Published in final edited form as:

Nucleosides Nucleotides Nucleic Acids. 2009 March ; 28(3): 165–174. doi:10.1080/15257770902831060.

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

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Abstract

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,N⁹-isomer. Minor amounts of (Z)-6-benzyloxy-2-formylamino-7-[(2-carbethoxycyclopropylidene)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-(carbethoxycyclopropylidene)methyl]guanine (**15**). Reduction of **14** furnished synguanol (**1**). Reaction of N⁴-acetylcytosine (**7**) with ester **2c** led to (Z,E)-1-(2-carbethoxycyclopropylidene)methylcytosine (**8**, Z/E ratio 6.1 : 1). Basicity of purine base, lower reactivity of alkylation intermediates as well as interaction of the purine N³ or cytosine O² 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 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 using dichloro ester **2c** in the reaction with *N*⁴-acetylcytosine (**7**) employing K₂CO₃/Cs₂CO₃ as a base in DMF at 100-105 °C to give ester **8** (*Z/E* 6.1 : 1, 56% yield, Scheme 2). Compound **2c** was obtained in 65% yield by addition of ethyl diazoacetate on 2,3-dichloro-1-propene catalyzed by Rh₂(OAc)₄ using the previously described[5] protocol for the corresponding dibromo derivative **2a**. It should be noted that reaction of **7** with dibromo ester **2a** under similar conditions (K₂CO₃, DMF, 100 °C) gave 47% yield of the ester **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 **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 (K₂CO₃, 110-115 °C, 40 h) 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'}-H₈ (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 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 H₈ (C₈) 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 N³ 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 N³ can be stronger than that observed in the *Z*-isomer[5] **17**. 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 N³- CO (ester) interaction will be strengthened in the presence of more basic heterocycles. The N-dimethylaminomethylene group can increase the electron density at the N³ 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 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 (¹H) and 75 or 100 MHz (¹³C) in CD₃SOCD₃ 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 $\text{Rh}_2(\text{OAc})_4$ (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 h and excess of KMnO_4 was removed by addition of solid $\text{Na}_2\text{S}_2\text{O}_3$. 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%). ^1H 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 ($\text{C}=\text{O}$). EI-MS 196, 198 (M, 2.5, 1.8), 133 (100.0), HRMS calcd for $\text{C}_7\text{H}_{10}^{35}\text{Cl}_2\text{O}_2$ 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 $100 - 105^\circ\text{C}$ for 7 h. The reaction mixture was cooled to 80°C , ethanol (15 mL) was added and the stirring was continued for 1 h. 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). ^1H NMR corresponded to compound **8** (Et = Me) except the *Z/E* ratio. ^1H 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, *E*-isomer H_3), 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, 7.65 (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 ($\text{C}=\text{O}$).

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 h. 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 $244 - 245^\circ\text{C}$. UV λ_{max} 293 nm (ϵ 26,400), 233 (ϵ 14,200), 202 (ϵ 23,800). ^1H 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, $\text{N}^2=\text{CH}$), 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, $\text{N}^2=\text{CH}$). EI-MS 296 (M, 5.2), 93 (100.0). HRMS calcd M 296.1386, found 296.1383. Anal. Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_6\text{O}$: 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-carbethoxycyclopropylidene)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 $110 - 115^\circ\text{C}$ under N_2 for 40 h. 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 CH₂Cl₂ - MeOH (100 : 1 to 20 : 1) to give the Z,N⁹-isomer **11** (239 mg, 41%), Z,N⁷-isomer **Z-13** (20 mg, 3.4%) and mixture of the Z- and E-N⁷-isomer **13** (50 mg, 8.6%). In another experiment run on a 4-mmol scale, compound **11** was obtained in 47% yield.

Z,N⁹-Isomer 11: Mp 162 - 163 °C. UV λ_{max} 271 (ϵ 18,000), 232 (ϵ 32,200), 210 nm (ϵ 32,800). ¹H NMR δ 1.07 (t, J = 6.8 Hz, 3H, CH₃), 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, CH₂ of Et), 5.59 (s, 2H, CH₂ of Bn), 7.34-7.41, 7.49-7.53 (2m, 6H, Ph and H_{1'}), 8.29 (s, 1H, H₈), 9.45 (d, J = 9.6 Hz, 1H, CH=O), 10.90 (d, J = 9.6 Hz, 1H, NH). ¹³C NMR 11.2 (C_{3'}), 14.6 (CH₃), 20.2 (C_{4'}), 61.4 (CH₂ of Et), 69.0 (CH₂ 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 C₂₀H₁₉N₅O₄: C, 61.06; H, 4.87; N, 17.80. Found: C, 61.07; H, 4.76; N, 17.79.

Z,N⁷-Isomer Z-13: Mp 153 - 154 °C. UV λ_{max} 285 (ϵ 7,000), 250 (ϵ 33,300), 206 (ϵ 23,300). ¹H NMR δ 1.10 (t, J = 6.4 Hz, 3H, CH₃), 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, CH₂ of Et), 5.62 (s, 2H, CH₂ 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, H₈), 9.39 (d, J = 10.0 Hz, 1H, CH=O), 10.86 (d, J = 10.0 Hz, 1H, NH). ¹³C NMR 10.8 (C_{3'}), 14.7 (CH₃), 19.4 (C_{4'}), 61.6 (CH₂ of Et), 69.2 (CH₂ 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 C₂₀H₁₉N₅O₄: 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 h. The solvent was removed and the residue was chromatographed on a silica gel column using CH₂Cl₂ - 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). ¹H NMR δ 1.13 (split t, J = 6.4 Hz, 3H, CH₃), 1.87-1.90 (m, 1H), 1.97 (t, J = 8.0 Hz, 1H, H₃), 2.85 (dt, J = 4.8 Hz, 2.4 Hz, 1H, H_{4'}), 4.05-4.11 (m, 2H, CH₂ of Et), 6.54 (s, 2H, NH₂), 7.24 (s, 1H, H_{1'}), 7.78 (s, 1H, H₈), 10.75 (s, 1H, NH). ¹³C NMR 10.8 (C_{3'}), 14.7 (CH₃), 19.5 (C_{4'}), 61.5 (CH₂ 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 C₁₂H₁₃N₅O₃ × 0.3 CH₂Cl₂: 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 mixture of the Z,N⁷-isomer **Z-13** (20 mg, 0.051 mmol) in 80% AcOH (1 mL) was heated at 85 °C for 16 h. The solvent was evaporated and residue was chromatographed on a silica gel column using CH₂Cl₂ - 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). ¹H NMR δ 1.13 (t, J = 6.4 Hz, 3H, CH₃), 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, CH₂ of Et), 6.49 (s, 2H, NH₂), 7.70 (s, 1H, H_{1'}), 8.05 (s, 1H, H₈), 11.20 (bs, 1H, NH). ¹³C NMR 10.5 (C_{3'}), 14.7 (CH₃), 19.3 (C_{4'}), 61.5 (CH₂ 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 N₂. After 0.5 h, another portion of DIBALH (0.5 mL, 0.9 mmol) was added and the stirring was continued

for 0.5 h. 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 CH₂Cl₂ - MeOH (8 : 1 to 4 : 1) to give synguanol (**1**, 49.5 mg, 79%) identical (¹H and ¹³C NMR) to an authentic sample.[5]

Acknowledgments

We thank Hongwang Zhang for some initial experiments and L. M. Hrihorczuk from the Central Instrumentation Facility (D. M. Coleman, Director) for mass spectra. The work described herein was supported by SBIR Grant 5 R44 AI0554135 to Microbiotix, Inc., Worcester, Massachusetts and Research Grant 1 RO1 CA32779 from the National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA.

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a. Base, DMF, Δ .

SCHEME 1.

Synthesis of methylenecyclopropane analogues by alkylation-elimination.

a. $\text{K}_2\text{CO}_3/\text{Cs}_2\text{CO}_3$, DMF, Δ .

SCHEME 2.

Stereoselective alkylation-elimination of N⁴-acetylcytosine (7) with ester 2c.

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

SCHEME 4.

Proposed mechanism of stereoselective alkylation-elimination.