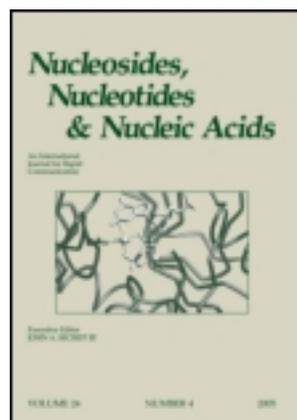


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Cyclopropyl and Related Analogs of the Anti-HIV Compound, Isodideoxyadenosine

Vasu Nair ^{a b c}, Travis Mickle ^b & Sanjib Bera ^b

^a Department of Pharmaceutical and Biomedical Sciences, University of Georgia, Athens, Georgia, USA

^b Department of Chemistry, University of Iowa, Iowa City, Iowa, USA

^c Department of Pharmaceutical and Biomedical Sciences, University of Georgia, Room 320A, R.C. Wilson PH, Athens, GA, 30602, USA

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Cyclopropyl and Related Analogs of the Anti-HIV Compound, Isodideoxyadenosine

Vasu Nair,^{1,2,*} Travis Mickle,² and Sanjib Bera²

¹Department of Pharmaceutical and Biomedical Sciences, University of Georgia,
Athens, Georgia, USA

²Department of Chemistry, University of Iowa, Iowa City, Iowa, USA

ABSTRACT

Novel 3'-substituted isonucleoside analogs were designed on the basis of the similarities of their electrostatic potential with the active anti-HIV compound, (*S,S*)-isodideoxy-adenosine. The key synthetic step involved coupling between the dideoxygenated sugar derivatives, **10** and **14**, and adenine under Mitsunobu conditions. Anti-HIV data are mentioned.

Key Words: Isonucleosides; Electrostatic potential; Synthesis; Antiviral.

INTRODUCTION

The synthesis, enzymology and antiviral properties of various isomeric nucleosides or isonucleosides have been the subject of intense investigation in our laboratory for a number of years.^[1] For example, 4(*S*)-(6-amino-9*H*-purin-9-yl)-tetrahydro-1-(*S*)-furanmethanol (**1**, isoddA), an isomeric dideoxynucleoside synthesized in our laboratory,^[2] has potent anti-HIV activity against HIV-1 and HIV-2.^[3]

*Correspondence: Vasu Nair, Department of Pharmaceutical and Biomedical Sciences, University of Georgia, Room 320A, R.C. Wilson PH, Athens, GA 30602, USA; E-mail: vnair@rx.uga.edu.



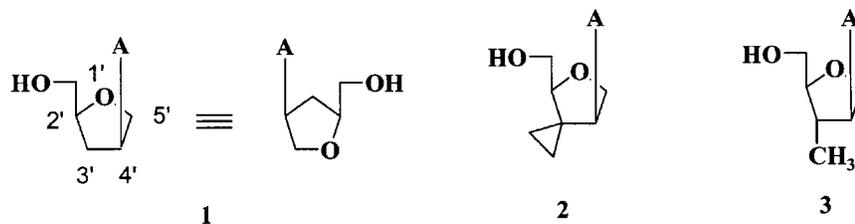


Figure 1.

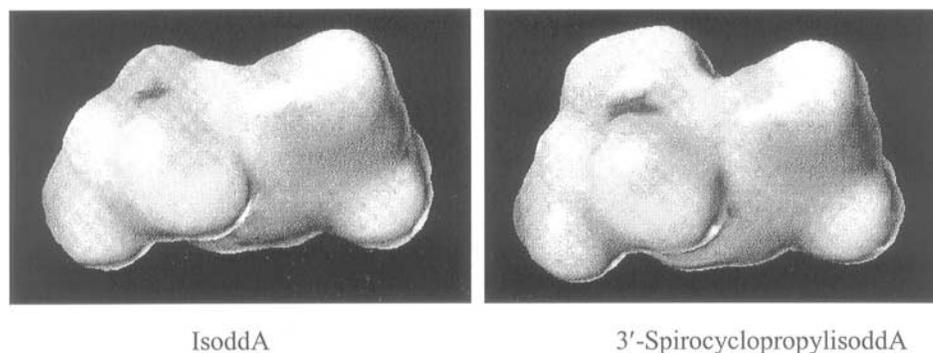
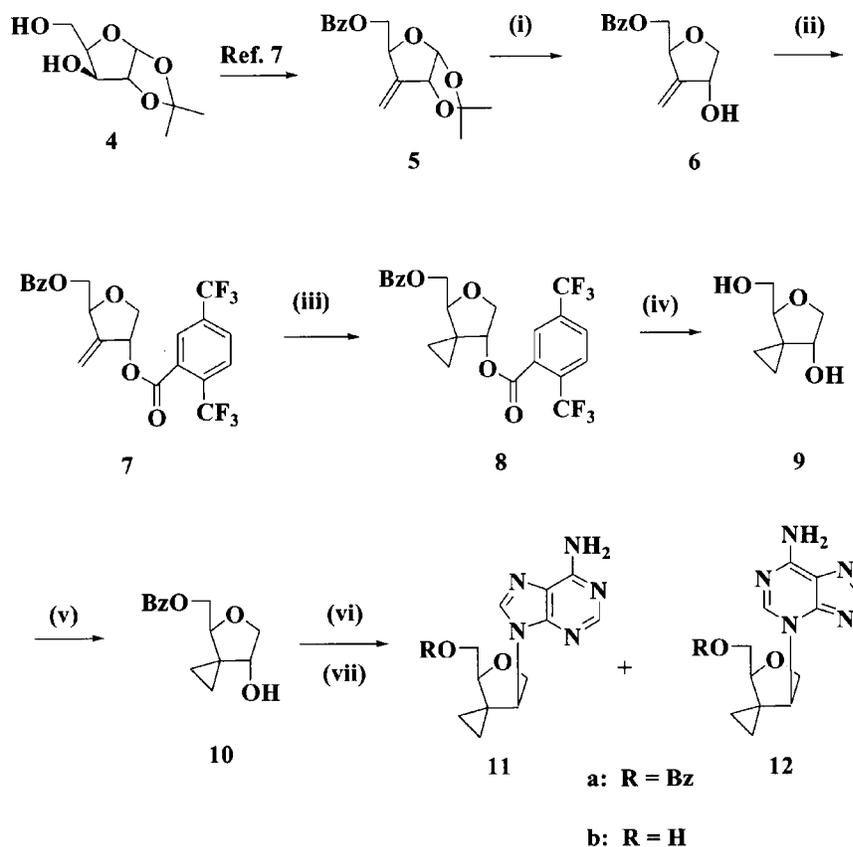


Figure 2.

(*S,S*)-IsoddA is a substrate for human recombinant deoxycytidine kinase.^[4] Its triphosphate is one of the most potent inhibitors of HIV RT known ($K_i = 16 \text{ nM}$).^[3] Our interest in synthesizing new analogs of (*S,S*)-isoddA led us to a comprehensive study of the correlation of antiviral activity with molecular conformation and electrostatic potential surfaces.^[5] Close examination of the bioactivity diagram for the isoddA series^[5] has shown some possible areas for change including the addition of an electropositive moiety at the 3'-position of (*S,S*)-isoddA (normal nucleoside numbering). Examples of an electropositive modification of this area include the addition of a spirocyclopropyl or methyl group (Fig. 1). Scrutiny of the steric interactions of the bioactivity diagram^[5] also showed that this region could allow for additional steric bulk. Electrostatic potential surface analysis for **2** and **3** showed that both new derivatives had similar electrostatic potential surfaces to (*S,S*)-isoddA with the spirocyclopropyl analog exhibiting the closest match (see Fig. 2).

RESULTS AND DISCUSSION

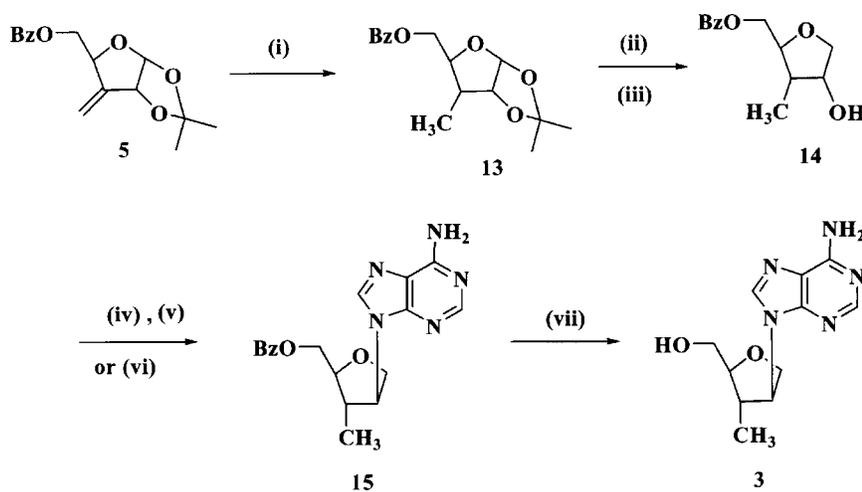
The target spirocyclopropyl nucleoside **2** (or **11**, R = H) was synthesized starting from the commercially available D-xylose derivative **4** and *via* the allylic alcohol **6** as a key intermediate (Sch. 1). Selective benzylation of the primary hydroxyl group of



Scheme 1. Reaction conditions: (i) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, Et_3SiH , CH_2Cl_2 ; (ii) 2,5-bis-trifluoromethylbenzoyl chloride, pyridine, 0°C ; (iii) (a) CH_2N_2 , CH_2Cl_2 , ether, (b) $h\nu$, Ph_2CO , benzene, CH_3CN ; (iv) NaOMe , MeOH ; (v) BzCl , pyridine, -10°C ; (vi) adenine, Ph_3P , DEAD, dioxane; (vii) NaOH , MeOH .

4, oxidation of the secondary hydroxyl group to the keto derivative followed by a Wittig reaction of the keto compound^[6,7] afforded compound **5** bearing the exocyclic methylene group. One-step reductive deoxygenation^[8] of the 1,2-O-isopropylidene group of **5** by treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and Et_3SiH afforded the tetrahydrofuran derivative **6**^[7] in 76% yield. For the successful introduction of the cyclopropyl group onto **6**, it was necessary to introduce a strong electron withdrawing (-I) protecting group^[9] on the secondary hydroxyl group adjacent to the exocyclic methylene functionality. Thus, treatment of **6** with 2,5-bis-trifluoromethylbenzoyl chloride in pyridine at 0°C gave the dibenzoate **7** in 92% yield. Cycloaddition of **7** with diazomethane followed by photosensitized extrusion^[9] of nitrogen from the diazo intermediate afforded the spirocyclopropane compound **8** in 57% overall yield for the two steps. Because of the difficulty of removing selectively the benzoyl protecting group on the secondary hydroxyl group, deprotection of both benzoyl groups of **8** was carried out with NaOMe in MeOH to give diol **9** (50%). This was followed





Scheme 2. Reaction conditions: (i) H_2 , Pd/C, ethanol; (ii) MeOH, HCl; (iii) (a) TMSCl, HMDS, (b) TMSOTf, Et_3SiH ; (iv) MsCl, pyridine; (v) adenine, K_2CO_3 , 18-crown-6, DMF; (vi) Ph_3P , adenine, DEAD, THF; (vii) NaOMe, MeOH.

by selective protection of the primary hydroxyl group of **9** with benzoyl chloride in pyridine at -10°C to give **10** in 79% yield. Treatment of **10** with adenine under Mitsunobu reaction conditions^[7,10] afforded both the N-9 and N-3 coupled products **11a** and **12a**. Deprotection of the benzoyl group on treatment with NaOMe/MeOH gave the free cyclopropyl nucleosides **11b** and **12b** in 31% overall yield. Their NMR and HRMS data confirmed the structures of both isomers. Differentiation between the isomers came from their UV spectral data. The UV spectrum of compound **11b** showed a λ_{max} at 261 nm indicative of the normal 9-substitution on the adenine ring^[2] whereas compound **12b** exhibited a λ_{max} at 275 nm, consistent with 3-substitution.^[11,12]

Synthesis of the 3'-methylisodda **3** also used the modified sugar **5** as the key synthetic intermediate. Catalytic hydrogenation of **5** using H_2 with Pd/C catalyst gave the methyl derivative **13** with α -stereochemistry of the methyl group. The stereochemistry obtained for the 3-methyl group is consistent with previous observations of the approach of reducing agents to the β -face of a furanosyl ring bearing a 1,2-*O*-isopropylidene group in the α -stereochemistry.^[13,14] Acid-catalyzed methanolysis of the acetonide group of **13** afforded the α - and β -methyl glycosides which were reductively demethoxylated^[2] to **14** by initial treatment with HMDS and TMSCl followed by reaction with TMS-triflate and triethylsilane (82% yield). Conversion of **13** to **14** is also possible with $\text{BF}_3 \cdot \text{Et}_2\text{O}$, Et_3SiH in CH_2Cl_2 (see Sch. 1) but the yield was lower than the two-step method. Protected isodideoxynucleoside **15** can be prepared in very low yield (7%) by treatment of **14** with adenine under Mitsunobu conditions. There was no evidence for the formation of the 3-substituted isomer in this case. The inefficiency of the Mitsunobu reaction prompted the investigation of a less direct method,^[2] i.e., conversion of **14** to its mesyl derivative (77%) followed by treatment of the mesylate with adenine in the presence of K_2CO_3 , 18-crown-6 in DMF (28%).

Deprotection of the resulting compound (**15**) by treatment with sodium methoxide gave **3** in 66% yield.

The anti-HIV studies of the target compounds **2** (**11b**, R = H), **12b** (R = H), and **3** showed that these compounds were devoid of any significant antiviral activity (HIV-1, HSV, VZV, CMV). Correlation of this inactivity with electrostatic potential surface data and the bioactivity diagram for the isodda series^[5] suggests that there may be less tolerance for steric bulk at this position than previously suggested by our bioactivity correlation.

EXPERIMENTAL

2(S)-(Benzoyloxymethyl)-4(R)-[O-(2,5-bis-trifluoromethyl)benzoyloxy]-3-spirocyclopropyltetrahydrofuran (8). To a solution of **5**^[7] (7.76 g, 26.8 mmol) in CH₂Cl₂ (150 mL) at 0°C was added Et₃SiH (42.6 mL, 268 mmol) followed immediately by BF₃·Et₂O (34.0 mL, 268 mmol). The solution was stirred at room temperature for 2 h followed by neutralization with saturated aqueous NaHCO₃. Extraction with CH₂Cl₂ (3 × 100 mL) and evaporation of the combined organic layers gave the crude product which was purified over silica gel to give **6** (4.79 g, 76%) as a gum which solidified on standing, m.p. 66–67°C. To a solution of **6** (2.61 g, 11.1 mmol) in pyridine (100 mL) at 0°C was added 2,5-bis-trifluoromethylbenzoyl chloride (4.04 mL, 22.2 mmol). The reaction solution was stirred at 0°C for 15 min. The reaction was quenched with saturated aqueous NaHCO₃ and the solvent was evaporated to dryness and the residue was purified over silica gel to give the dibenzoyl derivative **7** (4.82 g, 92% yield) as yellow oil. To a solution of **7** (9.70 g, 20.5 mmol) in CH₂Cl₂ (25 mL) was added diazomethane (excess) in diethyl ether (250 mL). The resulting solution was allowed to stir at ambient temperature for 48 h. Excess solvent was removed by evaporation. The crude product was purified over silica gel (60% ethyl acetate: hexanes) to give the spiro-pyrazoline derivative (10.04 g, 19.5 mmol, 95% yield). To a solution of the pyrazoline derivative in 1:1 benzene: acetonitrile solution (250 mL) was added benzophenone (1.83 g, 9.75 mmol). The solution was then irradiated at 3000 Å for 2 h. Excess solvent was removed and the crude product was purified over silica gel (0–10% ethyl acetate: hexanes) to give **8** (4.60 g, 11.5 mmol, 59% yield) as a pale yellow amorphous powder: ¹H NMR (CDCl₃) δ 0.77 (m, 1H, spiro-cyclopropyl), 0.90 (m, 1H, spiro-cyclopropyl), 1.03 (m, 1H), 1.61 (m, 1H), 4.11–4.21 (m, 3H), 4.43 (dd, 1H), 4.53 (m, 1H), 5.19 (d, 1H), 7.44 (t, 2H), 7.57 (t, 1H), 7.92 (d, 2H), 8.05 (d, 3H); ¹³C NMR (CDCl₃) δ 5.30, 9.64, 28.23, 64.45, 72.20, 77.48, 83.94, 127.50, 127.54, 127.72, 127.76, 129.69, 129.78, 133.21, 165.44, 166.33; HRMS (FAB): (M+H)⁺ calcd for C₂₃H₁₉F₆O₅ 489.1136, found 489.1129.

2(S)-(Benzoyloxymethyl)-4(R)-hydroxy-3-spirocyclopropyltetrahydrofuran (10). To a solution of **8** (0.8 g, 3.2 mmol) in MeOH (40 mL), was added 1N aqueous NaOH (5 mL). After the addition, the reaction mixture was stirred at room temperature for 1.5 h. The solution was neutralized with 0.5M HCl and evaporated to dryness. The residue was purified over silica gel to give **9** (0.23 g, 50%) as a colorless oil. To a solution of **9** (0.21 g, 1.45 mmol) in pyridine (40 mL) was added benzoyl chloride (0.18 mL, 1.6 mmol) in pyridine (5 mL) slowly over a period of 1 h at –10°C. The reaction mixture



was stirred for an additional 1h at -10°C , then quenched with water and evaporated to dryness. The residue was partitioned between saturated aqueous NaHCO_3 (60 mL) and CHCl_3 (50 mL) and the aqueous part was further extracted with CHCl_3 (50 mL). The combined CHCl_3 layers were dried over Na_2SO_4 , evaporated to dryness and purified over silica gel to give **10** (0.28 g, 78%) as a gum: ^1H NMR (CDCl_3) δ 0.63 (m, 2H), 0.87 (m, 1H), 1.06 (m, 1H), 3.90 (m, 2H), 4.08–4.22 (m, 3H), 4.46 (dd, 1H), 7.42 (t, 2H), 7.55 (t, 1H), 8.02 (d, 2H); ^{13}C NMR (CDCl_3) δ 3.78, 25.18, 60.01, 69.46, 72.74, 73.05, 123.49, 124.73, 128.23, 161.56; HRMS (FAB): $(\text{M} + \text{H})^+$ calcd for $\text{C}_{14}\text{H}_{17}\text{O}_4$ 249.1126, found 249.1130.

4(S)-(6-Amino-9H-purin-9-yl)-3-spirocyclopropyltetrahydro-2(S)-furanmethanol (11b) and 4(S)-(6-Amino-3H-purin-3-yl)-3-spirocyclopropyltetrahydro-2(S)-furanmethanol (12b). To a suspension of **10** (0.15 g, 0.6 mmol), adenine (0.12 g, 0.9 mmol), Ph_3P (0.24 g, 0.9 mmol) in dioxane (20 mL) was added DEAD (0.2 mL). After the addition, the reaction mixture was stirred at room temperature for 2 days. The solvent was then evaporated to dryness and the residue was purified over silica gel to give **11a** and **12a**. To a solution of **11a** in MeOH (12 mL) was added 1N NaOH (1 mL) and the solution was stirred at room temperature for 1.5 h, then neutralized with 0.5 M HCl and the solvent was evaporated to dryness. The residue was purified over silica gel to give **11b** (0.027 g, 17% from **10**) as a white solid. Compound **12a** was deprotected following the same method to give **12b** (0.22 g, 14% from **10**) as a white solid.

Compound **11b**: m.p: $180\text{--}181^{\circ}\text{C}$; UV (MeOH) λ_{max} 261 (13,800); ^1H -NMR (MeOH-d_4) δ 8.55 (s, 1H), 8.15 (s, 1H), 4.84 (s, 1H), 4.26 (m, 2H), 3.92 (m, 1H), 3.70 (dd, $J = 3.4, 12.2$ Hz, 1H), 3.47 (dd, $J = 4.2, 12.2$ Hz), 1.21 (m, 1H), 0.93 (m, 1H), 0.73 (m, 1H), 0.38 (m, 1H); ^{13}C -NMR (MeOH-d_4) δ 157.2, 153.6, 150.7, 141.7, 119.3, 84.5, 73.7, 63.5, 62.1, 29.8, 14.3, 8.8; HRMS (FAB): $(\text{M} + \text{H})^+$ calcd for $\text{C}_{12}\text{H}_{16}\text{N}_5\text{O}_2$ 262.1304, found 262.1304.

Compound **12b**: mp 244°C ; UV (MeOH) λ_{max} 275 (12,600); ^1H -NMR ($\text{d}_4\text{-MeOH}$): 8.95 (s, 1H), 7.85 (s, 1H), 5.12 (m, 1H), 4.31 (m, 2H), 4.94 (m, 1H), 3.78 (dd, $J = 3.2, 12.5$ Hz), 3.46 (dd, $J = 3.3, 13.4$ Hz), 1.32 (m, 1H), 1.04 (m, 1H), 0.79 (m, 1H), 0.46 (m, 1H); ^{13}C -NMR ($\text{d}_4\text{-MeOH}$): 156.5, 152.9, 150.9, 144.7, 120.5, 84.6, 73.7, 68.4, 61.3, 29.2, 14.9, 9.8. HRMS (FAB): $(\text{M} + \text{H})^+$ calcd for $\text{C}_{12}\text{H}_{16}\text{N}_5\text{O}_2$ 262.1304, found 262.1316.

5-O-Benzoyl-1,2-O-isopropylidene-3(R)-methyl- α -D-xylofuranose (13). To a solution of **5** (3.85 g, 13.3 mmol) in ethanol (150 mL) was added Pd/C (1.00 g). The suspension was stirred under 25 psi of H_2 for 24 h and filtered. The filtrate was evaporated and the residue was purified over silica gel to give **13** (3.84 g, 99%) as an oil: ^1H NMR (CDCl_3) δ 1.15 (d, 3H), 1.35 (s, 3H), 1.54 (s, 3H), 2.04 (m, 1H), 4.11 (m, 1H), 4.38 (m, 1H), 4.58 (m, 2H), 5.85 (d, 1H), 7.44 (t, 2H), 7.57 (t, 1H), 8.03 (d, 2H); ^{13}C NMR (CDCl_3) δ 9.35, 26.12, 26.31, 40.16, 64.30, 82.59, 105.05, 111.59, 128.36, 129.76, 133.10, 166.42; HRMS (FAB): $(\text{M} + \text{Na})^+$ calcd for $\text{C}_{16}\text{H}_{20}\text{NaO}_5$ 315.1208, found 315.1212.

2(S)-(Benzoyloxymethyl)-3(S)-methyltetrahydrofuran-4(R)-ol (14). Hydrogen chloride (0.03 g, 0.75 mmol) was bubbled through a solution of **13** (3.85 g,

13.3 mmol) in MeOH (75 mL) and the resulting solution was stirred overnight at room temperature. Excess acid was neutralized with saturated aqueous NaHCO₃ solution and the solvent was then removed under reduced pressure and the residue was purified over silica gel to give the anomeric mixture of methyl glycosides (3.13 g, 89%) as a clear oil. To a solution of the methyl glycosides (3.13 g, 11.8 mmol) in HMDS (150 mL) was added chlorotrimethylsilane (5 mL) and the mixture was heated under reflux for 20 h and excess HMDS was then removed under reduced pressure. The residue was dissolved in anhydrous dichloroethane (125 mL) and this was followed by the addition of triethylsilane (5.64 mL, 35.4 mmol) and then slow addition of TMS-triflate (6.40 mL, 35.4 mmol). After stirring at room temperature for 17 h, the reaction mixture was quenched by the addition of water (100 mL). The solution was allowed to stir for an additional 2 h, neutralized with aqueous NaHCO₃ and excess solvent was removed. The residue was purified over silica gel to give **14** (2.56 g, 10.8 mmol, 92%) as a light yellow low melting solid: ¹H NMR (CDCl₃) δ 1.85 (d, 3H), 2.12 (m, 1H), 3.87 (d, 1H), 4.09 (m, 2H), 4.36 (m, 2H), 4.55 (dd, 1H), 7.42 (t, 2H), 7.58 (t, 1H), 8.08 (d, 2H); HRMS (FAB): (M+H)⁺ calcd for C₁₃H₁₇O₄ 237.1127, found 237.1128.

4(S)-(6-Amino-9H-purin-9-yl)-3(S)-methyltetrahydro-2(S)-furanmethanol (3).

To a solution of **14** (2.56 g, 10.8 mmol) in pyridine (120 mL) was added methanesulfonyl chloride (4.18 mL, 54.0 mmol) at 0°C and the mixture was stirred at room temperature for 2 h. The reaction was quenched with water (5 mL), the excess solvent was removed and the residue was coevaporated with toluene (2 × 25 mL). The crude product was purified over silica gel to give the mesylate of **14** (2.60 g, 8.28 mmol, 77%) as a yellow oil: ¹H NMR (CDCl₃) δ 1.22 (d, 3H), 2.30 (m, 1H), 3.08 (s, 3H), 4.03 (m, 1H), 4.16 (m, 1H), 4.26–4.58 (m, 3H), 5.22 (bs, 1H), 7.44 (t, 2H), 7.56 (t, 1H), 8.02 (d, 2H); ¹³C NMR (CDCl₃) δ 10.33, 38.62, 39.93, 64.78, 73.16, 81.49, 83.56, 128.45, 129.68, 133.22, 166.39. Adenine (0.238 g, 1.91 mmol), 18-crown-6 (0.252 g, 0.955 mmol), and K₂CO₃ (0.264 g, 1.91 mmol) were suspended in DMF (25 mL) and heated at 100°C for 2 h. A solution of the mesylate of **14** (0.300 g, 0.955 mmol) in DMF (5 mL) was then added and the mixture was stirred at 100°C for 20 h. Excess DMF was then removed and the crude product was purified over silica gel to give **15** (0.095 g, 28%): ¹H NMR (acetone-d₆) δ 1.24 (d, 3H), 2.04 (m, 1H), 4.05 (m, 1H), 4.22 (t, 1H), 4.28 (m, 1H), 4.48–4.62 (m, 2H), 4.93 (q, 1H), 6.79 (d, 2H), 7.52 (t, 2H), 7.63 (t, 1H), 8.06 (d, 2H), 8.15 (s, 1H), 8.19 (s, 1H); ¹³C NMR (CDCl₃) δ 16.14, 43.45, 61.94, 64.85, 71.47, 84.19, 128.73, 129.90, 133.53, 153.30, 156.10, 166.70. [Compound **15** was also prepared by the Mitsunobu reaction. To a solution of **14** (0.203 g, 0.86 mmol) in THF (10 mL) was added Ph₃P (0.338 g, 1.29 mmol), adenine (0.174 g, 1.29 mmol), and DEAD (0.27 mL, 1.72 mmol). The reaction mixture was stirred at room temperature for 5 days. Excess solvent was removed and the crude product was purified over silica gel to yield **15** (0.022 g, 0.06 mmol, 7%). To a solution of **15** (0.095 g, 0.27 mmol) in MeOH (10 mL) was added NaOMe (0.01 g, 0.18 mmol) and the mixture was stirred for 6 h at room temperature. The solution was neutralized with HOAc, the solvent was then removed and the crude product was purified over silica gel to give **16** (0.044 g, 66%) as a white solid: m.p. 174–176°C; ¹H NMR (MeOH-d₄) δ 1.19 (d, 3H), 2.58 (m, 1H), 3.34 (m, 1H), 3.67 (m, 2H), 3.82 (m, 1H), 4.16 (m, 2H), 8.20 (s, 1H), 8.32 (s, 1H); UV (MeOH)



λ_{\max} 260 nm (ϵ 12800); HRMS (FAB): (M+H)⁺ calcd for C₁₁H₁₆N₅O₂ 250.1304, found 250.1303.

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