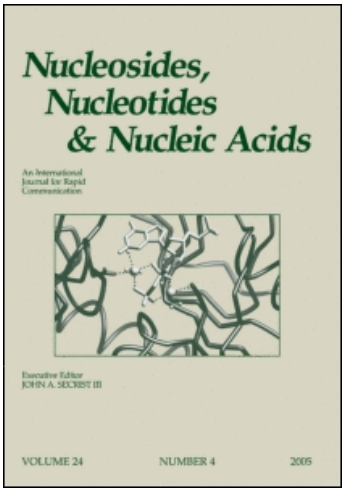

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Development of Novel Bridged and Caged Nucleoside Analogs as Biochemical Tools

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DEVELOPMENT OF NOVEL BRIDGED AND CAGED NUCLEOSIDE ANALOGS AS BIOCHEMICAL TOOLS

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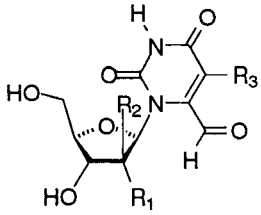
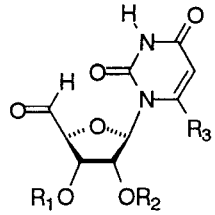
Abstract: New classes of closely biomimetic, *anti* conformation restricted, transglycosidic spiro, bridged, and caged pyrimidine nucleoside analogs are being developed. Progress towards accessing members of the new caged 2'-deoxyuridine mimic class is related.

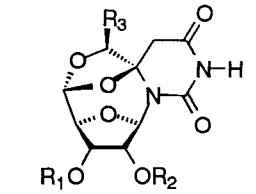
Of the many classes of transglycosidic cyclonucleoside analogs developed as bioactive or medicinal agents or as biochemical tools for conformation/bioactivity relationship studies, few are spiro or caged in nature and many are substantially different in structure by comparison to natural counterparts. The uridine-6-carboxaldehydes **1a-d**[1-3] are so highly electrophilic that, save for **1d**, each exhibits a strong proclivity towards adopting transglycosidic hemiacetal forms. In our laboratory, we are developing spiro nucleosides **3a-d** from **2a,b**, mono-bridged 5'-epimeric diastereomers **4a,b** from **3d**, and caged 2'-deoxyuridine mimics **5a-c** from **1c** and its 5' carboxaldehyde derivative. Access to targets **3a-d**, **4a-b**, and **5b,c** are all based on the chemistry of nucleoside 5'-carboxaldehydes, known to undergo hydrate and hemiacetal formation upon exposure to water or alcohol.[4]



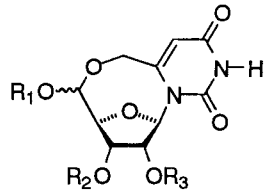
1a, R_1 = OH, R_2 = R_3 = H
b, R_1 = R_2 = R_3 = H
c, R_1 = R_3 = H, R_2 = OH
d, R_1 = R_2 = H, R_3 = Me



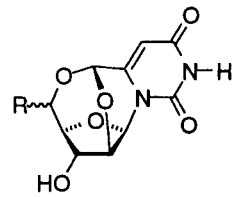
2a, R_1, R_2 = $(CH_3)_2C$, R_3 = CHO
b, R_1, R_2 = $(CH_3)_2C$, R_3 = CH_2OH



3a, R_1, R_2 = $(CH_3)_2C$, R_3 = OH
b, R_1 = R_2 = H, R_3 = OH
c, R_1, R_2 = $(CH_3)_2C$, R_3 = H
d, R_1 = R_2 = R_3 = H



4a, R_1 = R_2 = R_3 = Ac
b, R_1 = R_2 = R_3 = H

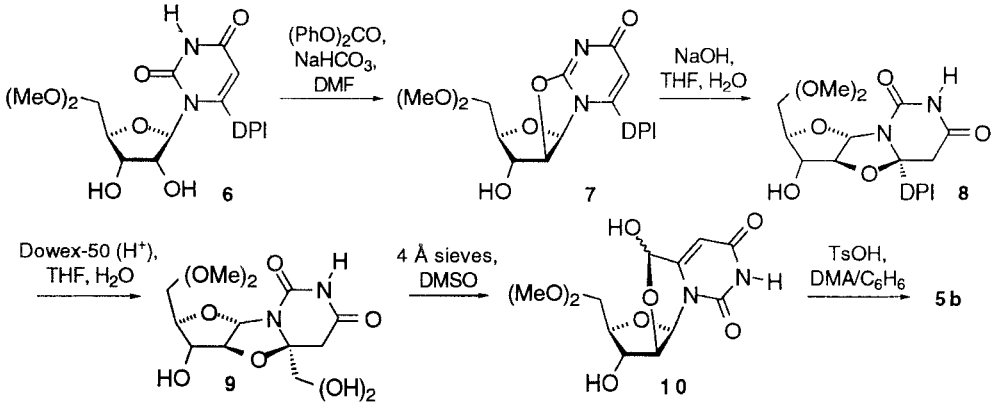


5a, R = H
b, R = OCH_3
c, R = OH

Whereas its unprotected counterpart (**2**, R_1=R_2=H, R_3=CHO) forms only a dihydrate in water, **2a** forms spiro **3a** *via* intramolecular Michael-type addition.[5,6] Aldehyde **2b** likewise forms **3c**.[7] When acetylated, **3d** affords bridged **4a**,[7] now being processed to **4b**.

RESULTS AND DISCUSSION

To our knowledge, the classes of transglycosidic-bridged nucleosides[8,9] contain only one subclass of caged compounds.[10] In a recent advancement towards accessing the novel caged 2'-deoxyuridine mimics **5c**, we have recently completed a synthesis of a methoxy-bearing **5b**. 1,3-Diphenylimidazolidine (DPI) **6**, obtained (86%) from its corresponding aldehyde, led to **7** (31%) together with its 3'-phenyl carbonate (58%) under 2,2'-anhydro forming conditions. Saponification of either of these gave the O2',6-cyclic intermediate **8**. Deprotection (100%) at the 6-position of the dihydrouracil ring of **8** gave hydrate **9**. In a key step for subsequent cage construction, hydrate **9** reverted to **10** (100%) simply upon desiccation. As does **5c**,[6b,c] **10** exists as a 3:1 mixture of hemiacetal diastereomers. Deprotection of **10** was sluggish but proceeded (60%) to give a 2:1 diastereomeric mixture of 7,O2'-cyclic hemiacetals rather than **5c**. Attempts to link the 7-hemiacetal OH group with the 5'-carbonyl one in the 7,O2'-cyclic hemiacetals to **5c** have thus far been unsuccessful. However, an intramolecular acetal formation mediated by TsOH in 1:2 DMA/benzene afforded **5b**,[11] isolated as a single diastereomer in a 25% yield. Efforts are now underway to effect demethylation of this to **5c**, the unprotected caged nucleoside.



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11. Characterization data for **5b**: ^{1}H NMR ($(CD_3)_2SO$) δ 11.5 (1, br, NH), 6.37 (1, d, H1', $^3J_{1'-2'}$ = 6.4 Hz), 5.83 and 5.77 (each 1, each s, H5 and H7), 5.71 (1, d, 3'-OH, $^3J_{3'-3'-OH}$ = 4.3 Hz), 4.93 (1, d, H5', $^3J_{4'-5'}$ = 3.8 Hz), 4.67 (1, d, H2'), 4.38 (1, d, H3'), 4.21 (1, d, H4'), 3.23 (3, s, CH_3O). ^{13}C NMR ($(CD_3)_2SO$) δ 162.4 (C4), 150.8 and 149.1 (C2/C6), 99.4 and 99.2 (C5'/C5), 88.0 (C7), 83.1 (C4'), 79.7 (C1'), 76.7 and 76.4 (C2'/C3'), 55.3 (CH_3O). LRFAB-MS, *m/e* 285.1 (40%, MH^+). HRFAB-MS ($C_{33}H_{33}N_4O_8$): calcd 285.0723, found 285.0722.