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SYNTHESIS OF 3'-DEOXYADENOSINE-3'-SPIROCYCLOPROPANE, 3'-DEOXYURIDINE-3'-SPIROCYCLOPROPANE, AND 5'-DEOXY-4',5'-METHANOADENOSINE[1]

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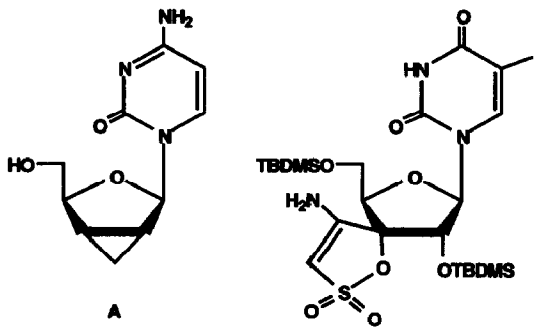
Abstract: Cycloaddition of diazomethane with 3'-deoxy-3'-methylene- and 4',5'-didehydro-5'-deoxynucleoside derivatives followed by sensitized photochemical extrusion of nitrogen provided the previously unreported 3'- and 4'-spirocyclopropane nucleoside derivatives. Enhancement of the cycloaddition reactions by electron withdrawing benzoyl protecting groups was observed.

The development of AZT, DDI, and DDC as therapeutic agents for the treatment of AIDS has stimulated research on structurally novel nucleoside analogues with a variety of biological activities.[2] Examples of newer sugar-modified nucleoside analogues are 2',3'-dideoxy-2',3'-α-methanocytidine (**A**)[3] and TSAO (**B**).[4]



Nucleoside analogues which function as mechanism-based inhibitors of important enzymes in the nucleic acid manifold represent an important class of "rationally designed" agents with significant biomedical potential.[5] We recently reported the design, synthesis, and radical-induced ring opening reactions of 2'-deoxyadenosine-2'-spirocyclopropane (**C**) and its uridine analogue **D** as mechanistic probes for ribonucleotide reductases.[6] The precursor 3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2'-deoxy-2'-methylene derivatives underwent cycloaddition with diazomethane smoothly at ambient temperature in diethyl ether within 48 h to give isomeric 2'-deoxynucleoside

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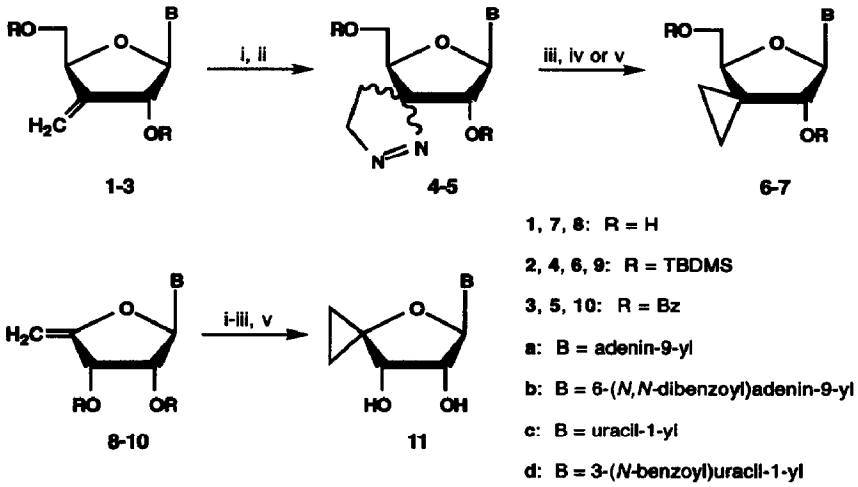
2'-spiropyrazoline derivatives. This mixture was subjected to sequential benzophenone-sensitized photolysis and deprotection to give the 2'-deoxynucleoside 2'-spirocyclopropanes **C** and **D**.[6] Very sluggish cycloadditions occurred with the 3'-methylene analogues, and a 4',5'-unsaturated derivative did not react. We now describe syntheses of the target 3'-deoxyadenosine(and uridine)-3'-spirocyclopropanes (**7a,c**) and the 4'-spiro analogue, 5'-deoxy-4',5'-methanoadenosine (**11a**, Scheme 1).

Scheme 1[a]



[a](i) BzCl/[Et(*i*-Pr)$_2$N]/pyridine. (ii) CH_2N_2/Et_2O. (iii) hv/Ph_2CO/MeCN/C_6H_6. (iv) $Bu_4N^+F^-$/THF. (v) NH_3/MeOH.

The cycloaddition of diazomethane (excess CH_2N_2/Et_2O/ambient temperature/32 days) with 2',5'-bis-*O*-(*tert*-butyldimethylsilyl)-3'-deoxy-3'-methyleneadenosine (**2a**)[7] occurred very slowly to give a diastereomeric mixture of 3'-deoxyadenosine-3'-spiropyrazolines **4a** and starting **2a** (10:1, 95%; ^{1}H NMR) which was difficult to separate by chromatography on silica gel. Treatment of 2',3'-bis-*O*-TBDMS-4',5'-didehydro-5'-deoxyadenosine[8] (**9a**) for a month under identical conditions gave no evidence of cycloaddition. Diazomethane was reported to add to enol ethers in the presence of bis(benzonitrile)palladium(II) dichloride.[9] However, the nucleoside enol ether **9a** was equally unreactive under those modified conditions.

Polarized alkenes with conjugating and/or electron withdrawing substituents usually undergo cycloaddition with diazomethane smoothly and with predictable regioselectivity.[10] In the 3',5'-bis-*O*-TBDMS-2'-deoxy-2'-methylene nucleosides,[6] the exocyclic double bond is vicinal to the anomeric center. This *N,O*-acetal carbon (C1'), which is at the aldehyde oxidation level, apparently promotes the cycloaddition effectively. We reasoned that reactions of **2a** and **9a** with diazomethane might be accelerated by increasing the electron withdrawing

character of their protecting groups. Electron withdrawal should favor cycloaddition by lowering the energies of the alkene LUMOs relative to those of their less polarized (carbon-substituted and vinyl ether) analogues.[11,12]

To test this hypothesis we prepared the fully benzoylated derivatives **3b** (98%), **3d** (95%), and **10b** (92%) by treatment of **1a**[7] and **8a**[13] with excess benzoyl chloride in pyridine, and **1c**[14] with benzoyl chloride/ethyldiisopropylamine/pyridine.[15] Enhancement of electron withdrawal from the alkene moiety of **3b** by the benzoyl groups was indicated qualitatively by the downfield ^{1}H NMR shifts ($\Delta\delta$ ~0.4 ppm) of the vinyl proton signals for **3b** (δ 5.55 and 5.70) relative to those of the bis-silyl ether **2a** (δ 5.17 and 5.25).

Dramatically enhanced rates of the cycloaddition reactions were observed upon treatment of **3b** and **3d** with diazomethane (excess $CH_2N_2/Et_2O/CH_2Cl_2$/ambient temperature). The starting alkenes were consumed within 48 h to provide diastereomeric mixtures of the pyrazolines **5b** (95%) and **5d** (70%), respectively. The sensitized photolysis[3] (benzophenone/acetonitrile/benzene) of **5b** and **5d** followed by removal of the benzoyl groups (NH_3/MeOH) gave 3'-deoxyadenosine-3'-spirocyclopropane[16a] (**7a**, 90%) and 3'-deoxyuridine-3'-spirocyclopropane[16b] (**7c**, 80%), respectively.

Treatment of **10b** with diazomethane (excess $CH_2N_2/Et_2O/CH_2Cl_2$/ambient temperature/30 days) gave an unstable diastereomeric mixture of 4'-spiropyrazoline derivatives (15%) plus recovered **10b** (75%) which was easily separated by chromatography on silica gel. Attempts to catalyze this cycloaddition with Lewis acids (e.g. $ZnCl_2$, $AlCl_3$) failed. Sensitized photolysis of the 4'-spiropyrazoline mixture and deprotection (NH_3/MeOH) gave the 4'-spirocyclopropane target, 5'-deoxy-4',5'-methanoadenosine[16c] (**11a**, 45%).

In summary, we have synthesized the previously unreported 3'-deoxyadenosine-3'-spirocyclopropane, 3'-deoxyuridine-3'-spirocyclopropane, and 5'-deoxy-4',5'-methanoadenosine from their methylene analogues by sequential cycloaddition of diazomethane and sensitized photolytic extrusion of nitrogen. Acceleration of the rates of the cycloaddition reactions by replacement of the silyl ether protecting groups with benzoyl esters was demonstrated. Although an electronic rationalization for this acceleration is theoretically plausible and in harmony with the observed downfield ^{1}H NMR shifts, the possibility of accompanying steric factors cannot be excluded by our present results.

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16. Solutions of compounds in Me_2SO-d_6/Me_4Si were used for all ^1H NMR spectra. (a) **7a**: mp 203-204 °C; ^1H NMR δ 0.40-0.60 & 0.80-1.00 (m & m, 2 & 2, cyclopropyl), 5.83 (d, 1, H1'), 8.18 & 8.38 (s & s, 1 & 1, H2 & H8); Anal. Calcd. for $C_{12}H_{15}N_5O_3 \cdot 0.75H_2O$: C, 49.56; H, 5.72: N, 24.08. Found: C, 49.47; H, 5.84; N, 23.96. (b) **7c**: mp 182-183 °C; ^1H NMR δ 0.40-0.60 & 0.80-1.00 (m & m, 2 & 2, cyclopropyl), 5.79 (d, 1, H1'), 5.68 & 7.98 (d & d, 1 & 1, H5 & H6); Anal. Calcd. for $C_{11}H_{14}N_2O_5$: C, 51.97; H, 5.55; N, 11.02. Found: C, 52.11; H, 5.78; N, 11.22. (c) **11a**: mp 208-210 °C; ^1H NMR δ 0.70-0.90 (m, 4, cyclopropyl), 5.97 (d, 1, H1'), 8.18 & 8.36 (s & s, 1 & 1, H2 & H8); Anal. Calcd. for $C_{11}H_{13}N_5O_3$: C, 50.19; H, 4.98: N, 26.60. Found: C, 50.25; H, 5.09; N, 26.39.

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