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9-Deaza-5′-noraristeromycin

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Abstract—9-Deaza-5′-noraristeromycin (**2**) has been prepared in 10 steps from the readily available (+)-(1*R*,4*S*)-4-*t*-butyldimethylsilyloxycyclopent-2-en-1-yl acetate. Compound **2** was evaluated against a large number of viruses. No activity was found nor did **2** display cyctotoxicity towards the viral host cells.

Introduction

For the past 12 years, we[1] have been investigating the antiviral properties of 5′-norcarbanucleosides of which 5′-noraristeromycin (**1**)[2] and analogues therefrom represent the most promising series of compounds. Missing from the latter group is the 9-deaza derivative **2**, which is a carbocyclic C-nucleoside.[3] In light of the biological properties of 9-deazaadenosine,[4] we were encouraged to pursue **2**.[3] Its preparation and antiviral analysis is reported here (Fig 1).

Chemistry

Adapting a published procedure,[5] the synthesis of 9-deaza-5′-noraristeromycin began with the reaction of (+)-(1*R*,4*S*)-4-*t*-butyldimethylsilyloxy-2-cyclopenten-1-yl acetate (**3**),[6] readily available from (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate (**4**),[7] with ethyl cyanoacetate in the presence of Pd(O) to give **5**. Oxidation of **5** with osmium tetraoxide to **6** was followed by acetonide **7** formation under standard conditions (Scheme 1).

Selective reduction of **7** with di*iso*butylaluminum hydride gave **8**. Condensation of **8** with aminoacetonitrile bisulfate led to the pyrrole precursor **9**. Protection of the amino nitrogen of **9** as a carbamate with ethyl chloroformate was followed by ring closure with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and subsequent deprotection of the resultant pyrrole nitrogen to avail the substituted pyrrole **10**. Reaction of **10** with formamidine acetate yielded the requisite pyrrolo[3,2-*d*]pyrimidine **11**. Disilylation of **11** to **12** was followed by acid (HCl) deprotection to provide the target **2** as its hydrochloride. Numerous attempts to isolate **2** as the free base failed. X-ray analysis confirmed the structure of **2**.

Antiviral Results

Compound **2** was subjected to antiviral analysis[8] and found to be inactive. It also showed no cytotoxicity towards the viral host cells.[9]

Conclusion

While 3-deaza-[10] and 7-deaza-5′-noraristeromycin[11] displayed antiviral activity, the 9-deaza analogue **2** was ineffective, similar to that reported[5b] for 9-deazaaristeromycin. This result may be the due to the stereoelectronic alteration that accompanied changing from the sp^3 N-9 nitrogen of **1** to the sp^2 carbon of **2**, manifesting

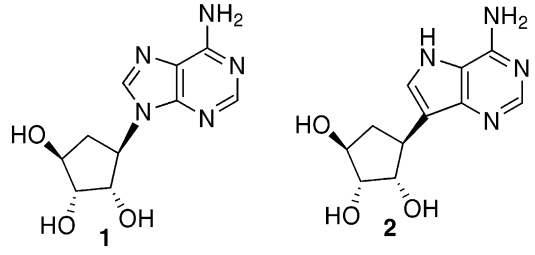

Figure 1.

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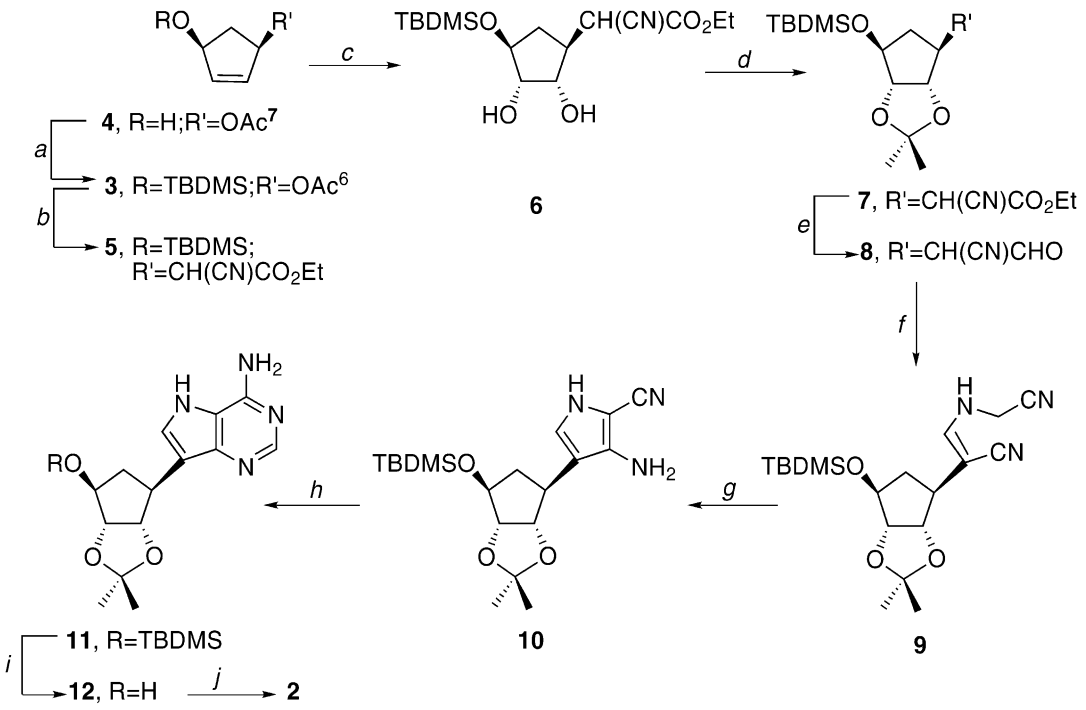

Scheme 1. Reaction conditions: (a) TBDMSCl, imidazole, DMF, rt[6b] (81%); (b) $NCCH_2CO_2Et$ and NaH, $(Ph_3P)_4Pd/PPh_3$, THF, rt then to 55 °C (78%); (c) using **5**, OsO_4, NMO, acetone–H_2O (49%); (d) $Me_2C(OMe)_2$, acetone, H^+ (84%); (e) DIBAL-H, Et_2O, −78 °C; (f) $H_2NCH_2CN{\cdot}H_2SO_4$, $NaOAc{\cdot}3H_2O$, MeOH, rt (29%); (g) (i) $ClCO_2Et$, DBN, CH_2Cl_2, rt; (ii) Na_2CO_3, MeOH, rt (16% from **7**); (h) $HC(=NH)NH_2{\cdot}AcOH$, EtOH, reflux (63%); (i) Bu_4NF, THF, rt (91%); (j) 2N HCl, MeOH, rt, 4 h (51%).

in decreased inhibition of *S*-adenosylhomocysteine hydrolase, the likely cause of the antiviral activity of **1**.[12] This conclusion is supported by the lack of any effect of **2** on vaccinia virus.[13]

Experimental

General

Melting points were recorded on a Meltemp II melting point apparatus and are uncorrected. Combustion analyses were performed by Atlantic Microlab, Inc., Norcross, GA, USA. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 250 spectrometer (operated at 250 and 62.5 MHz, respectively) and are referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), and br (broad). The optical rotation was measured on a Jasco P-1010 polarimeter. Reactions were monitored by thin-layer chromatography (TLC) using 0.5-mm Whatman Diamond silica gel 60-F_{254} precoated plates with visualization by irradiation with a Mineralight UVGL-25 lamp. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials.

Ethyl (2*R*/*S*,1′*R*,4′*S*)-2-[4′-(*t*-butyldimethylsilyloxy)cyclopent-2′-en-1′-yl]-2-cyanoacetate (5). To a suspension of NaH (0.8 g, 31.79 mmol, 95%, dry) in anhydrous THF (80 mL) in a 200-mL round-bottomed flask kept under N_2 was added ethyl cyanoacetate (3.38 mL, 31.79 mmol). The mixture was stirred at rt for 40 min. To this solution was added, successively, *tetraki*striphenylphosphine palladium (0.90 g, 0.78 mmol), triphenylphosphine (0.62 g, 2.3 mmol) and (+)-(1*R*,4*S*)-4-*t*-butyldimethylsilyloxycyclopent-2-en-1-yl acetate (**3**)[6b] (4 g, 15.62 mmol) in anhydrous THF (70 mL). The flask was immediately transferred to an oil bath, preheated at 55 °C. The mixture was stirred under N_2 at this temperature for 40 h. Next, the reaction mixture was passed through a SiO_2 plug layered with anhydrous $MgSO_4$ assisted by purified ether (this step removes suspended materials and some of the catalyst). After concentration of the filtrate under vacuum, the residue was purified by silica gel column chromatography (hexanes–EtOAc, 10:1–8:1) to give **5** (3.77 g, 78%) as a colorless oil. ^1H NMR ($CDCl_3$): δ 0.07 and 0.08 (2s, 2 × 3H), 0.89 (s, 9H), 1.35 (t, 3H), 1.58 (m, 1H), 2.47 (m, 1H), 3.17 (m, 1H), 3.44 (d, 0.46H, $J = 8.57$ Hz), 3.56 (d, 0.54H, $J = 7.82$ Hz), 4.27 (q, 2H), 4.83 (m, 1H), 5.76–5.93 (m, 2H). ^{13}C NMR ($CDCl_3$) δ −4.9, −4.8, 13.9, 17.9, 25.7, 38.1, 38.4, 42.7, 42.8, 44.1, 44.2, 62.5, 76.2, 76.3, 115.6, 131.4, 137.0, 165.3. Anal. calcd for $C_{16}H_{27}NO_3Si$: C, 62.10; H, 8.79; N, 4.53. Found: C, 62.06; H, 8.85; N, 4.57.

Ethyl (2*R*/*S*,1′*R*,2′*S*,3′*S*,4′*S*)-2-[4′-(*t*-butyldimethylsilyloxy)-2′,3′-dihydroxycyclopent-1′-yl]-2-cyanoacetate (6). To a solution of **5** (3.19 g, 10.3 mmol) and 50% aqueous solution of 4-methylmorpholine *N*-oxide (8 mL, 34 mmol) in a mixture of acetone (50 mL) and H_2O (enough to make the solution clear) was added osmium tetraoxide (OsO_4) (100 mg) in one portion. After stirring this solution at rt for 31 h, the solution was washed through a plug of silica gel with EtOAc–MeOH (9:1).

The solvents were removed under reduced pressure. The residue was purified by flash column chromatography eluting with hexanes–EtOAc (1.5:1–1:1) to afford 1.75 g (49%) of **6** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.07 and 0.09 (2s, 2 × 3H), 0.89 (s, 9H), 1.33 (t, 3H), 1.49 (m, 1H), 2.07 (m, 1H), 2.32 (m, 1H), 2.52 (m, 1H), 3.05 (d, 1H), 3.33 (d, 1H), 3.65–3.87 (m, 2H), 4.07 (m, 1H), 4.32 (q, 2H). ^{13}C NMR ($CDCl_3$) δ −4.8, −4.7, 14.1, 18.1, 25.9, 34.6, 35.3, 41.2, 43.2, 43.3, 63.3, 74.3, 74.9, 75.9, 76.0, 78.3, 78.4, 115.7, 115.8, 166.1, 166.3. Anal. calcd for $C_{16}H_{29}NO_3Si$·0.5 EtOAc: C, 55.79; H, 8.50; N, 3.69. Found: C, 55.39, H, 8.58; N, 3.61.

Ethyl (2*R*/*S*,1′*R*,2′*S*,3′*S*,4′*S*)-2-[4′-(*t*-butyldimethylsilyloxy)-2′,3′-*iso*propylidenedioxycyclopent-1′-yl]-2-cyanoacetate (7). To a solution of **6** (2.73 g, 7.9 mmol) in dry acetone (50 mL) and 2,3-dimethoxypropane (6 mL) in a 100 mL round-bottomed flask was added a small crystal of *p*-toluenesulfonic acid under N_2. This mixture was stirred at rt for 20 h and then was passed through a plug of silica gel assisted by reagent grade acetone. The resulting solution was evaporated under reduced pressure and the residue was chromatographed (hexanes–EtOAc, 6:1) to afford 2.55 g (84%) of **7** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.10 and 0.12 (2s, 2 × 3H), 0.90 (s, 9H), 1.26–1.42 (m, 10H), 2.23 (m, 1H), 2.65 (m, 1H), 3.76 (d, 0.62H, J = 11.38 Hz), 3.91 (d, 0.38H, J = 11.60 Hz), 4.20 (m, 1H), 4.29 (q, 2H), 4.34 (t, 1H), 4.52–4.77 (dd, 1H). ^{13}C NMR ($CDCl_3$) δ −5.5, −5.4, 13.5, 17.5, 23.6, 25.3, 25.9, 34.1, 34.6, 39.5, 40.5, 45.2, 45.6, 62.3, 62.4, 76.2, 76.7, 82.5, 82.8, 86.4, 110.3, 110.4, 115.6, 115.7, 164.9, 165.2. Anal. calcd for $C_{19}H_{33}NO_5Si$: C, 59.60; H, 8.67; N, 3.65. Found: C, 59.71; H, 8.74; N, 3.47.

(1′*R*,2′*S*,3′*S*,4′*S*)-3-Amino-2-cyano-4-[(4′-*t*-butyldimethylsilyloxy)-2′,3′-*iso*propylidenedioxycyclopent-1′-yl]-1*H*-pyrrole (10). To a solution of **7** (4.01 g, 10.45 mmol) in anhydrous ethyl ether (60 mL) at −78 °C was added DIBAL-H (1 M in hexanes, 21 mL) over 15 min. The mixture was stirred at −78 °C for 30 min and MeOH (90 mL) was added. The mixture was stirred for 30 min and concentrated. The resultant solid cake was suspended in EtOAc–MeOH (25:2) then stirred for 40 min and filtered. After removal of the filtrate under reduced pressure, the residue containing **8** was dissolved in MeOH (70 mL). Aminoacetonitrile bisulfate (3.98 g, 25.82 mmol) and NaOAc·3H_2O (3.39 g, 24.9 mmol) were added. The mixture was stirred at rt for 43 h. The solvent was evaporated at rt and the residue was co-evaporated with MeOH (3 × 60 mL). Ethyl acetate (200 mL) was added to the residue and this mixture stirred for 45 min. The mixture was filtered, the filtrate concentrated and the residue chromatographed (hexanes–EtOAc, 2:1) to give 1.13 g (29%) of **9** as a white solid. To a solution of **9** (1.13 g, 2.99 mmol) in dry CH_2Cl_2 (55 mL) at 0 °C was added DBN (6.46 mL, 52.29 mmol) and ethyl chloroformate (2.99 mL, 31.27 mmol). The mixture was stirred for 1 h at rt and then washed with H_2O. The organic phase was dried ($MgSO_4$), concentrated and the residue chromatographed (hexanes–EtOAc, 2:1) to give, after evaporation of the solvent, a material that was dissolved in MeOH (35 mL). Sodium carbonate (40 mg, 0.37 mmol) was added to this solution. The new mixture was stirred 1 h at rt and solvent was removed under reduced pressure. The resultant residue was purified by silica gel column chromatography (hexanes–EtOAc, 4:1) to give **10** (630 mg, 16% from **7**) as a semi-white solid: mp 50 °C. ^{1}H NMR ($CDCl_3$): δ 0.08 and 0.09 (2s, 2 × 3H), 0.90 (s, 9H), 1.29 (s, 3H), 1.54 (s, 3H), 1.85 (m, 1H), 2.39 (m, 1H), 2.90 (m, 1H), 4.07 (s, 2H), 4.27–4.41 (m, 3H), 6.48 (s, 1H), 7.9 (s, 1H). ^{13}C NMR ($CDCl_3$) δ −4.6, 18.3, 25.2, 26.0, 27.5, 38.5, 40.4, 85.8, 86.6, 88.3, 112.8, 114.6, 115.2, 120.6, 142.8. Anal. calcd for $C_{19}H_{31}N_3O_3Si$·0.3 EtOAc: C, 60.06; H, 8.33; N, 10.40. Found: C, 60.11; H, 8.45 ; N, 10.13.

(1′*R*,2′*S*,3′*S*,4′*S*)-4-Amino-7-[4′-(*t*-butyldimethylsilyloxy)-2′,3′-*iso*propyl-idenedioxycyclopent-1′-yl]-5*H*-pyrrolo[3,2-*d*]pyrimidine (11). To a solution of **10** (610 mg, 1.61 mmol) in EtOH (30 mL) was added formamidine acetate (667 mg, 6.41 mmol) and this mixture refluxed for 8 h. The solvent was then removed by evaporation under reduced pressure and the residue purified via column chromatography, eluting with EtOAc. Fractions containing the product were combined and evaporated to afford 410 mg (63%) of **11** as a white solid: mp 134 °C dec. ^{1}H NMR (DMSO-d_6) δ −0.02 and 0.06 (2s, 2 × 3H), 0.82 (s, 9H), 1.21 (s, 3H), 1.41 (s, 3H), 2.10 (m, 1H), 2.30 (m, 1H), 4.16 (t, 1H), 4.42 (t, 1H), 4.87 (q, 1H), 6.62 (s, 2H), 7.36 (s, 1H), 8.08 (s, 1H), 10.70 (s, 1H). ^{13}C NMR (DMSO-d_6) δ −4.8, 17.7, 21.0, 24.8, 25.6, 27.1, 78.1, 84.2, 87.2, 111.1, 113.9, 115.4, 125.1, 145.1, 149.6, 150.3. Anal. calcd for $C_{20}H_{32}N_4O_3Si$·0.6 CH_3OH: C, 58.33; H, 8.11; N, 13.21. Found: C, 58.10; H, 7.99; N, 12.82.

(1′*R*,2′*S*,3′*R*,4′*S*)-4-Amino-7-(4′-hydroxy-2′,3′-*iso*propylidenedioxycyclopent-1′-yl]-5*H*-pyrrolo[3,2-*d*]pyrimidine (12). A solution of **11** (400 mg, 0.99 mmol) in anhydrous THF (40 mL) and Bu_4NF (1.0 M solution in THF, 2.8 mL) was stirred at rt for 23 h. The solvent was evaporated under reduced pressure and the residue purified via column chromatography, eluting with EtOAc–MeOH (4:1) to afford 260 mg (91%) of **12** as a white solid: mp 248 °C. ^{1}H NMR (DMSO-d_6) δ 1.20 (s, 3H), 1.41 (s, 3H), 1.99 (m, 1H), 2.37 (m, 1H), 3.23 (m, 1H), 4.04 (m, 1H), 4.41 (q, 1H), 4.78 (q, 1H), 5.67 (br s, 1H), 6.70 (s, 2H), 7.40 (s, 1H), 8.08 (s, 1H), 10.70 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 24.6, 27.1, 75.9, 85.1, 87.2, 110.5, 113.8, 115.8, 125.3, 144.6, 149.4, 150.3. Anal. calcd for $C_{14}H_{18}N_4O_3$·0.5H_2O: C, 56.18; H, 6.40; N, 18.72. Found C, 55.94; H, 6.39; N, 18.53.

(1′*R*,2′*S*,3′*R*,4′*S*)-4-Amino-7-(2′,3′,4′-trihydroxycyclopent-1′-yl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (9-deaza-5′-noraristeromycin) (2) hydrochloride. Compound **12** (170 mg, 0.58 mmol) was suspended in HCl (2 N solution in MeOH, 35 mL) and this mixture was stirred for 4 h. The solvent was evaporated under reduced pressure and the residue was co-evaporated with MeOH (3 × 30 mL). This material was recrystallized from MeOH to provide **2** (85 mg, 51%) as a white solid: mp 246 °C; $[\alpha]_D^{23.6}$ −39.52 (*c* 0.084, H_2O). ^{1}H NMR (DMSO-d_6) δ 1.47 (m, 1H, H-5′), 2.47 (m, 1H, H-5′), 3.20 (m, 1H,

H-1′), 3.71 (m, 1H, H-4′), 3.94 (m, 2H, H-2′ and H-3′), 4.4-5.1 (br s, 2H, 2 × OH), 7.74 (d, 1H, H-6), 8.51 (s, 1H, H-2), 8.93 (br s, 2H, NH_2), 12.67 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 36.8, 37.4, 75.2, 77.6, 77.9, 112.6, 114.3, 128.6, 133.0, 144.7, 152.4. Anal. calcd for $C_{11}H_{14}N_4O_3$·HCl: C, 46.08; H, 5.27; N, 19.54. Found: C, 46.27; H, 5.31; N, 19.31.

Antiviral assays. The antiviral and toxicity analyses were performed following standard procedures reported by us previously.[2,14]

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