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Methylene-2-ethynylcyclopropanes: synthesis and biological activity of (*Z*)- and (*E*)-9-{[2-ethynyl-2-(hydroxymethyl)cyclopropylidene]methyl}adenine and -guanine

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Abstract—Synthesis of methylene-2-ethynylcyclopropane analogues of nucleosides **12a**, **12b**, **13a**, and **13b** is described. Ethyl methylenecyclopropane carboxylate **14** was hydroxymethylated to give alcohol **15**, which was reduced to diol **16**. Selective protection with *tert*-butyldimethylsilyl group gave derivative **17**, which was oxidized to aldehyde **18**. Wittig reaction with CBr_4 gave dibromoalkene **19**. Elimination of both bromine atoms afforded methylene-2-ethynylcyclopropane **20**. Bromoselenenylation using *N*-bromosuccinimide and diphenyldiselenide gave intermediate **21**. Alkylation of adenine and 2-amino-6-chloropurine with **21** provided the *Z*,*E*-isomeric mixtures **22a** and **22c**. Oxidation afforded selenoxides **23a** and **23c**. Mild thermolysis furnished methylenecyclopropanes ***Z*-24a**, ***E*-24a**, and **24c**. Deprotection and separation of *Z*,*E*-isomers gave adenine analogues **12a** and **13a**, and 2-amino-6-chloropurine intermediates **12c** and **13c**. Hydrolytic dechlorination of **12c** and **13c** afforded guanine analogues **12b** and **13b**. Adenine *Z*-isomer **12a** inhibits replication of Epstein-Barr virus through its cytotoxicity. The *E*-isomer **13a** is a substrate for adenosine deaminase.

1. Introduction

4′-Substituted 2′-deoxynucleosides have received much attention as anti-HIV agents effective against various laboratory and clinical strains of the virus. Thus 4′-azido analogues **1** derived from all DNA bases exhibited a submicromolar potency against HIV-1 in vitro.[1] More recently, the 4′-ethynyl-2′-deoxynucleosides **2** were found to inhibit HIV-1 with EC_{50}s in a similar concentration range.[2–4] It has been suggested[5] that the presence of the 3′-OH group is indispensable for a high anti-HIV potency of cytosine ethynyl analogue **2d** (Chart 1). Thus the 3′-deoxy derivative of **2d** was inactive but its triphosphate was a potent inhibitor of HIV-1 reverse transcriptase. However, a high potency[6–9] of ethynyl analogues of stavudine **3a** and **3b** lacking the 3′-OH has indicated that the presence of the latter function is not a prerequisite for anti-HIV activity of 4′-substituted nucleosides. By contrast, 3′-fluoro-4′-ethynyl unsaturated nucleosides **4a**, **4d**, and **5a** exhibited only borderline antiviral effects.[10,11] The exact role of the ethynyl group for a high anti-HIV potency of analogues **2**, **3a**, and **3b** has not been elucidated.

The *Z*-methylenecyclopropane analogues of purine nucleosides **6** are established antiviral agents whereas the *E*-isomers **7** are effective only exceptionally.[12–14] Introduction of substituents next to the hydroxymethyl group led to several effective antivirals. For example, the guanine bis-hydroxymethyl analogue cyclopropavir (**8b**) is a potent anti-cytomegalovirus agent[15,16] that is currently undergoing preclinical studies. Again, the *E*-isomers **9** are inactive or much less potent antivirals. By contrast, *Z*- and *E*-fluoro analogues **10** and **11** yielded several agents effective against HIV-1, human cytomegalovirus (HCMV), Epstein-Barr virus (EBV) or varicella zoster virus (VZV).[17] The position of the ethynyl group in methylenecyclopropane analogues **12** and **13** approximates that of nucleosides **2** and **3**. It was then of interest to synthesize ethynyl methylenecyclopropanes **12a**, **12b**, **13a**, and **13b** and investigate their biological properties.

2. Results and discussion

The synthesis of analogues **12a**, **12b**, **13a**, and **13b** started with hydroxymethylation of the methylenecyclopropane carboxylate[18] **14** via the corresponding carbanion using formaldehyde as recently described for diethyl ester of Feist's acid[19] (Scheme 1). The hydroxymethyl derivative **15** was obtained in 66% yield. When gaseous formaldehyde was replaced by paraformaldehyde the yield of **15** was 50–55%. Reduction with $LiAlH_4$ in THF afforded

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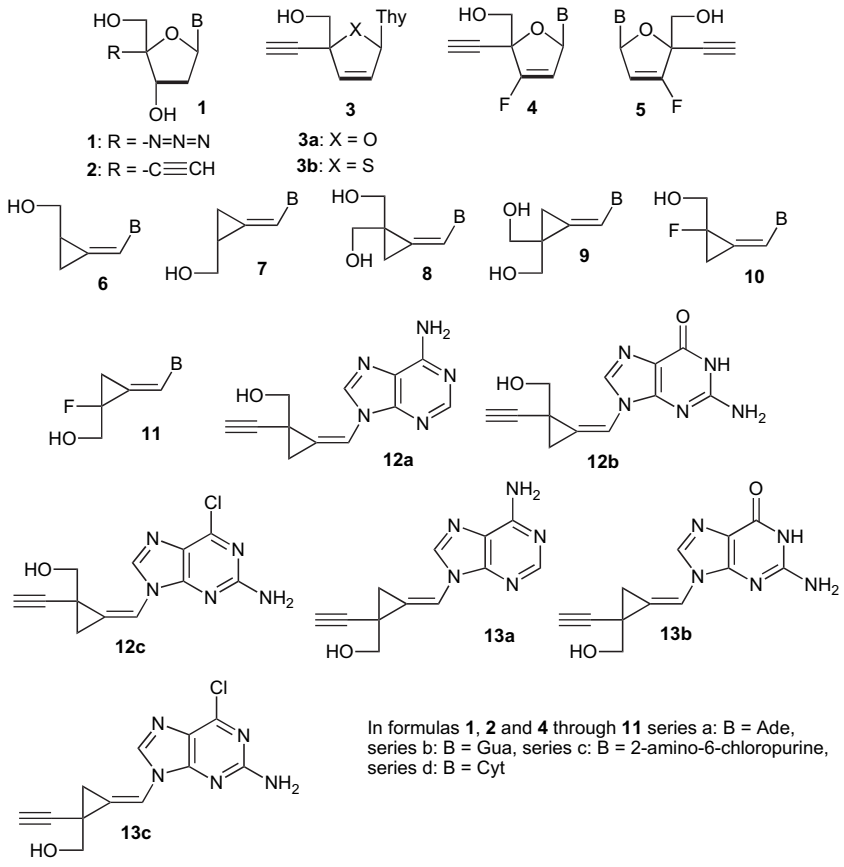
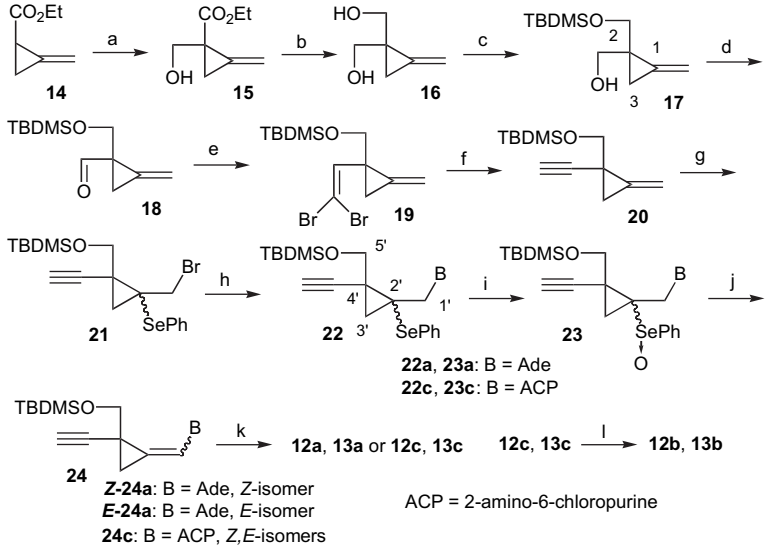


Chart 1.

methylenecyclopropane diol **16** (83%). It should be noted that sequence methylenecyclopropane carboxylate **14**→alcohol **15**→diol **16** is an alternate synthesis of the key intermediate **16** in the synthesis of cyclopropavir[15,20] (**8b**). Selective protection of a single hydroxymethyl group was achieved using 1 M equivalent of TBDMSCl in pyridine and DMAP as a catalyst to give intermediate **17** in 84% yield. Oxidation[21] with pyridinium chlorochromate (PCC)



Scheme 1.

in CH_2Cl_2 gave aldehyde **18** (84%). The aldehyde/ethynyl transformation followed the Corey protocol[22] that was also used for the synthesis of analogues[3] **2**. Thus the reaction of aldehyde **18** with CBr_4–Ph_3P reagent in CH_2Cl_2 afforded dibromoethenyl derivative **19** in 95% yield. Conversion to ethynyl derivative **20** was performed using BuLi in THF at −78 °C under argon (89%). To the best of our knowledge, compound **20** is the first methylenecyclopropane substituted with ethynyl in the cyclopropane portion. The simplest member of this series, methylene-2-ethynylcyclopropane, is an isomer of benzene and it was a subject of a theoretical study.[23] In addition, synthesis of methylenecyclopropane derivatives is of much current interest.[24,25]

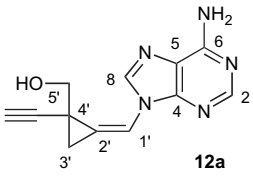
The simultaneous presence of a double and triple bond in **20** might have complicated a selective synthesis of vicinal dibromide for the alkylation–elimination procedure.[12,13] Therefore, a method previously employed for the fluoromethylenecyclopropanes[26] and methylenecyclopropane phosphonates[27] was adapted as follows. Bromoselenenylation of **20** using PhSeBr generated in situ from *N*-bromosuccinimide (NBS) and Ph_2Se_2 in CH_2Cl_2 gave intermediate **21** in 40% yield. Unlike the previous cases, where carbethoxy[26] or phosphonate[27] substituents were capable of directing the addition of PhSeBr to a *syn* face of the double bond, the reaction was not stereoselective giving *cis–trans* isomeric mixture of **21**. Alkylation of adenine with **21** gave compound **22a** (83%). Oxidation with 30% H_2O_2 in CH_2Cl_2 provided crude selenoxide **23a**, which was subjected to thermolysis in toluene at 80 °C to afford the *Z*- and *E*-isomers of compounds ***Z*-24a** and ***E*-24a**, which were separated by chromatography in 43% and 36% yields, respectively. Desilylation of the individual isomers with Bu_4NF in THF gave the target analogues **12a** (87%) and **13a** (90%). In a similar fashion, alkylation of 2-amino-6-chloropurine with **21** gave intermediate **22c** in 79% yield. Oxidation led to crude selenoxide **23c** whose thermolysis furnished the *Z*,*E*-isomeric mixture of silylated methylene-2-ethynylcyclopropane **24c** (81%). Desilylation provided the *Z*- and *E*-isomers **12c** and **13c**, which were separated by chromatography in 41% and 45% yields, respectively. Hydrolytic dechlorination with 80% HCO_2H gave the target guanine analogues **12b** (86%) and **13b** (81%). Elemental analysis indicated the presence of 0.7 mol of silica gel (H_2SiO_3), which must have been already present in starting compounds **12c** and **13c**. Attempts to remove this contaminant by crystallization or chromatography on Dowex 1 ($OH^{(-)}$) column[28] failed but a simple absorption on Dowex 50 ($H^{(+)}$) and elution with water followed by NH_4OH provided pure analogues **12b** and **13b**.

Table 1. Chemical shifts (δ) of the relevant ^1H NMR signals of 2,2-disubstituted methylenecyclopropanes **8a**, **9a**, **8b**, **9b**, **12a**, **13a**, **12b**, and **13b**

Compound[a]	OH	$H_{1'}$	H_8	$C_{3'}$	$C_{4'}$
8a	5.07	7.37	8.82	11.7	31.4
9a	4.76	7.48	8.49	14.4	29.7
8b	4.99	7.07	8.41	11.5	31.3
9b	4.76	7.21	8.03	14.3	29.5
12a	5.47	7.47	8.62	15.7	20.0
13a	5.14	7.63	8.48	18.5	18.8
12b	5.42	7.16	8.18	15.6	19.9
13b	5.13	7.35	8.02	18.3	18.6

[a] CD_3SOCD_3 as solvent. For numbering of signals, see Table 2. Values for **8a**, **9a**, **8b**, and **9b** were taken from Ref. 15.

Table 2. The NOE enhancements of relevant ^1H NMR signals of methylene-2-ethynylcyclopropanes **12a** and **13a**



Compound	H_{iir}	δ	H_{obs}	δ	NOE (%)
12a	H_8	8.62	$H_{5'}$	3.32	3.92
	$H_{5'}$	3.83	H_8	8.62	1.30
	$H_{5'}$	3.32	H_8	8.62	0.85
	H_8	8.62	C≡CH	3.04	0.53
	C≡CH	3.06	H_8	8.62	0.87
	OH	5.46	H_8	8.62	3.24
	$H_{3'}$	1.85–1.81	$H_{1'}$	7.48	1.88
	$H_{1'}$	7.47	$H_{3'}$	1.85–1.81	2.20
13a	H_8	8.48	$H_{3'}$	2.00	1.53
	$H_{3'}$	2.00	H_8	8.48	5.08
	$H_{3'}$	2.00	$H_{1'}$	7.63	0.48

As in previous cases[12–14] of methylenecyclopropane analogues, the *Z*-isomers **12** are always less polar, moving faster on silica gel, than *E*-isomers **13**. Comparison of the ^1H and ^{13}C NMR chemical shifts of **12a**, **12b**, **13a**, and **13b** gave patterns comparable with the reference compounds **8a**, **8b**, **9a**, and **9b** (Table 1). Thus, the H_8, OH, and $C_{4'}$ signals of the *Z*-isomers **8a**, **8b**, **12a**, and **12b** are located downfield from those of the *E*-isomers **9a**, **9b**, **13a**, and **13b**. An opposite trend was observed in the $H_{1'}$ and $C_{3'}$ chemical shifts. These assignments were confirmed by NOE experiments (Table 2). In the *Z*-isomer **12a**, the NOE enhancements were observed between the *cis*-orientated protons of H_8 and $H_{5'}$, C≡CH, and OH whereas none were seen between the H_8 and *trans*-positioned $H_{3'}$. By contrast, the NOE interactions were noted between the H_8 and $H_{3'}$ of the *E*-isomer **13a**. As expected, the enhancements between the *cis*-configured $H_{1'}$ and $H_{3'}$ were much stronger in the *Z*-isomer **12a** than in *E*-isomer **13a** where this relationship is *trans*.

The antiviral activity of analogues **12a**, **13a**, **12b**, and **13b** was tested against the following viruses: HIV-1, HBV, HSV-1, HSV-2, HCMV, VZV, and EBV. The adenine *Z*-analogue **12a** had EC_{50} >3.2 μM against EBV in Akata cell culture but this effect was poorly separated from cytotoxicity (CC_{50} 13.2 μM). The EC_{50} of acyclovir used as a control was 4.3 μM. No significant activity was found against other tested viruses. The adenine *E*-isomer **13a** was deaminated from 70% after 24 h incubation with adenosine deaminase (ADA) at room temperature whereas the *Z*-isomer **12a** was resistant. The reactivity toward ADA-catalyzed deamination (*E*-isomer>*Z*-isomer) is in accord with the previous results.[12,13]

3. Conclusions

The synthesis of methylene-2-ethynylcyclopropane analogues of purine nucleosides **12a**, **12b**, **13a**, and **13b** is described. A new method of preparation of methylenecyclopropane diol **16**, a key intermediate in the synthesis of anticytomegalovirus agent cyclopropavir (**8b**) is also reported.

The first synthesis of a methylene-2-ethynylcyclopropane scaffold can be of interest in areas other than nucleoside analogues. The adenine *Z*-isomer **12a** inhibited the replication of EBV but it was cytotoxic. The *E*-isomer **13a** is a substrate for adenosine deaminase.

4. Experimental

4.1. General methods

The UV spectra were measured in ethanol and NMR spectra were determined at 300 or 400 MHz (^{1}H), 75 or 100 MHz (^{13}C) in CD_3SOCD_3 unless otherwise stated. Mass spectra were determined in electrospray ionization mode (ESI-MS, methanol–NaCl).

4.1.1. Ethyl 2-hydroxymethyl-1-methylenecyclopropane 2-carboxylate (15). *Using gaseous formaldehyde*. A stirred mixture of ethyl methylenecyclopropane carboxylate[18] (**14**, 2.78 g, 22.2 mmol) and LiCl (5.67 g, 0.13 mol, dried at room temperature and 0.01–0.02 Torr for 48 h and 80–90 °C/0.2 Torr for 3 h) in THF (90 mL) was kept under Ar at −78 °C. After 10 min, LDA in THF (1.8 M, 14.83 mL, 26.7 mmol) was added dropwise during 15 min. The stirring was continued for 45 min whereupon gaseous formaldehyde generated from paraformaldehyde (1.32 g, 44 mmol, dried for 2 days over P_2O_5 at room temperature and atmospheric pressure) at 180–200 °C was introduced into the reaction mixture. The stirring was continued for another 30 min at −78 °C. The reaction was quenched with 5% HCl (5%, 50 mL), THF was evaporated in vacuo, and ether (200 mL) was added. The organic phase was successively washed with HCl (5%, 3×30 mL), water (3×30 mL), and aqueous sodium hydrogen carbonate (3×30 mL), and it was dried with sodium sulfate. Evaporation of the solvent gave the crude product, which was chromatographed on a silica gel column in hexanes–Et_2O (10:1 to 5:1 to 3:1) to give 2.27 g (66%) of compound **15** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H, J=7.2 Hz, CH_3), 1.57 (dt, 1H, J=9.2, 2.4 Hz), 2.05 (d, 1H, J=8.8 Hz, H_3), 2.42 (br s, 1H, OH), 3.57, 3.85 (AB, 2H, J_{AB}=12.2 Hz, CH_2OH), 4.15 (m, 2H, CH_2 of Et), 5.48 (t, 1H, J=1.6 Hz), 5.52 (t, 1H, J=5.6 Hz, CH_2=). ^{13}C NMR 14.3 (C_3), 17.0 (CH_3), 30.0 (C_2), 61.3 (CH_2 of Et), 65.1 (CH_2OH), 104.4 (CH_2=), 133.4 (C_1), 173.1 (CO). ESI-MS 157.0 (M+H, 10.5), 179.0 (M+Na, 100.0).

Using paraformaldehyde. A stirred mixture of compound **14** (250 mg, 2 mmol), LiCl (510 mg, 12 mmol), and LDA (2.4 mmol) obtained as described in Method A was kept under N_2 at −78 °C for 45 min. Paraformaldehyde (180 mg, 6 mmol) was added and the stirring was continued for 30 min. The work-up followed the procedure described in Method A. Chromatography in hexanes–ether (5:1–3:1) afforded compound **15** (160 mg, 51%) identical with the product obtained by Method A.

4.1.2. 2,2-Bis(hydroxymethyl)-1-methylenecyclopropane (16). $LiAlH_4$ (1.62 g, 42.6 mmol) was added in portions to a solution of compound **15** (5.5 g, 35.2 mmol) in THF (55 mL) with stirring and external ice cooling. The mixture was then refluxed for 4 h, cooled, and aqueous NaOH (10%, 8 mL) was added. The insoluble portion was filtered off and the filter cake was washed with EtOAc (150 mL). Evaporation of the solvent gave the crude product, which was chromatographed on a silica gel column in hexanes–Et_2O (10:1–3:1) to give diol **16** (3.34 g, 83%) as a colorless oil, which was identical (^{1}H NMR) with an authentic sample.[15,20] ^{13}C NMR ($CDCl_3$) 13.6 (C_3), 28.4 (C_2), 67.2 (CH_2OH), 104.5 (CH_2=), 135.5 (C_1).

4.1.3. 2-*tert*-Butyldimethylsilyloxymethyl-2-hydroxymethyl-1-methylenecyclopropane (17). Diol **16** (3.2 g, 28.1 mmol) was dissolved in CH_2Cl_2 (20 mL). TBDMSCl (4.2 g, 28 mmol), DMAP (0.5 g, 4.1 mmol), and pyridine (6.4 mL, 82.7 mmol) were added and the mixture was stirred for 24 h at room temperature. The volatile components were evaporated and the residue was chromatographed on a silica gel column in hexane–Et_2O (10:1–6:1) to give product **17** (5.25 g, 82%) as a colorless oil. A sample for analysis was distilled at 50–55 °C (bath temperature) and 0.15 Torr. ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, CH_3 of *t*-Bu), 1.14, 1.25 (AB, 2H, $J_{AB=}$8.4 Hz, H_3), 2.73 (br s, 1H, OH), 3.56 (d, 2H, J=10.0 Hz), 3.75, 3.79 (2d, 2H, J=11.2, 10.8 Hz, CH_2OH, $CH_2OTBDMS$), 5.37 (s, 1H), 5.44 (t, 1H, J=3.2 Hz, CH_2=). ^{13}C NMR −5.24, −5.21 ($Si(CH_3)_2$), 13.9 (C_3), 18.4 (C of *t*-Bu), 26.1 (CH_3 of *t*-Bu), 28.1 (C_2), 67.8, 68.6 (CH_2OH, $CH_2OTBDMS$), 104.2 (CH_2=), 135.9 (C_1). ESI-MS 229 (M+H, 7.4), 251 (M+Na, 100.0). Anal. Calcd for $C_{12}H_{24}O_2Si$: C, 63.10; H, 10.59. Found: C, 62.82; H, 10.81.

4.1.4. 2-*tert*-Butyldimethylsilyloxymethyl-2-formyl-1-methylenecyclopropane (18). Compound **17** (5.2 g, 22.8 mmol) was dissolved in CH_2Cl_2 (40 mL) and PCC (10.29 g, 27.4 mmol) was added in portions at room temperature with stirring, which was continued for 34 h. The solids were filtered off, washed with ether (100 mL), and the filtrate was concentrated. The crude product was chromatographed on a silica gel column in hexanes–Et_2O (30:1–10:1) to give aldehyde **18** (4.31 g, 83.5%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.02 (s, 6H, $Si(CH_3)_2$, 0.84 (s, 9H, CH_3 of *t*-Bu), 1.84 (m, 2H, H_3), 3.75, 4.05 (AB, 2H, J_{AB}=13.6 Hz, CH_2O), 5.52 (t, 1H, J=3.6 Hz), 5.58 (poorly resolved t, 1H, CH_2=), 8.78 (s, 1H, CH=O). ^{13}C NMR −5.30, −5.26 ($Si(CH_3)_2$), 14.2 (C_3), 18.5 (C of *t*-Bu), 26.0 (CH_3 of *t*-Bu), 39.6 (C_2), 60.6 (CH_2O), 107.0 (CH_2=), 131.7 (C_1), 197.3 (CH=O). ESI-MS 227 (M+H, 100.0), 249 (M+Na, 80.1).

4.1.5. 2-*tert*-Butyldimethylsilyloxymethyl-2-(2,2-dibromoethenyl)-1-methylenecyclopropane (19). A mixture of aldehyde **18** (4.30 g, 19.0 mmol), CBr_4 (12.62 g, 38.0 mmol), and Ph_3P (19.91 g, 76 mmol) in CH_2Cl_2 (100 mL) was stirred for 1 h at 0 °C and then 30 min at room temperature. Triethylamine (16 mL, 0.115 mol) was added and the mixture was poured into hexane (400 mL). The insoluble portion was filtered off and the filtrate was concentrated. The crude product was chromatographed on a silica gel column using hexanes–Et_2O (100:0–50:1) to give compound **19** as a colorless oil (6.87 g, 94.6%). ^{1}H NMR ($CDCl_3$) δ 0.04, 0.05 (2s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, CH_3 of *t*-Bu), 1.41 (m, 2H, H_3), 3.56, 3.75 (AB, 2H, J_{AB}=9.8 Hz, CH_2O), 5.45 (s, 1H), 5.65 (t, 1H, J=2.8 Hz, CH_2=), 6.64 (s, 1H, CH=). ^{13}C NMR −5.1 ($Si(CH_3)_2$), 15.2 (C_3), 18.6 (C of *t*-Bu), 26.1 (CH_3 of *t*-Bu), 29.5 (C_2), 66.8 (CH_2O), 93.3 (CBr_2=), 105.5

(CH_2=), 135.6 (C_1), 137.5 (CH=). Compound **19** is not stable under the conditions of MS.

4.1.6. 2-*tert*-Butyldimethylsilyloxymethyl-2-ethynyl-1-methylenecyclopropane (20). BuLi (2.5 M in hexanes, 17.8 mL, 44.5 mmol) was added to a solution of compound **19** (6.8 g, 17.79 mmol) in THF (60 mL) at −78 °C under Ar and the mixture was stirred for 30 min at the same temperature. After addition of water (100 mL), the mixture was warmed to room temperature whereupon it was extracted with Et_2O (4×50 mL). The organic phase was dried over $MgSO_4$ and the solvent was evaporated. The residue was chromatographed on a silica gel column using pentane to give compound **20** (3.52 g, 89%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.06, 0.07 (2s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, CH_3 of *t*-Bu), 1.52 (dt, 1H, J=8.8, 2.4 Hz), 1.59 (m, 1H, H_3), 1.95 (s, 1H, C≡CH), 3.59, 3.72 (AB, 2H, J_{AB}=10.6 Hz, CH_2O), 5.45 (t, 1H, J=4.4 Hz), 5.59 (t, 1H, J=5.6 Hz, CH_2=). ^{13}C NMR −5.03, −5.00 ($Si(CH_3)_2$), 16.7 (C_3), 18.1 (C_2), 18.6 (C of *t*-Bu), 26.1 (CH_3 of *t*-Bu), 66.0 (≡CH), 66.8 (CH_2O), 85.7 (C≡), 104.5 (CH_2=), 134.9 (C_1). ESI-MS (MeOH+NaCl+KOAc) 118 (100.0), 245 (M+Na, 48.8), 261 (M+K, 30.4). Anal. Calcd for $C_{13}H_{22}OSi\cdot 0.15H_2SiO_3$: C, 66.69; H, 9.60. Found: C, 66.80; H, 9.41. A sample of **20** was distilled at room temperature and 0.15 Torr (the receiver was cooled in dry ice–acetone mixture). Anal. Calcd for $C_{13}H_{22}OSi\cdot 0.3H_2O$: C, 68.54; H, 10.00. Found: C, 68.18; H, 9.56.

4.1.7. (*cis*,*trans*)-1-Bromomethyl-2-ethynyl-2-*tert*-butyldimethylsilyloxymethyl-1-phenylselenenylcyclopropane (21). NBS (2.81 g, 15.8 mmol) and Ph_2Se_2 (2.46 g, 7.88 mmol) were added to a stirred solution of compound **20** (3.5 g, 15.8 mmol) in CH_2Cl_2 (45 mL) at −20 °C. The stirring was continued for 10 min at −20 °C and 15 min at −10 °C. Solvent was evaporated and the residue was chromatographed on a silica gel column using hexanes–Et_2O (100:1–50:1) to give product **21** (2.93 g, 40.4%) as a colorless oil (isomeric ratio 2:1). ^{1}H NMR ($CDCl_3$) δ 0.08, 0.11, 0.12 (3s, 6H, $Si(CH_3)_2$), 0.89, 0.93 (2s, 9H, CH_3 of *t*-Bu), 1.22 (J=6.4 Hz), 1.35 (J=6.0 Hz), 1.52, 1.49 (AB, 2H, J_{AB}=5.6 Hz, $H_{3'}$), 2.12, 2.21 (2s, 1H, C≡CH), 3.73, 3.94, 4.05, 4.24 (m, 4H, CH_2Br, CH_2O), 7.25–7.30, 7.63–7.65, 7.68–7.70 (3m, 5H, Ph). ESI-MS 479, 481, 483 (M+Na, 44.8, 100.0, 80.0).

4.1.8. (*cis*,*trans*)-9-[(2-*tert*-Butyldimethylsilyloxymethyl-2-ethynyl-1-phenylselenenyl-1-cyclopropyl)methyl]adenine (22a). A mixture of compound **21** (150 mg, 0.33 mmol), adenine (50 mg, 0.37 mmol), and K_2CO_3 (140 mg, 1.01 mmol) in DMF (15 mL) was stirred for 16 h at room temperature. The insoluble portion was filtered through a silica gel pad, which washed with DMF (45 mL). Solvent was evaporated in vacuo and the residue was chromatographed on a silica gel column using hexanes–EtOAc (2:1 to 100% EtOAc) to give the product **22a** (140 mg, 83%) as a white solid, mp 154–155 °C. UV λ_{max} 203 (ε 27,000), 263 nm (ε 12,900). ^{1}H NMR ($CDCl_3$) δ 0.13, 0.16, 0.18, 0.21 (4s, 6H, $Si(CH_3)_2$), 0.967, 0.972 (2s, 9H, CH_3 of *t*-Bu), 1.24, 1.87 (J=5.6 Hz) 1.32, 1.68 (2AB, 4H, J=6.4 Hz, H_3), 2.16, 2.18 (2s, 1H, C≡CH), 4.90, 4.13 (J=14.4 Hz), 4.58, 4.44 (J=14.4 Hz), 4.47, 3.92 (J=11.6 Hz), 4.26, 3.91 (four partly overlapped AB, 4H, J=10.4 Hz, $H_{1'}$, $H_{5'}$), 5.86, 5.97 (2br s, 2H, NH_2), 7.20–7.28, 7.47–7.49, 7.67–7.69 (3m, 5H, Ph), 7.84, 8.25, 8.29, 8.33 (4s, 2H, H_8, H_2). ESI-MS (MeOH) 512, 514 (M+H, 51.8, 100.0).

4.1.9. (*Z*)- and (*E*)-9-[2-(*tert*-Butyldimethylsilyloxymethyl-2-ethynylcyclopropylidene)methyl]adenine (*Z*-24a) and (*E*-24a). Aqueous H_2O_2 (30%, 1.4 mL, 12.3 mmol) was added dropwise to a solution of compound **22a** (1.80 g, 3.51 mmol) in CH_2Cl_2 (35 mL) at room temperature with stirring. The stirring was continued for 3.5 h and the solvent was evaporated to give a crude selenoxide **23a** (1.85 g, 100%). UV λ_{max} 203 (ε 24,400), 260 nm (ε 10,900). ESI-MS 528, 530 (M+H, 51.5, 100.0). A solution of this product (1.85 g, 3.5 mmol) in toluene (40 mL) was stirred at 80 °C for 20 min. Solvent was evaporated and the residue was chromatographed on a silica gel column using EtOAc–hexanes (2:1 to 100% EtOAc) to give the faster moving *Z*-isomer ***Z*-24a** (540 mg, 42.8%) followed by *E*-isomer ***E*-24a** (450 mg, 35.7%). In addition, phenylselenenyl derivative **22a** (100 mg, 5.6%) was also obtained.

Z-isomer ***Z*-24a**: mp 185–187 °C. UV λ_{max} 229 (ε 26,400), 279 nm (ε 9700). ^{1}H NMR ($CDCl_3$) δ 0.04, 0.06 (2s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, CH_3 of *t*-Bu), 1.76, 1.89 (dAB, 2H, J_{AB}=9.0, 1.6 Hz, $H_{3'}$), 2.11 (s, 1H, C≡CH), 3.49, 4.13 (2d, 2H, J=9.6 Hz, $H_{5'}$), 5.95 (s, 2H, NH_2), 7.53 (s, 1H, $H_{1'}$), 8.38 (s, 1H, H_2), 8.75 (s, 1H, H_8). ^{13}C NMR −5.24, −5.18 ($Si(CH_3)_2$), 15.5 ($C_{3'}$), 18.7 (C of *t*-Bu), 19.8 ($C_{4'}$), 26.06, 26.08 (CH_3 of *t*-Bu), 67.6 (≡CH), 68.78, 68.85 ($C_{5'}$), 83.2 (≡C), 111.4 ($C_{1'}$), 115.7 ($C_{2'}$), 119.5 (C_5), 139.2 (C_8), 149.0 (C_4), 153.3 (C_2), 155.6 (C_6). ESI-MS 356 (M+H, 100.0), 378 (M+Na, 47.8).

E-isomer ***E*-24a**: mp 164–165 °C. UV λ_{max} 228 (ε 28,800), 278 nm (ε 9500). ^{1}H NMR ($CDCl_3$) δ 0.062, 0.078 (2s, 6H, CH_3 of $Si(CH_3)_2$), 0.87 (s, 9H, CH_3 of *t*-Bu), 1.97 (m, 2H, $H_{3'}$), 2.04 (s, 1H, C≡CH), 3.77, 3.82 (AB, 2H, J_{AB}=10.4 Hz, $H_{5'}$), 6.03 (s, 2H, NH_2), 7.71 (s, 1H, $H_{1'}$), 8.22, 8.39 (2s, 2H, H_2, H_8). ^{13}C NMR −5.07, −5.04 ($Si(CH_3)_2$), 17.5 ($C_{3'}$), 18.4, 18.6 (C of *t*-Bu, $C_{4'}$), 26.03, 26.04 (CH_3 of *t*-Bu), 66.0 (≡CH), 67.50, 67.56 ($C_{5'}$), 83.9 (≡C), 112.2 ($C_{1'}$), 116.4 ($C_{2'}$), 119.6 (C_5), 137.3 (C_8), 149.2 (C_4), 153.6 (C_2), 155.7 (C_6). ESI-MS 356 (M+H, 100.0), 378 (M+Na, 14.7).

4.1.10. (*Z*)-9-[(2-Hydroxymethyl-2-ethynylcyclopropylidene)methyl]adenine (12a). A mixture of the *Z*-isomer ***Z*-24a** (450 mg, 1.11 mmol) and tetrabutylammonium fluoride (1.0 M in THF, 1.5 mL, 1.5 mmol) in THF (12.5 mL) was stirred at room temperature for 2 h. The solvent was removed and the residue was chromatographed on a silica gel column using EtOAc–MeOH (30:0–20:1) to give the *Z*-isomer **12a** (263 mg, 87.2%), mp 197–199 °C. UV λ_{max} 226 (ε 30,600), 276 nm (ε 10,900). ^{1}H NMR δ 1.85, 1.81 (AB, 2H, J_{AB}=9.0 Hz, $H_{3'}$), 3.06 (s, 1H, C≡CH), 3.36, 3.39, 3.84, 3.87 (2AB, 1H, J_{AB}=5.6 Hz, $H_{5'}$), 5.47 (t, 1H, J=5.6 Hz, OH), 7.37 (s, 2H, NH_2), 7.47 (s, 1H, $H_{1'}$), 8.18 (s, 1H, H_2), 8.62 (s, 1H, H_8). ^{13}C NMR 15.7 ($C_{3'}$), 20.0 ($C_{4'}$), 65.9 ($C_{5'}$), 71.3 (≡CH), 84.5 (≡C), 111.2 ($C_{1'}$), 116.3 ($C_{2'}$), 118.9 (C_5), 138.2 (C_8), 148.7 (C_4), 153.9 (C_2), 156.8 (C_6). ESI-MS 242 (M+H, 95.2), 264 (M+Na, 100.0). Anal. Calcd for $C_{12}H_{11}N_5O\cdot 0.15H_2O$: C, 59.08; H, 4.67; N, 28.70. Found: C, 59.24; H, 4.71; N, 28.43.

4.1.11. (*E*)-9-[(2-Hydroxymethyl-2-ethynylcyclopropylidene)methyl]adenine (13a). The protocol described for the *Z*-isomer **12a** was followed with the *E*-isomer ***E*-24a** (400 mg, 0.99 mmol) to give compound **13a** (240 mg, 89.6%), mp 217–219 °C. UV λ_{max} 226 (ε 29,700), 276 nm (ε 10,100). ^{1}H NMR δ 2.01, 1.96 (dAB, 2H, J_{AB}=8.4, 1.6 Hz, $H_{3'}$), 2.91 (s, 1H, C≡CH), 3.45–3.54 (two overlapped AB, 2H, $H_{5'}$), 5.14 (t, 1H, J=6.2 Hz, OH), 7.36 (s, 2H, NH_2), 7.63 (s, 1H, $H_{1'}$), 8.18 (s, 1H, H_2), 8.48 (s, 1H, H_8). ^{13}C NMR 18.5 ($C_{3'}$), 18.8 ($C_{4'}$), 65.8 ($C_{5'}$), 70.1 (≡CH), 85.6 (≡C), 112.1 ($C_{2'}$), 117.4 ($C_{1'}$), 119.1 (C_5), 138.1 (C_8), 149.1 (C_4), 153.9 (C_2), 156.8 (C_6). ESI-MS 242 (M+H, 100.0), 264 (M+Na, 30.5). Anal. Calcd for $C_{12}H_{11}N_5O\cdot0.2H_2O$: C, 58.86; H, 4.69; N, 28.60. Found: C, 59.01; H, 4.67; N, 28.35.

4.1.12. (*cis*,*trans*)-2-Amino-6-chloro-9-[(2-*tert*-butyldimethylsilyloxymethyl-2-ethynyl-1-phenylselenenyl-1-cyclopropyl)methyl]purine (22c). A mixture of compound **21** (2.02 g, 4.41 mmol), 2-amino-6-chloropurine (785 mg, 4.64 mmol), and K_2CO_3 (183 mg, 13.26 mmol) in DMF (25 mL) was stirred for 24 h at room temperature. The work-up followed the protocol described for compound **22a**. Chromatography in hexanes–EtOAc (5:1–2:1) gave product **22c** (1.91 g, 79.2%) as a white solid, mp 137–139 °C. UV λ_{max} 222 (ε 28,900), 243 (ε 9100), 311 nm (ε 8200). ^{1}H NMR ($CDCl_3$) δ 0.09, 0.13, 0.14, 0.18 (4s, 6H, $Si(CH_3)_2$), 0.92, 0.93 (2s, 9H, CH_3 of *t*-Bu), 1.26, 1.75, 1.29, 1.63 (2AB, 2H, J=5.6–6.4 Hz, $H_{3'}$), 2.15, 2.18 (2s, 1H, C≡CH), 3.82, 3.87, 4.04, 4.20, 4.32, 4.40, 4.41, 4.68 (four partly overlapped AB, J=10.4–15.6 Hz, 4H, $H_{1'}$, $H_{5'}$), 5.43 (br s, 2H, NH_2), 7.17–7.28 (m, 3H), 7.43 (poorly resolved dd, 1H), 7.60 (poorly resolved dd, 1H, Ph), 7.75, 8.11 (2s, 1H, H_8). ESI-MS (MeOH) 546, 548, 550 (M+H, 40.4, 81.1, 41.6), 88 (100.0).

4.1.13. (*Z*,*E*)-2-Amino-6-chloro-9-[(2-*tert*-butyldimethylsilyloxymethyl-2-ethynyl-cyclopropylidene)methyl]purine (24c). The procedure described for adenine derivatives ***Z*-24a** and ***E*-24a** was followed using compound **22c** (1.85 g, 3.38 mmol) and 30% H_2O_2 (30%, 1.15 mL, 10.1 mmol), reaction time 1 h to give crude selenoxide **23c** (1.90 g, 99.8%). UV λ_{max} 222 (ε 27,000), 245 (ε 9100), 310 nm (ε 7300). ESI-MS 562, 564, 566 (M+H, 49.7, 100.0, 50.6), 600, 602, 604 (M+Na, 13.2, 24.0, 11.4). Thermolysis of this product in toluene (35 mL) at 80–85 °C for 20 min gave, after chromatography in EtOAc–hexanes (4:1–1:1), the *Z*,*E*-isomeric mixture **24c** (948 mg, 81%), mp 162–164 °C. UV λ_{max} 234 (ε 30,000), 311 nm (ε 7900). ^{1}H NMR ($CDCl_3$) δ 0.04, 0.05, 0.06, 0.08 (4s, 6H, $Si(CH_3)_2$), 0.86, 0.87 (2s, CH_3 of *t*-Bu), 1.77, 1.88 (split AB, 1H, J_{AB}=8.8 Hz), 1.97 (poorly resolved t, 1H, $H_{3'}$), 2.04, 2.10 (2s, 1H, C≡CH), 3.51, 4.09 (AB, J_{AB}=10.6 Hz), 3.79 (s, 2H, $H_{5'}$), 5.18 (s, 2H, NH_2), 7.35, 7.54 (2s, 1H, $H_{1'}$), 8.66, 8.15 (2s, 1H, H_8). ESI-MS 88 (100.0), 390, 392 (M+H, 78.4, 29.0), 412, 414 (M+Na, 17.4, 6.0). In addition, phenylselenenyl derivative **22c** (210 mg, 11.4%) was obtained.

4.1.14. (*Z*)- and (*E*)-2-Amino-6-chloro-9-[(2-hydroxymethyl-2-ethynylcyclopropylidene)methyl]purine (12c) and (13c). Tetrabutylammonium fluoride (1.0 M in THF, 2.5 mL, 2.5 mmol) was added dropwise with stirring at room temperature into isomeric mixture **24c** (0.9 g, 2.31 mmol) in THF (15 mL). The stirring was continued for 30 min, THF was evaporated, and the residue was chromatographed on a silica gel column using hexanes–EtOAc (2:1–1:4) to give the *Z*-isomer **12c** (262 mg, 41.2%) followed by *E*-isomer **13c** (285 mg, 44.8%).

Z-isomer **12c**: mp 184–186 °C. UV λ_{max} 233 (ε 30,900), 311 nm (ε 8100). ^{1}H NMR δ 1.83 (two overlapped AB, 2H, $H_{3'}$), 3.07 (s, 1H, C≡CH), 3.31, 3.85, 3.87 (2AB, overlapped with H_2O, J=4.8–6.4 Hz), 5.47 (t, 1H, J=5.8 Hz, OH), 7.06 (s, 2H, NH_2), 7.28 (s, 1H, $H_{1'}$), 8.59 (s, 1H, H_8). ^{13}C NMR 15.8 ($C_{3'}$), 20.1 ($C_{4'}$), 65.9 ($C_{5'}$), 71.5 (≡CH), 84.4 (C≡), 110.8 ($C_{1'}$), 117.1 ($C_{2'}$), 123.6 (C_5), 140.2 (C_8), 150.5 (C_4), 153.0 (C_2), 160.9 (C_6). ESI-MS 186 (100.0), 276, 278 (M+H, 40.7, 12.0), 298, 300 (M+Na, 21.9, 6.9).

E-isomer **13c**: mp 190–191 °C. UV λ_{max} 232 (ε 30,500), 311 (ε 7900). ^{1}H NMR 1.95, 2.02 (dAB, 2H, J_{AB}=9.8, 1.6 Hz, $H_{3'}$), 2.92 (s, 1H, C≡CH), 3.43, 3.53, 3.46, 3.51 (2AB, 2H, J_{AB}=6.4, 5.6 Hz, $H_{5'}$), 5.15 (t, 1H, J=6.2 Hz, OH), 7.03 (s, 2H, NH_2), 7.47 (s, 1H, $H_{1'}$), 8.43 (s, 1H, H_8). ^{13}C NMR 18.7 ($C_{3'}$), 18.9 ($C_{4'}$), 65.8 ($C_{5'}$), 70.1 (≡CH), 85.5 (C≡), 111.8 ($C_{1'}$), 118.5 ($C_{2'}$), 123.8 (C_5), 140.4 (C_8), 150.4 (C_4), 153.4 (C_2), 160.8 (C_6). ESI-MS (MeOH+KOAc) 123 (100.0), 314, 316 (M+K, 48, 20).

4.1.15. (*Z*)-9-[(2-Hydroxymethyl-2-ethynylcyclopropylidene)methyl]guanine (12b). A solution of compound **12c** (150 mg, 0.544 mmol) in formic acid (80%, 12 mL) was heated at 80 °C with stirring for 3 h. After cooling, the volatile components were evaporated in vacuo and the residue was stirred in 4% NH_3 in methanol (50 mL) at 0 °C for 1 h. NH_3 and methanol were evaporated and the product was recrystallized from methanol to give the *Z*-isomer **12b** (120 mg, 86%, mp >300 °C. UV λ_{max} 232 (ε 25,000), 273 nm (ε 10,600). ^{1}H NMR δ 1.77, 1.80 (AB, 2H, J_{AB}=8.6 Hz, $H_{3'}$), 3.05 (s, 1H, C≡CH), 2.76–3.84, 3.32–3.38 (2AB partly overlapped with H_2O), 5.42 (t, 1H, J=5.6 Hz, OH), 6.68 (s, 2H, NH_2), 7.16 (s, 1H, $H_{1'}$), 8.18 (s, 1H, H_8), 10.81 (s, 1H, NH). ^{13}C NMR 15.6 ($C_{3'}$), 19.9 ($C_{4'}$), 65.7 ($C_{5'}$), 71.3 (≡CH), 84.5 (C≡), 111.1 ($C_{1'}$), 115.8 ($C_{2'}$), 116.8 (C_5), 134.7 (C_8), 150.4 (C_4), 155.0 (C_2), 157.3 (C_6). ESI-MS 107 (100.0), 258 (M+H, 5.3), 280 (M+Na, 35.9), 537 (2M+Na, 12.2). Anal. Calcd for $C_{12}H_{11}N_5O_2\cdot0.7H_2SiO_3$: C, 46.21; H, 4.01; N, 22.45. Found: C, 46.25; H, 4.04; N, 22.79. The silica gel was removed from this product as follows. Compound **12b** (67 mg, 0.22 mmol) was absorbed on Dowex 50 ($H^{(+)}$, 100–200 mesh, 3.5×1.8 cm) column as an aqueous suspension. The column was eluted with water (50 mL) and NH_4OH (28%, 100 mL). The latter eluate was concentrated and the resultant solid was washed with $CHCl_3$ (25 mL) and water (25 mL). It was dried at 0.03–0.04 Torr and room temperature for 24 h to give the *Z*-isomer **12b** (57.4 mg, 97%). UV λ_{max} 232 (ε 26,000), 271 nm (ε 11,000). Mp and ^{1}H NMR were identical with that of the product containing silica gel. Anal. Calcd for $C_{12}H_{11}N_5O_2\cdot0.65H_2O$: C, 53.59; H, 4.61; N, 26.04. Found: C, 53.59; H, 4.37; N, 25.71.

4.1.16. (*E*)-9-[(2-Hydroxymethyl-2-ethynylcyclopropylidene)methyl]guanine (13b). The protocol for the *Z*-isomer **12b** was followed using *E*-isomer **13c** (190 mg, 0.69 mmol)

to give compound **13b** (143 mg, 81%), mp >300 °C. UV λ_{max} 232 (ε 23,400), 273 nm (ε 10,000). ^{1}H NMR δ 1.90, 1.96 (AB, 2H, J_{AB}=9.0 Hz, $H_{3'}$), 2.89 (s, 1H, C≡CH), 3.40–3.51 (m, 2H, $H_{5'}$), 5.13 (poorly resolved t, 1H, OH), 6.61 (s, 2H, NH_2), 7.35 (s, 1H, $H_{1'}$), 8.02 (s, 1H, H_8), 10.78 (s, 1H, NH). ^{13}C NMR 18.3 ($C_{3'}$), 18.6 ($C_{4'}$), 65.8 ($C_{5'}$), 69.9 (≡CH), 85.7 (C≡), 112.0 ($C_{1'}$), 117.0, 117.1 ($C_{2'}$, C_5), 134.5 (C_8), 150.7 (C_4), 154.9 (C_2), 157.3 (C_6). ESI-MS 258 (M+H, 32.8), 280 (M+Na, 100.0), 537 (2M+Na, 21.3). Anal. Calcd for $C_{12}H_{11}N_5O_2 \cdot 0.7H_2SiO_3$: C, 46.21; H, 4.01; N, 22.45. Found: C, 46.24; H, 4.17; N, 22.83. The silica gel was removed as described for the *Z*-isomer **12b** to give the *E*-isomer **13b**. UV λ_{max} 232 (ε 27,500), 271 nm (ε 11,500). Mp and ^{1}H NMR were identical with that of the product containing silica gel. Anal. Calcd for $C_{12}H_{11}N_5O_2 \cdot 0.65H_2O$: C, 53.59; H, 4.61; N, 26.04. Found: C, 53.54; H, 4.37; N, 25.71.

4.1.17. Adenosine deaminase (ADA) assay. Compounds **12a** and **13a** (2.2 μmol) were magnetically stirred with ADA from calf intestine (Worthington Biochemical Corp., Lakewood, New Jersey, dry powder, 0.59 U) in 0.05 M Na_2HPO_4 (pH 7.4, 0.4 mL) at room temperature. Aliquots were periodically withdrawn and examined by TLC in CH_2Cl_2–MeOH (10:1). The extent of deamination of **13a** was 70–75% after 24 h. Compound **12a** was not deaminated.

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