Carbocyclic Isoadenosine Analogues of Neplanocin A

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Supporting Information

General. Melting points were recorded on a Meltemp II melting point apparatus and are uncorrected. Combustion analyses were performed by Atlantic Microlabs, Inc., Atlanta, GA. UV spectral data was obtained on a Varian Cary 100 Bio UV-Vis spectrometer. ^{1}H and ^{13}C spectra were recorded on a Bruker 300 spectrometer (operated at 300 and 75 MHz, respectively) all 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), and m (multiplet). Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm Whatman Diamond silica gel 60-F_{254} precoated plates with visualization by irradiation with a Mineralight UVGL-25 lamp. Column chromatography was performed on Whatman silica, 200-400 mesh, 60 Å and elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials.

(+)-2,3-(Isopropylidenedioxy)-4-cyclopenten-1-ol (4): To a stirred solution of cyclopentenone **(-)-3**[1] (2.31 g, 15.00 mmol) and $CeCl_3 \cdot 7H_2O$ (5.59 g, 15.00 mmol) in MeOH (70 mL) at 0 ˚C was added in small portions $NaBH_4$ (1.13 g, 30.00 mmol).[2] After stirring at rt for 1 h the mixture was neutralized with conc. HCl, reduced to 2/3 volume, extracted with brine and ether, and the organic layers combined, dried ($MgSO_4$), and concentrated to give **4** as a yellow syrup (2.32 g, 99%) which was used directly in the next step. Spectral data was in agreement with literature values.[3]

1-Bromo-2,3-(isopropylidenedioxy)cyclopent-4-ene (5): To a stirred solution of 4-nitrobenzoic acid (3.00 g, 17.95 mmol), PPh_3 (4.71 g, 17.95 mmol) in dry THF (100 mL) was added DIAD (3.63 g, 17.95 mmol), and the mixture stirred under argon at rt for 15 min. A solution of **4** (1.4 g, 8.97 mmol) in dry THF (50 mL) was then added, and the mixture stirred at 55 ˚C for 3 d. The solvent was removed under vacuum and the resulting syrup purified by column chromatography eluting with hexane:EtOAc (9:1) to give 2,3-(isopropylidenedioxy)-1-[(*p*-nitrobenzoyl)oxy]cyclopent-4-ene a white solid (2.40 g, 88%) which was used directly in the next step without further purificantion.[4]

To a stirred solution of 2,3-(isopropylidenedioxy)-1-[(*p*-nitrobenzoyl)oxy]cyclopent-4-ene (1.52 g, 5.00 mmol) in MeOH (100 mL) in H_2O, was added KOH (0.56 g, 10.00 mmol) and the reaction mixture was stirred at rt for 1h. The MeOH was removed by evaporation, and the resulting aqueous mixture extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated to give (-)-2,3-(isopropylidenedioxy)-4-cyclopenten-1-ol as a yellow syrup (0.73 g, 94%), which was used directly in the next step. Spectral data was in agreement with literature values.[3]

To a stirred solution of (-)-2,3-(isopropylidenedioxy)-4-cyclopenten-1-ol (0.73 g, 4.70 mmol) and PPh_3 (2.46 g, 9.4 mmol) in DMF (15 mL) was added at 0 ˚C NBS (1.67 g, 9.4 mmol). After stirring at rt for 3 h the mixture was added to H_2O, extracted with CH_2Cl_2, dried ($MgSO_4$), concentrated, and purified by column chromatography eluting with hexane:EtOAc (5:1) to give **5** as an unstable yellow syrup (0.61 g, 60%). ^{1}H NMR ($CDCl_3$) d1.36 (s, 3H), 1.39 (s, 3H), 4.84 (s, 1H), 4.96 (d, 1H), 5.33 (m, 1H), 5.98 (m, 2H); ^{13}C NMR ($CDCl_3$) d 26.7, 27.9, 54.9, 84.4, 86.3, 112.4, 134.3, 135.3.

(-)-2,3-(Isopropylidenedioxy)-1-[(methanesulfonyl)oxy]-cyclopent-4-ene (6): To a stirred solution of **4** (1.63 g, 10.46 mmol) and pyridine (25 mL) in CH_2Cl_2 (50 mL) at 0 ˚C was added MsCl (3.59 g, 31.38 mmol). After stirring at rt for 3 h, cold H_2O (50 mL) was added to the reaction mixture and then washed sequentially with 1 N HCl (2 x 50 mL) and brine (2 x 50 mL), dried ($MgSO_4$), concentrated, and purified by column chromatography eluting with hexane:EtOAc (5:1) to afford **6** as a yellow syrup (2.01 g, 82.1%). Spectral data was in agreement with literature values.[4]

(-)-2,3-(Isopropylidenedioxy)-1-[(*p*-tolylsulfonyl)oxy]-cyclopent-4-ene (7): Using the identical method as was used for **6**, but substituting TsCl (2.31 g, 14.82 mmol), afforded **7** as a yellow syrup (3.86 g, 84%). Spectral data was in agreement with literature values.[4]

(-)-3-(2',3'-Dihydroxycyclopent-4'-enyl)adenine (1): A solution of adenine (0.78 g, 5.80 mmol) and **5** (1.40 g, 6.30 mmol) in *N*,*N*-dimethylacetamide (10 mL) was heated at 110 ˚C for 2 d. The reaction mixture was cooled to rt and the solvent was removed under vacuum. The resulting brown solid was dissolved in a small amount of hot H_2O, neutralized with NH_4OH, and placed in the refrigerator. After 5 h a tan precipitate formed, which was isolated and purified by column chromatography eluting with EtOAc:MeOH (9:1) to afford 3-(2',3'-isopropylidenedioxy-4',5'-cyclopentene)adenine as a white solid (1.12 g, 64%), mp >260 ˚C. ^{1}H NMR (CD_3OD) d 1.33 (s, 3H), 1.47 (s, 3H), 4.80 (d, 1H), 5.56 (dd, 1H), 5.85 (s, 1H), 6.03 (dd, 1H), 6.40 (dd, 1H), 7.93 (s, 1H), 8.13 (s, 1H); ^{13}C NMR (CD_3OD) d 25.4, 27.1, 70.8, 72.7, 83.6, 85.5, 113.3, 121.4, 130.0, 140.3, 142.2, 150.3, 153.6, 157.8. Anal. Calcd. for $C_{13}H_{15}N_5O_2$: C, 56.21; H,5.63; N, 25.20. Found: C, 56.31; H, 5.57; N, 24.84.

A solution of 3-(2',3'-isopropylidenedioxy-4',5'-cyclopentene)adenine (100 mg, 0.36 mmol) in TFA/H_2O (2:1) was stirred at rt for 2 h. The solution was concentrated and co-evaporated with MeOH to remove all traces of TFA, and the resulting syrup crystallized using ethyl acetate:MeOH (9:1) to afford **1** as a fine white powder (84 mg, 99%); mp 181-183 ˚C. UV (H_2O), 274 nm. ^{1}H NMR (CD_3OD) d 4.50 (t, 1H), 4.69 (m, 1H), 5.62 (m, 1H), 6.15 (dd, 1H), 6.30 (m, 1H), 7.90 (s, 1H), 8.20 (s, 1H); ^{13}C NMR (CD_3OD) d 72.8, 74.5, 77.6, 121.3, 132.5, 138.4, 144.0, 150.6, 153.1, 156.8. HRMS [m/z +1] Calcd. 234.090. Found 234.099.

(+)-3-(2',3'-Dihydroxycyclopent-4'-enyl)adenine (2): Synthesized in an analogous fashion as was used for **1**, however starting with **(+)-3** gave **2** as a fine white powder (0.89 g, 43% in six steps from **(+)-3**)); mp 182-183 ˚C. UV (H_2O) 274 nm. ^{1}H NMR (CD_3OD) d 4.57 (t, 1H), 4.72 (m, 1H), 5.77 (m, 1H), 6.13 (dd, 1H), 6.33 (m, 1H), 8.44 (s, 1H), 8.54 (s, 1H); ^{13}C NMR (CD_3OD) d 71.8, 73.3, 76.9, 111.1, 130.8, 137.6, 144.8, 146.3, 148.4, 154.1; HRMS [m/z+1] Calcd. 234.090, Found 234.099

References

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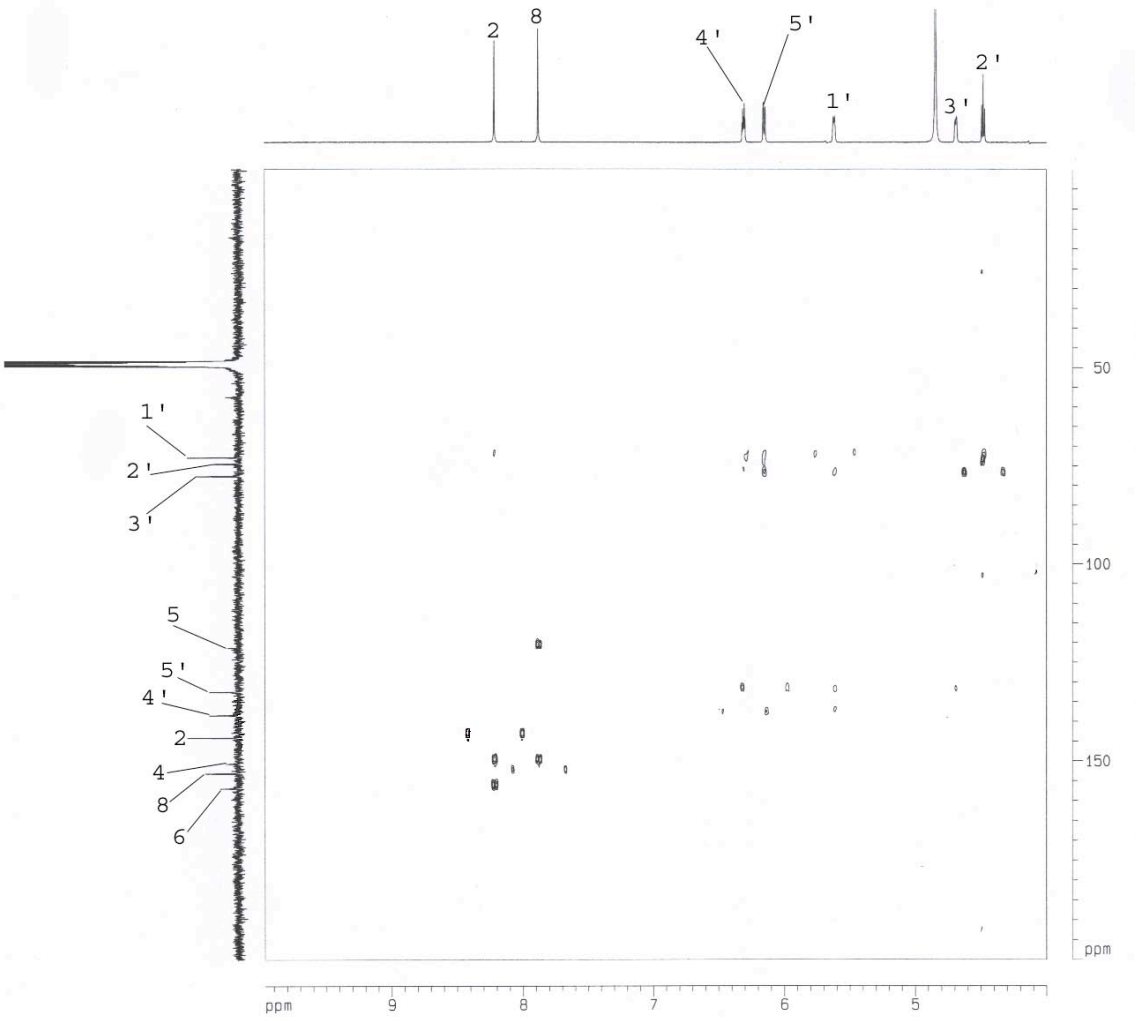
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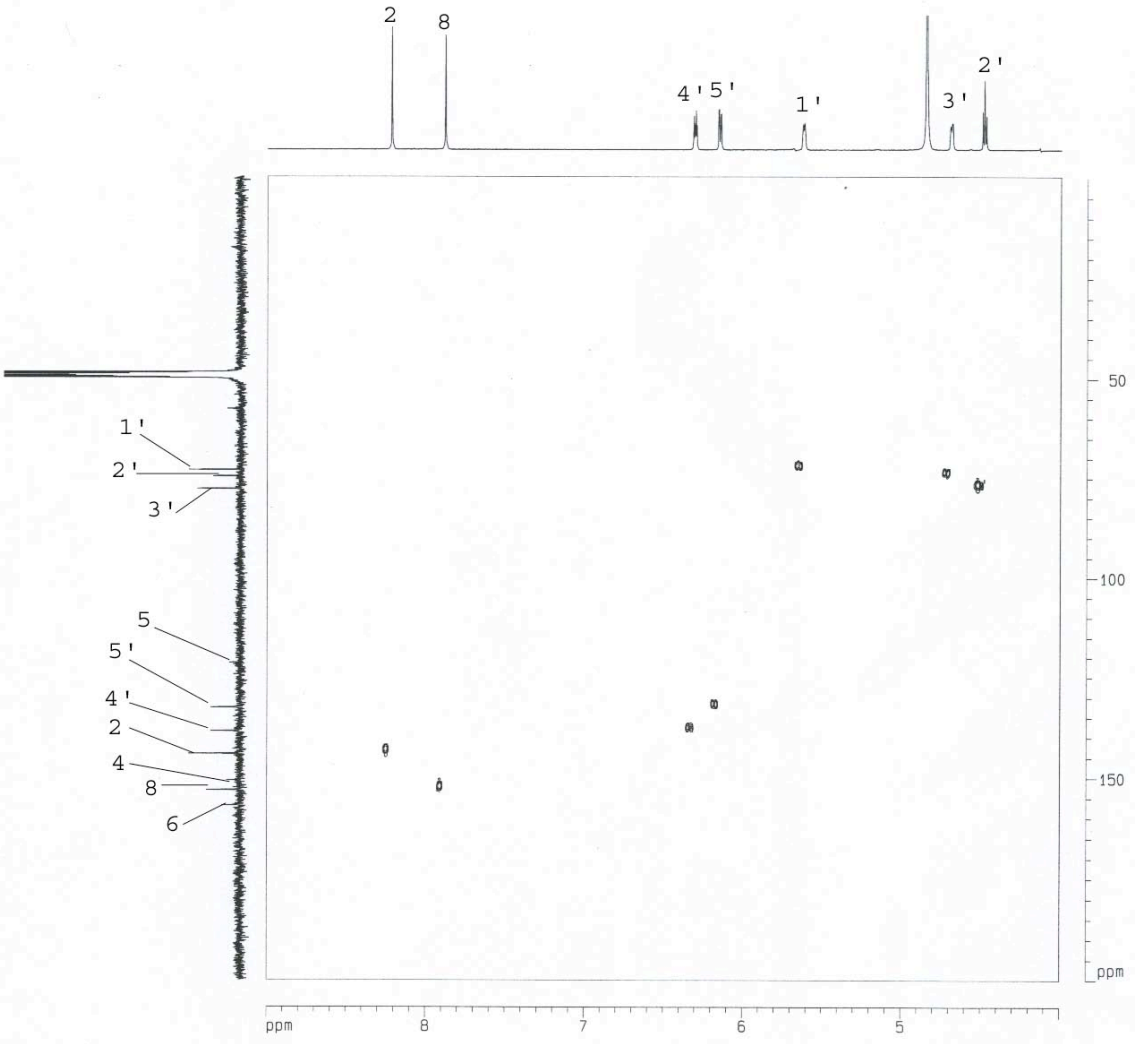
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