Published in final edited form as:

Tetrahedron. 2005 July 25; 61(30): 7112–7116.

A New Alkylation-Elimination Method for Synthesis of Antiviral Fluoromethylenecyclopropane Analogues of Nucleosides

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Abstract

A new method for the synthesis of fluoromethylenecyclopropane nucleosides by alkylation-elimination procedure is described. Fluorination of methylenecyclopropane carboxylate **6** gave fluoroester **7**. Treatment of **7** with phenylselenenyl bromide afforded the desired ethyl (*E*)-2-bromomethyl-1-fluoro-2-phenylselenenylcyclopropane-1-carboxylate **11** in 85% yield. DIBALH reduction of **11** gave **13**, which after acetylation to **14** was reacted with 2-amino-6-chloropurine to give the 9-alkylated product **15** in 87% yield. Se-oxydation of **15** with hydrogen peroxide afforded **16**, which underwent smooth elimination in a mixture of THF-DMF at 60 °C giving rise to a *Z,E* mixture of protected nucleosides **17**. Deacetylation gave **Z-1a** and **E-1a** which were separated on a silica gel column. Both **Z-1a** and **E-1a** were converted into the respective guanine analogues **Z-1b** and **E-1b**.

Keywords

Alkylation-elimination; fluoromethylenecyclopropane nucleoside analogues; methylenecyclopropanes

1. Introduction

Methylenecyclopropane analogues of nucleosides are potent antivirals effective especially against human cytomegalovirus (HCMV) and Epstein Barr virus (EBV).^{1,2} The anti-HCMV activity resides in the *Z*-isomers of purine analogues but both *Z*- and *E*-isomers are effective anti-EBV agents. Recently, we have described the synthesis of antiviral fluoroanalogues of methylenecyclopropanes **1** by a direct fluorination of carbanions of the respective carboxylic esters **2** and subsequent reduction of the resultant fluoroesters **3** (Scheme 1).³ The need to prepare methylenecyclopropane esters^{4,5} from individual nucleic acid bases or corresponding precursors is a substantial drawback of this procedure. In addition, the preparation of the 2-amino-6-chloropurine fluoroester **3a** from **2a** failed.³ The presence of a reactive 2-amino-6-chloropurine moiety⁶ would be of considerable advantage for the synthesis of a series of 2-amino-6-substituted purine fluoromethylenecyclopropane analogues.

2. Results and Discussion

An alkylation-elimination approach proved successful for synthesis of non-fluorinated methylenecyclopropane analogues^{1,2,4,5,7–10} of nucleosides **4a** and **4b** (Scheme 2). The *gem*-difluoromethylenecyclopropane analogues were obtained in a similar fashion.¹¹ A major advantage of this procedure is that reagents **5a** - **5c** can be used for reaction with any nucleic acid base or suitable precursor. Therefore, we became interested in applying of this approach

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to fluoromethylenecyclopropanes **1**. Methylenecyclopropane carboxylate¹² **6** was fluorinated with N-fluorobenzenesulfonimide (NFSI) via the corresponding carbanion to give fluoroester **7** in 62% yield* following the protocol for a similar fluorination³ of esters **2** (Scheme 3). Compound **7** was successfully converted to alkylation-elimination reagents **8** and **10** using procedures described^{4,5,7-9} previously for non-fluorinated methylenecyclopropanes via addition of bromine (**8**, 83%), reduction (**9**, 87%) and acetylation (**10**, 83%). Nevertheless, alkylation-elimination with adenine and reagents **8** or **10** under a variety of conditions gave either none or <10% of the expected methylenecyclopropane.

We reasoned that a strategy separating the alkylation and elimination steps could overcome this obstacle. The presence of a less reactive leaving group activated just before the elimination was considered an important requisite for success. A similar approach was employed in the synthesis of methylenecyclobutane nucleoside analogues but several steps had to be performed with intermediates containing a nucleic acid base.^{13,14} The 1,2 electrophilic additions of phenylselenenyl chloride to alkenes are well-established^{15,16} although they usually proceed with a limited regioselectivity.^{17,18} Additions to allylic acetates which were highly regioselective form an important exception.¹⁷ Reaction of phenylselenenyl bromide, generated in situ from NBS and diphenyl diselenide in analogy to the corresponding chloride,¹⁹ with fluoroester **7** gave selenide **11** in 85% yield (Scheme 4). The addition was regioselective and the presence of a single stereoisomer of **11** was established by NMR. To the best of our knowledge, this is the first stereoselective addition of phenylselenenyl halide to a methylenecyclopropane system. The episelenonium ion **12** is a likely intermediate in this transformation (Scheme 5), with the carboxylic ester function playing a role similar to the acetoxy group in allylic acetates¹⁷ by directing the addition of phenylselenenyl group to the *syn* face of double bond of fluoroester **7**. A nucleophilic attack of bromide then gave the *E* isomer of selenide **11** and reduction of **11** with DIBALH afforded the hydroxymethyl derivative **13** (88% yield). Acetylation provided acetate **14** (95%). The *E(trans)*-isomeric structure of **14** was confirmed by NOE. As expected, the NOE enhancements were observed between the H₃ and CH₂OAc or H₃ and CH₂Br (Table 1).

As indicated at the outset, a direct fluorination of 2-amino-6-chloropurine ester **2a** failed. Therefore, 2-amino-6-chloropurine was chosen as a precursor of nucleobase for alkylation with acetate **14** (K₂CO₃ in DMF at rt) to give intermediate **15** in 87% yield. Oxidation with H₂O₂ in THF provided selenoxide **16** as two stereoisomers (ratio 2.4 : 1) in 95% yield. Mild thermolysis in THF - DMF (10 : 1) at 60 °C furnished (*Z,E*)-methylenecyclopropane acetate (76%) and deacetylation followed by chromatography afforded the *Z*- and *E*-isomers of **1a** in 45 and 41% yield, respectively. Hydrolysis of the individual isomers with formic acid gave the *Z*- and *E*-guanine analogues of **1b** (78 and 73%) which were identical with compounds prepared by a different procedure.³ Overall yields of the *Z*- and *E*-isomers of **1b** (10.2 and 8.7% from ester **6**) are significantly improved over those obtained previously³ (4.1 and 2.5%).

3. Conclusion

A method for the synthesis of fluoromethylenecyclopropane analogues based on a novel alkylation-elimination approach is reported. The yields of guanine analogues **Z-1b** and **E-1b** were improved by a factor of 2 – 3 over the previous protocol. It is likely that the differential reactivity of 1,2-haloselenides in alkylation-elimination will find general use in the synthesis of methylenecyclopropane analogues, especially in cases where the reaction products are less stable toward bases. The regio- and stereoselective addition of phenylselenenyl halide to

*In the absence of LiCl, the yield of fluoroester **7** was only 43%. A similar beneficial effect of an excess of LiCl was observed³ in fluorination of esters **2**.

methylenecyclopropane carboxylate **7** may then find application in areas other than nucleoside analogues.

4. Experimental

4.1. General Methods

The UV spectra were measured in ethanol and NMR spectra were determined at 300 or 400 MHz (¹H), 75 or 100 MHz (¹³C) and 376 MHz (¹⁹F) in CD₃SOCD₃ unless stated otherwise. For ¹⁹F NMR CFC₃ was used as a reference. Mass spectra were determined in electron-impact (EI-MS) or electrospray ionization (ESI-MS, methanol - NaCl) mode.

4.1.1. Ethyl 1-Fluoro-2-methylenecyclopropane-1-carboxylate (7)—A suspension of dried ¹LiCl and ester **6** (750 mg, 6.0 mmol) in THF (30 mL) was cooled to -78 °C. After 10 min, LDA (4.0 mL, 7.2 mmol) was added dropwise with stirring which was continued for 40 min. N-fluorobenzenesulfonimide (NFSI, 2.24g, 7.2 mmol) in THF (3 mL) was then added and, after 10 min, the reaction was quenched with aqueous NH₄Cl (15mL). Pentane (100 mL) was added, the organic phase was washed with 5% HCl (3 x 25 mL) and 5% NaHCO₃ (3 x 25 mL) whereupon it was dried (MgSO₄). The solvents were evaporated at atmospheric pressure and the residue was chromatographed on a silica gel column (pentane : Et₂O = 100 : 1 to 40 : 1) to give product **7** (540 mg, 62%) as an oil. ¹H NMR (CDCl₃) δ 1.29 (t, 3H, J = 7.2 Hz, Me), 2.00 (tt, 1H, J = 12.0, 3.2 Hz), 2.24 (dt, 1H, J = 12.0, 2.8 Hz, H₃), 4.25 (m, 2H, CH₂ of Et), 5.68 (t, 1H, J = 3.2 Hz), 5.86 (t, 1H, J = 3.2 Hz, =CH₂). ¹³C NMR 14.3 (CH₃), 19.6 (d, J = 13.5 Hz, C₃), 62.1 (CH₂ of Et), 72.3 (d, J = 236.5 Hz, C₁), 109.2 (=CH₂), 130.1 (d, J = 4.5 Hz, C₂), 168.8 (d, J = 27.7 Hz, C=O). ¹⁹F NMR - 189.9 (d, J = 10.5 Hz). EI-MS 144 (M, trace), 116 (M - C₂H₄, 100.0). EI-HRMS calcd for C₅H₅FO₂ (M - C₂H₄) 116.0274, found 116.0277.

4.1.2. Ethyl (Z,E)-2-Bromo-2-bromomethyl-1-fluorocyclopropane-1-carboxylate (8)—A solution of ester **7** (145 mg, 1.0 mmol) in CCl₄ (5 mL) was treated with bromine (320 mg, 2.0 mmol) at 0 °C. The reaction mixture was allowed to stand at rt for 30 min. It was diluted with EtOAc (30 mL) and washed with saturated Na₂S₂O₃ - NaHCO₃ solution and water. The organic phase was dried over Na₂SO₄, solvent was evaporated and the crude product was purified by chromatography on silica gel (hexane : EtOAc = 30 : 1) to give product **8** as a colorless oil (254 mg, 83%). ¹H NMR (CDCl₃) δ 1.37 (2 overlapped t, 3H, J = 7.2 Hz, Me), 1.83 (dd, J = 19.6, 9.0 Hz), 2.05 (dd, J = 15.2, 9.0 Hz) and 2.21 (dd, J = 19.2, 11.6 Hz, total 2H, H₃), 3.83 (dd, J = 12.8, 8.8 Hz), 3.91 (dd, J = 10.4, 2.8 Hz), 4.01 (dd, J = 12.4, 2.4 Hz, total 2H, CH₂Br), 4.36 (2 overlapped q, 2H, J = 7.2 Hz, CH₂ of Et). ¹⁹F NMR -181.6 (m), -193.9 (dd, J = 18.4, 9.0 Hz). EI-MS 302, 304, 306 (1.0, 2.0, 1.0, M), 195 (100.0). EI-HRMS calcd for C₇H₉O₂F⁷⁹Br₂ (M) 301.8953, found 301.8956.

4.1.3. (Z,E)-2-Bromo-2-bromomethyl-1-fluoro-1-hydroxymethylcyclopropane (9)—A solution of 1 M DIBALH in hexane (1 mL, 1 mmol) was added to ester **8** (145 mg, 0.47 mmol) in hexane (5 mL) at 0 °C under N₂. The stirring was continued at rt for 3 h. The reaction was quenched by a dropwise addition of 5% HCl (10 mL) and then it was extracted with Et₂O (4 x 20 mL). The organic phase was washed successively with saturated NaHCO₃ (2 x 10 mL) and water (2 x 10 mL) and it was dried over MgSO₄. The solvent was evaporated and the residue was chromatographed on a silica gel column in hexane : EtOAc = 5 : 1 to give compound **9** as a colorless oil (106 mg, 87%). ¹H NMR (CDCl₃) δ 1.45 – 1.79 (m, 2H, H₃), 2.39 (bs, 1H, OH), 3.71 – 4.32 (m, 4H, CH₂Br, CH₂OH). ¹⁹F NMR -172.9, -193.4 (2m). EI-MS 73 (100.0), 242, 244, 246 (0.007, 0.014, 0.007, M - OH). ESI-MS 283, 285, 287 (47.9, 100.0, 38.6, M + Na). EI-HRMS calcd for C₅H₆F⁷⁹Br₂ (M - OH) 242.8820, found 242.8819.

4.1.4. (Z,E)-1-Acetoxymethyl-2-bromo-2-bromomethyl-1-fluorocyclopropane

(10)—Acetic anhydride (1 mL) was added dropwise with stirring to a solution of compound **9** (106 mg, 0.87 mmol) in N,N-dimethyl-N-ethylamine (3 mL) at rt. The stirring was continued for 5 h whereupon the volatile components were evaporated in vacuo and the residue was chromatographed on a silica gel column (hexanes : EtOAc = 20 : 1) to give product **10** as a colorless oil (100 mg, 82%). ¹H NMR (CDCl₃) δ 1.47–1.82 (m, 2H, H₃), 2.13, 2.14 (2s, 3H, Me), 3.62–3.91 (m, 2H, CH₂Br), 4.37–4.81 (m, 2H, CH₂O). ¹⁹F NMR -169.9, -190.5 (2m). ESI-MS 325, 327, 329 (50.6, 100.0, 49.1, M + Na).

4.1.5. Ethyl (E)-2-Bromomethyl-1-fluoro-2-phenylselenenylcyclopropane-1-carboxylate (11)

—NBS (3.07 g, 17.27 mmol) and Ph₂Se₂ (5.38 g, 17.27 mmol) were added to a solution of fluoroester **7** (2.26 g, 15.7 mmol) in CH₂Cl₂ (100mL) at -5–0 °C with stirring. After 35 min, the reaction was quenched with aqueous NH₄Cl (20 mL), EtOAc (200 mL) was added and the organic phase was washed with saturated Na₂S₂O₃-NaHCO₃ solution and water. The organic phase was dried over Na₂SO₄, solvent was evaporated and the residue was chromatographed on a silica gel column (hexanes : Et₂O = 20 : 1) to give product **11** (5.1g, 85%) as a colorless oil. ¹H NMR (CDCl₃) δ 1.34 (t, 3H, J = 7.0 Hz, Me), 1.65 (dd, 1H, J = 18.8, 8.0 Hz) and 1.84 (t, 1H, J = 8.8 Hz, H₃), 3.65 (d, 1H, J = 11.2 Hz), 3.84 (dd, 1H, J = 11.2, 2.4 Hz, CH₂Br), 4.82 (dq, 2H, J = 7.2, 2.4 Hz, CH₂O), 7.30–7.34 (m, 3H), 7.57 (dd, 2H, J = 8.0, 1.6 Hz, Ph). ¹³C NMR 14.4 (Me), 26.4 (d, J = 9.7 Hz, C₃), 34.6 (d, J = 9.0 Hz, C₂), 37.4 (d, J = 9.7 Hz, CH₂Br), 62.7 (CH₂O), 84.9 (d, J = 245.6 Hz, C₁), 127.4, 128.9, 129.6, 135.2 (Ph), 166.3 (d, J = 26.2 Hz, C=O). ¹⁹F NMR -191.3 (dd, J = 18.3, 10.5 Hz). ESI-MS (KOAc) 379, 381, 383 (45.6, 100.0, 79.1, M + H), 417, 419, 421 (44.3, 100.0, 83.5, M + K). Anal. Calcd for C₁₃H₁₄BrFO₂Se: C, 41.08; H, 3.71. Found: C, 41.21; H, 3.70.

4.1.6. (E)-2-Bromomethyl-1-fluoro-1-hydroxymethyl-2-phenylselenenylcyclopropane (13)

—DIBALH in hexane (1 M, 30 mL, 30 mmol) was added to a solution of **11** (4.5 g, 11.8 mmol) in hexane (40 mL) at 0 °C with stirring during 10 min under N₂. The stirring was continued at 0 °C for 2.5 h. The reaction was quenched by a dropwise addition of 0.1 N HCl (20 mL) and the mixture was extracted with Et₂O (4 x 30 mL). The combined organic phase was washed successively with saturated NaHCO₃ (2 x 30 mL) and water (2 x 30 mL). Solvents were evaporated and the crude product was chromatographed on silica gel (hexanes : Et₂O = 10 : 1 to 5 : 1) to give **13** as a colorless oil (3.51g, 88%). ¹H NMR (CDCl₃) δ 1.24 (dd, 1H, J = 10.4, 8.0 Hz), 1.49 (dd, 1H, J = 20.4, 8.0 Hz, H₃), 2.08 (bs, 1H, OH), 3.69 (dd, 1H, J = 11.2, 2.0 Hz), 3.90 (dd, 1H, J = 11.2, 2.0 Hz, CH₂Br), 4.15 (AB, 1H, J = 12.8 Hz), 4.33 (AB, 1H, J = 13.4 Hz, CH₂O), 7.31–7.35 (m, 3H), 7.58 (dd, 2H, J = 8.0, 1.6 Hz, Ph). ¹³C NMR 25.7 (d, J = 11.2 Hz, C₃), 33.4 (d, J = 8.2 Hz, C₂), 38.6 (d, J = 10.4 Hz, CH₂Br), 65.5 (d, J = 23.1 Hz, CH₂O), 88.3 (d, J = 232.8 Hz, C₁), 127.7, 128.8, 129.7, 134.8 (Ph). ¹⁹F NMR -190.0 (m). ESI-MS 337, 339, 341 (45.6, 100.0, 78.5, M + H), 319, 321, 323 (44.9, 100.0, 78.5, M - OH). Anal. Calcd for C₁₁H₁₂BrFOSe: C, 39.08; H, 3.58. Found: C, 39.31; H, 3.52.

4.1.7. (E)-1-Acetoxymethyl-2-bromomethyl-1-fluoro-2-phenylselenenylcyclopropane (14)

—Acetic anhydride (0.5 mL) was added dropwise with stirring to a solution of **13** (340 mg, 1.0 mmol) in pyridine (3 mL) at rt. The stirring was continued for 16 h whereupon the reaction was quenched with water and the mixture was extracted with pentane (50 mL). The combined organic phase was washed successively with saturated CuSO₄, 5% HCl, aqueous NaHCO₃. It was dried over MgSO₄, the solvent was evaporated and the residue was chromatographed on a silica gel column (hexanes - Et₂O, 20 : 1) to give product **14** as a colorless oil (365 mg, 95%). ¹H NMR (CDCl₃) δ 1.28 (t, 1H, J = 9.4 Hz, H₃), 1.52 (dd, 1H, J = 19.6, 8 Hz, H₃), 2.13 (s, 3H, Me), 3.67 (d, 1H, J = 10.4 Hz), 3.88 (dt, 1H, J = 10.4, 2.0 Hz, CH₂Br), 4.57 (d, 1H, J = 13.2 Hz) and 4.89 (dd, 1H, J = 13.2,

1.6 Hz, CH₂O), 7.32 (m, 3H) and 7.55 (dd, 2H, J = 7.2, 1.6 Hz, Ph). ¹³C NMR 21.1 (Me), 25.8 (d, J = 11.3 Hz, C₃), 38.0 (d, J = 10.5 Hz, CH₂Br), 66.8 (d, J = 21.6 Hz, CH₂O), 85.8 (d, J = 233.5 Hz), 128.8, 129.7, 134.7 (Ph), 170.9 (C=O). ¹⁹F NMR -187.8 (m). EI-MS 301 (M - Br, 100.0). ESI-MS 379, 381, 383 (10.8, 23.1, 13.2, M + H), 401, 403, 405 (45.6, 100.0, 78.8, M + K). EI-HRMS calcd. for C₁₃H₁₄FO₂⁸⁰Se (M - Br) 301.0143, found 301.0145. Anal. Calcd for C₁₃H₁₄BrFO₂Se: C, 41.08; H, 3.71. Found: C, 41.30; H, 3.87.

4.1.8. (E)-2-Amino-6-chloro-9-[(2-acetoxymethyl-2-fluoro-1-phenylselenenyl)-1-cyclopropylmethyl]purine (15)—A mixture of compound **14** (343 mg, 0.9 mmol), 2-amino-6-chloropurine (153 mg, 0.9 mmol) and K₂CO₃ (140 mg, 1.01 mmol) was stirred in DMF (3.5 mL) at rt for 36 h. The solid was filtered off using a silica gel pad and it was washed with DMF (60 mL). DMF was evaporated in vacuo and the residue was chromatographed on a silica gel column (CH₂Cl₂ : MeOH = 60 : 1 to 30 : 1) to give compound **15** as a white solid (353 mg, 87%), mp 154–155 °C. UV max 221 nm (ε 29,500), 243 (ε 7,800), 310 (ε 7,800). ¹H NMR (CDCl₃) δ 1.38 (t, 1H, J = 9.6 Hz), 1.87 (dd, 1H, J = 20.0, 8.4 Hz, H₃'), 2.16 (s, 3H, Me), 4.10 (d, 1H, J = 14.8 Hz), 4.80 (AB, 1H, J = 14.4 Hz, 1.6 Hz, H₁'), 4.56 (dd, 1H, J = 31.6, 12.8 Hz), 4.97 (dd, 1H, J = 17.4, 13.4 Hz, H₅'), 5.13 (bs, 2H, NH₂), 7.24–7.32 (m, 3H), 7.42 (d, 2H, J = 6.4 Hz, Ph), 7.90 (s, 1H, H₈). ¹³C NMR 21.1 (Me), 23.7 (J = 11.2 Hz, C₃'), 31.1 (d, J = 9.0 Hz, C₄'), 46.3 (d, J = 11.2 Hz, C₁'), 66.9 (d, J = 21.6 Hz, CH₂O), 84.0 (d, J = 231.3 Hz, C₄'), 126.9, 128.9, 129.7, 134.4 (Ph), 125.0, 142.8 /split/, 151.3, 154.5, 159.3 (purine), 170.7 (C=O). ¹⁹F NMR -185.7 (ddt, J = 30.9, 19.9, 10.9 Hz). ESI-MS 468, 470, 472 (47.6, 100.0, 45.2, M + H), 490, 492, 494 (40.5, 81.6, 38.1, M + Na). Anal. Calcd for C₁₈H₁₇ClFN₅O₂Se: C, 46.12; H, 3.66; N, 14.94. Found: C, 46.03; H, 3.69; N, 14.72.

4.1.9. (E)-2-Amino-6-chloro-9-[(2-acetoxymethyl-2-fluoro-1-phenylselenenyl)-1-cyclopropylmethyl]purine Oxide (16)—Hydrogen peroxide (30%, 0.15 mL, 1.3 mmol) was added dropwise with stirring to a solution of compound **15** (350 mg, 0.74 mmol) in CH₂Cl₂ (10 mL) at rt. The stirring was continued for 2.5 h whereupon the volatile components were evaporated in vacuo to give selenoxide **16** (341 mg, 95%), mp 139–142 °C (decomp). UV max 222 nm (ε 27,900), 248 (ε 8,600), 311 (ε 7,500). ¹H NMR δ 1.62 (dd, J = 20.2, 8.2 Hz), 1.98–2.11 (m, partly overlapped with Me), 2.25 (dd, J = 19.2, 8.4 Hz, 2H, H₃'), 1.71, 2.03 (2s, 3H, Me), 4.17–4.55, 4.67–4.86 (2 clusters of m, 4H, H₁' + H₅'), 6.81, 7.10 (2s, 2H, NH₂), 7.42 (d), 7.58 (d), 7.64 (t), 7.81 (s), 7.96 (m, 6H, Ph + H₈). ¹⁹F NMR -175.0 (ddd, 33.5, 18.1 Hz), -181.1 (ddt, 30.5, 18.4, 12.4 Hz). ESI-MS 484, 486, 488 (47.8, 100.0, 47.8, M + H), 506, 508, 510 (49.8, 100.0, 44.7, M + Na).

4.1.10. (Z)- and (E)-2-Amino-6-chloro-9-[(4-fluoro-4-hydroxymethyl)-cyclopropylidenemethyl]purine (Z-1a) and (E-1a)—Selenoxide **16** (250 mg, 0.51 mmol) was dissolved in THF-DMF (10 : 1, 6.6 mL) and the mixture was stirred at 60 °C for 12 h. Solvents were removed in vacuo and the product was chromatographed on a silica gel column (CH₂Cl₂ : MeOH = 40 : 1) to give a mixture of *Z,E*-isomeric acetates **17** (122 mg, 76%), mp 161–165 °C. UV max 202 nm (ε 27,200), 224 (ε 28,200), 310 (ε 7,700). ¹H NMR (CDCl₃) δ 2.09, 2.17 (2s, 3H, Me) overlapped with 1.93–2.21 (m, 2H, H₃'), 4.30–4.59 (m), 4.75 (dd, 2H, H₅'), 5.34 (bs, 2H, NH₂), 7.38 (t), 7.81 (bs, 1H, H₁'), 8.21, 8.26 (2s, 1H, H₈). ¹⁹F NMR -179.6 (ddd), -179.8 (m). ESI-MS 312, 314 (M + H, 35.0, 11.7), 334, 336 (M + Na, 57.8, 20.1), 102 (100.0).

A solution of product **17** (353 mg, 1.13 mmol) and K₂CO₃ (125 mg, 0.91 mmol) in MeOH - water (9 : 1, 40 mL) at rt for 15 h. The solvents were evaporated in vacuo and the product was chromatographed on silica gel (EtOAc : hexanes = 2 : 1 to 100% EtOAc) to give faster moving **Z-1a** (129 mg, 42%) and slower moving **E-1a** (107 mg, 35%).

Z-1a: Mp 218–219 °C, UV max 237 nm (ϵ 27,200), 274 (ϵ 5,900), 310 (ϵ 7,400). ^1H NMR δ 1.94 (td, 1H, J = 12.0, 1.6 Hz), 2.00 (td, 1H, J = 11.2, 2.4 Hz, $\text{H}_{3'}$), 3.65 (dd, 1H, J = 29.0, 13.4 Hz), 4.18 (dd, 1H, J = 14.8, 12.8 Hz, $\text{H}_{5'}$), 5.67 (s, 1H, OH), 7.11 (s, 2H, NH_2), 7.31 (s, 1H, $\text{H}_{1'}$), 8.57 (s, 1H, H_8). ^{13}C NMR 15.7 (d, J = 12.7 Hz, $\text{C}_{3'}$), 63.7 (d, J = 24.7 Hz, $\text{C}_{5'}$), 77.8 (d, J = 231.3 Hz, $\text{C}_{4'}$), 112.4 (d, J = 4.5 Hz, $\text{C}_{2'}$), 113.4 ($\text{C}_{1'}$), 123.7, 140.2, 150.5, 153.0, 160.9 (purine). ^{19}F NMR -179.4 (ddd, J = 26.0, 13.6, 10.5 Hz). EI-MS 269, 271 (23.1, 8.2, M), 252, 254 (100.0, 33.0, M - OH), 169, 171 (59.5, 24.4, 2-amino-6-chloropurine). EI-HRMS calcd for $\text{C}_{10}\text{H}_9^{35}\text{ClFN}_5\text{O}$ (M): 269.0480, found: 269.0486.

E-1a: Mp 212–214 °C, UV max 236 nm (ϵ 28,100), 274 (ϵ 6,100), 310 (ϵ 7,700). ^1H NMR δ 1.94 (dd, 1H, J = 12.4, 1.8 Hz), 2.20 (td, 1H, J = 10.8, 2.4 Hz, $\text{H}_{3'}$), 3.77 (dt, 2H, J = 21.2 and 6.4 Hz, $\text{H}_{5'}$), 5.32 (t, 1H, J = 6.0 Hz, OH), 7.10 (s, 2H, NH_2), 7.71 (s, 1H, $\text{H}_{1'}$), 8.51 (s, 1H, H_8). ^{13}C NMR 18.1 (d, J = 13.5 Hz, $\text{C}_{3'}$), 63.3 (d, J = 26.1 Hz, $\text{C}_{5'}$), 77.6 (d, J = 229.8 Hz, $\text{C}_{4'}$), 113.4 (d, J = 5.2 Hz, $\text{C}_{2'}$), 114.7 ($\text{C}_{1'}$), 123.8, 140.2, 150.5, 153.5, 160.8 (purine). ^{19}F NMR -179.0 (td, J = 21.5, 10.9 Hz). EI-MS 269, 271 (23.18, 8.11, M), 252, 254 (100.0, 32.7, M - OH), 169, 171 (57.1, 23.2, 2-amino-6-chloropurine). EI-HRMS calcd. for ($\text{C}_{10}\text{H}_9^{35}\text{ClFN}_5\text{O}$): 269.0480, found: 269.0480.

4.1.11. (Z)- and (E)-[2-Fluoro-2-(hydroxymethyl)cyclopropylidene]methyl} guanine (Z-1b and E-1b)—Z-1a (85 mg, 0.32 mmol) was heated in HCO_2H (80%, 10 mL) at 80 °C with stirring for 4 h. After cooling, the volatile components were evaporated in vacuo and the crude product was stirred in NH_3/MeOH (5%, 40 mL) at 0 °C for 4 h. Solvents were removed, the product **Z-1b** was recrystallized from methanol (69 mg, 87%). **E-1b** was prepared in a similar fashion from **E-1a** (80 mg, 0.30 mmol) to yield 71 mg (95%). Both isomers were identical (TLC, UV and ^1H NMR) with authentic compounds.¹

Acknowledgements

We thank L. M. Hrihorczuk from the Central Instrumentation Facility (D. M. Coleman, Director), Department of Chemistry, Wayne State University, for mass spectra. The work described herein was supported by grant R01-CA32779 from the National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

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Scheme 1.

5a: $R_1 = \text{CO}_2\text{Et}$, $R_2 = \text{H}$

4a: $R = \text{H}$

5b: $R_1 = \text{CH}_2\text{OAc}$, $R_2 = \text{H}$

4b: $R = \text{CH}_2\text{OH}$

5c: $R_1 = R_2 = \text{CH}_2\text{OAc}$

Scheme 2.

Scheme 3.

- a. NBS, Ph_2Se_2 , CH_2Cl_2 . b. DIBALH, THF.
 c. Ac_2O , pyridine. d. 2-Amino-6-chloropurine, K_2CO_3 , DMF.
 e. H_2O_2 , THF. f. THF - DMF (10 : 1), $^\circ$.
 g. K_2CO_3 , MeOH- H_2O (9:1). h. 1. HCO_2H , $^\circ$. 2. NH_4OH .

Scheme 4.

Scheme 5.

Table 1

Selected NOE data^a of compound **14**

H_{irr} (δ)	H_{obs} (δ)	% NOE
H ₃ (1.28)	CH ₂ Oac (4.57)	1.31
	CH ₂ Oac (4.89)	0.7
H ₃ ' (1.52)	CH ₂ Br (3.67)	0.95
	CH ₂ Br (3.88)	1.08
CH ₂ OAc (4.60)	H ₃ (1.52)	1.61
CH ₂ Br (3.89)	H ₃ (1.28)	1.41

^a Assignments of H₃ and H₃' were based on coupling constants J_{H,F} (J_{H,F-cis} > J_{H,F-trans}),^{20,21} see Experimental.