carbethoxycyclopropylidene) methyl]purine (11) and (*Z*)-6-Benzyloxy-2-formylamino-7-[(2-carbethoxy-cyclopropylidene)methyl]purine (13). A mixture of compound **10** (450 mg, 1.49 mmol), dichloro ester **2c** (600 mg, 3.0 mmol) and K_2CO_3 (1.24 g, 8.93 mmol) in DMF (8 mL) was stirred at 110–115°C under N_2 for 40 hours. After cooling, the insoluble portion was filtered off and it was washed with DMF. The filtrate was concentrated and residue was chromatographed on a silica gel column using CH_2Cl_2-MeOH (100:1 to 20:1) to give the *Z*,N^9-isomer **11** (239 mg, 41%), *Z*,N^7-isomer **Z-13** (20 mg, 3.4%) and mixture of the *Z*- and *E*-N^7-isomer **13** (50 mg, 8.6%). In another experiment run on a 4-mmol scale, compound **11** was obtained in 47% yield.

Z,N^9-Isomer **11**: Mp 162–163°C. UV λ_{max} 271 (ε 18,000), 232 (ε 32,200), 210 nm (ε 32,800). ^{1}H NMR δ 1.07 (t, $J = 6.8$ Hz, 3H, CH_3), 1.92 (m, 1H), 2.03 (t, 1H, J = 8.8 Hz, $H_{3'}$), 2.98 (m, 1H, $H_{4'}$), 4.02 (q, 2H, $J = 6.8$ Hz, CH_2 of Et), 5.59 (s, 2H, CH_2 of Bn), 7.34–7.41, 7.49–7.53 (2m, 6H, Ph and $H_{1'}$), 8.29 (s, 1H, H_8), 9.45 (d, $J = 9.6$ Hz, 1H, CH=O), 10.90 (d, $J = 9.6$ Hz, 1H, NH). ^{13}C NMR 11.2 ($C_{3'}$), 14.6 (CH_3), 20.2 ($C_{4'}$), 61.4 (CH_2 of Et), 69.0 (CH_2 of Bn), 111.9, 114.5, 118.1, 140.1, 152.3, 153.5, 160.8 ($C_{1'}$, $C_{2'}$, purine), 129.0, 129.2, 129.4, 136.7 (Ph), 164.5 (CH=O), 170.8 (C=O, ester). EI-MS 393 (M, 15.6), 91 (100.0). HRMS calcd M 393.1437, found 393.1437. Anal. Calcd for $C_{20}H_{19}N_5O_4$: C, 61.06; H, 4.87; N, 17.80. Found: C, 61.07; H, 4.76; N, 17.79.

Z,N^7-Isomer **Z-13**: Mp 153–154°C. UV λ_{max} 285 (ε 7,000), 250 (ε 33,300), 206 (ε 23,300). ^{1}H NMR δ 1.10 (t, $J = 6.4$ Hz, 3H, CH_3), 1.92–1.95 (m, 1H), 2.01 (t, $J = 8.8$ Hz, 1H, $H_{3'}$), 2.94 (t, $J = 5.6$ Hz, 1H, $H_{4'}$), 4.04–4.07 (m, 2H, CH_2 of Et), 5.62 (s, 2H, CH_2 of Bn), 7.34–7.41 (m, 3H), 7.55 (d,

J = 7.6 Hz, 3H, Ph overlapped with $H_{1'}$), 8.51 (s, 1H, H_8), 9.39 (d, J = 10.0 Hz, 1H, CH=O), 10.86 (d, J = 10.0 Hz, 1H, NH), ^{13}C NMR 10.8 ($C_{3'}$), 14.7 (CH_3), 19.4 ($C_{4'}$), 61.6 (CH_2 of Et), 69.2 (CH_2 of Bn), 109.1, 113.9, 114.3, 143.8, 153.2, 157.3, 162.7 ($C_{1'}$, $C_{2'}$, purine), 164.3 (CH=O), 129.0, 129.1, 129.3, 136.6 (Ph), 170.4 (C=O, ester), ESI-MS (MeOH + AcOK) 432 (M + K, 100.0), 394 (M + H, 66.7). Anal. Calcd for $C_{20}H_{19}N_5O_4$: C, 61.06; H, 4.87; N, 17.80. Found: C, 60.87; H, 4.93; N, 17.81.

(*Z*)-9-[2-(Carbethoxycyclopropylidene)methyl]guanine (14). A solution of compound **11** (230 mg, 0.59 mmol) in 80% acetic acid (10 mL) was heated at 75–85°C for 5 hours. The solvent was removed and the residue was chromatographed on a silica gel column using CH_2Cl_2-MeOH (20:1 to 8:1) to give compound **14** (137 mg, 85%), mp 247–249°C (decomp). UV λ_{max} 273 (ε 10,500). 231 nm (ε 23,800), ^{1}H NMR δ 1.13 (split t, J = 6.4 Hz, 3H, CH_3), 1.87–1.90 (m, 1H,′), 1.97 (t, J = 8.0 Hz, 1H, H_3), 2.85 (dt, J = 4.8 Hz, 2.4 Hz, 1H, $H_{4'}$), 4.05–4.11 (m, 2H, CH_2 of Et), 6.54 (s, 2H, NH_2), 7.24 (s, 1H, $H_{1'}$), 7.78 (s, 1H, H_8), 10.75 (s, 1H, NH). ^{13}C NMR 10.8 ($C_{3'}$), 14.7 (CH_3), 19.5 ($C_{4'}$), 61.5 (CH_2 of Et), 111.5, 112.7, 116.5, 134.0, 150.6, 154.8, 157.3 ($C_{1'}$, $C_{2'}$, guanine), 170.9 (C=O, ester). EI-MS 275 (M, 17.7), 55 (100.0). HRMS calcd M 275.1018, found 275.1020. Anal. Calcd for $C_{12}H_{13}N_5O_3 \times 0.3\ CH_2Cl_2$: C, 49.12; H, 4.56; N, 23.29. Found: C, 49.07; H, 4.61; N, 23.07.

(*Z*)-7-[2-(Carbethoxycyclopropylidene)methyl]guanine (15). A mixure of the *Z*,N^7-isomer ***Z*-13** (20 mg, 0.051 mmol) in 80% AcOH (1 mL) was heated at 85°C for 16 hours. The solvent was evaporated and residue was chromatographed on a silica gel column using CH_2Cl_2-MeOH (20:1 to 8:1) to give product **15** (10 mg, 71%). Mp 255°C (decomp). UV λ_{max} 304 nm (ε 2,900), 233 (ε 8,100). ^{1}H NMR δ 1.13 (t, J = 6.4 Hz, 3H, CH_3), 1.89 (m, 1H), 1.96 (t, J = 8.0 Hz, 1H, $H_{3'}$), 2.86 (poorly resolved t, $C_{4'}$), 4.08 (m, 2H, CH_2 of Et), 6.49 (s, 2H, NH_2), 7.70 (s, 1H, $H_{1'}$), 8.05 (s, 1H, H_8), 11.20 (bs, 1H, NH), ^{13}C NMR 10.5 ($C_{3'}$), 14.7 (CH_3), 19.3 ($C_{4'}$), 61.5 (CH_2 of Et), 107.6, 112.1, 113.8, 139.5, 154.1, 155.3, 160.3 ($C_{1'}$, $C_{2'}$., guanine), 170.7 (C=O, ester), ESI-MS 276 (M + H, 83.3), 298 (M + Na, 100.0). ESI-HRMS calcd for M + H 276.1113, found 276.1110.

Synguanol (1). DIBALH in THF (1.8 M, 0.5 mL, 0.9 mmol) was added dropwise into a solution of ester **15a** (73 mg, 0.27 mmol) in THF (10 mL) at 0°C with stirring under N_2. After 0.5 hours, another portion of DIBALH (0.5 mL, 0.9 mmol) was added and the stirring was continued for 0.5 hours. Aqueous methanol (50%, 1 mL) was added and the mixture was stirred overnight at room temperature. The solvents were evaporated and crude product was chromatographed on silica gel column using CH_2Cl_2-MeOH (8:1 to 4:1) to give synguanol (**1**, 49.5 mg, 79%) identical (^{1}H a and ^{13}C NMR) to an authentic sample.[5]

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