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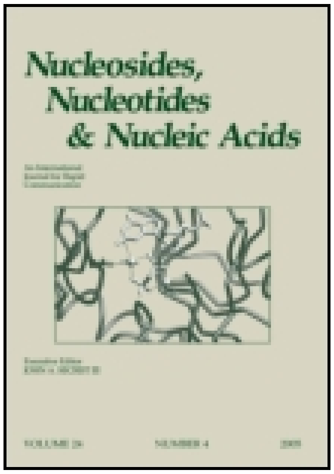

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Stereocontrolled Synthesis of Diene and Enyne Sugar-Modified Nucleosides and Their Interaction with S-Adenosyl-L-homocysteine Hydrolase

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Stereocontrolled Synthesis of Diene and Enyne Sugar-Modified Nucleosides and Their Interaction with *S*-Adenosyl-L-homocysteine Hydrolase

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ABSTRACT

Conjugated diene **5–7** and enyne **8** analogs derived from adenosine and uridine were synthesized employing Pd-catalyzed cross-coupling reactions.

Key Words: *S*-Adenosyl-L-homocysteine hydrolase; Coupling reactions; Enzyme inhibitors; Nucleosides.

The cellular enzyme *S*-adenosyl-L-homocysteine hydrolase effects hydrolytic cleavage of *S*-adenosyl-L-homocysteine, a potent inhibitor of crucial transmethylation enzymes, to adenosine and L-homocysteine.[1] Dienes **5** and **6** and enynes **8** derived from adenosine were designed as putative substrates of the ''hydrolytic activity'' of AdoHcy hydrolase.[2] Conceptually, enzyme-mediated addition of water

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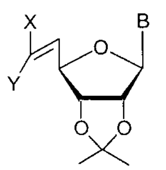
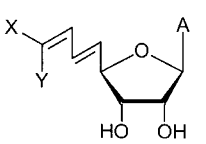
might occur as a 1,2 or 1,4-process across the conjugated dienes/enynes resulting in the generation of new species bearing hydroxyl, keto or acyl binding sites within the enzymes.

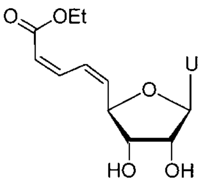
Oxidation of the 2′,3′-O-isopropylideneadenosine and Wittig treatment of the crude 5′-aldehyde with $Ph_3P=CHTs$ gave 6′(*E*)-vinyl sulfone homonucleosides **1**. Stannyldesulfonylation (Bu_3SnH/AIBN/toluene) of **1** yielded separable mixtures of the vinyl 6′(*E* and *Z*)-stannanes **2** and **3** (B = A).[3] Stille coupling[4] [$(PPh_3)_4Pd$/THF] of vinyl 6′(*E*)-stannane **2** (B = A) with ethyl (*E*)-3-iodopropenoate and deacetonization (TFA/H_2O) gave dienoic ester **5** (5′*E*/7′*E*, s-*trans*; 75%), whereas reaction with ethyl (*Z*)-3-iodopropenoate gave the conjugated diene **6** (5′*E*/7′*Z*).[5] Analogous Pd-catalyzed coupling of 6′(*Z*)-stannane derived from uridine (**3**, B = U) with ethyl (*Z*)-3-iodopropenoate and deacetonization afforded **7** (5′*Z*/7′*Z*; 68%).[a]



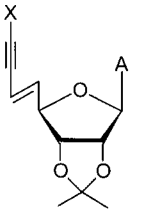
1 X = Ts, Y= H
2 X = Bu_3Sn, Y = H
3 X = H, Y = Bu_3Sn
4 X = I, Y = H



5 X = CO_2Et, Y = H
6 X = H, Y = CO_2Et



7



8 X = $SiMe_3$

Dienoic esters **5** and **6** produced time- and concentration-dependent inactivation of AdoHcy hydrolase with significant decreases in the enzyme's NAD^+ content. However, **5** and **6** upon incubation with the enzyme were not metabolized suggesting that these dienes do not show "hydrolytic substrate activity".

Sonogashira coupling[4] [CuI/$(PPh_3)_2PdCl_2$/Et_2NH] of (*E*)-iodohomovinyl[3] **4** (B = A) with (trimethylsilyl)acetylene gave enyne **8** (71%) with expected *E*-stereochemistry. Enyne analogues (e.g., deprotected **8**) with linear triple bond attach to C6′ would require a different vicinity for binding and/or addition of enzyme-bound water and can be further modified at C8′(X = halogen, COOH).

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[a] Ethyl 1,5,6,7,8-Pentadeoxy-1-(uracil-1-yl)-β-D-*ribo*-non-5(*Z*),7(*Z*)-dienofuranuronate (7). For general coupling and deprotection procedures see Ref.[5]: UV max 262 nm (ε 37 700), min 223 nm (ε 8 000); ^1H NMR (Me_2SO-d_6) δ 1.21 (t, *J* = 7.1 Hz, 3, CH_3), 3.88 (q, *J* = 5.5 Hz, 1, H3′), 4.08–4.16 (m, 3, H2′ & CH_2), 4.79 (dd, *J* = 5.9, 8.8 Hz, 1, H4′), 5.40 (d, *J* = 6.0 Hz, 1, OH3′), 5.58 (d, *J* = 5.6 Hz, 1, OH2′), 5.66 (d, *J* = 8.1 Hz, 1, H5), 5.76 (d, *J* = 4.3 Hz, 1, H1′), 5.80 (d, *J* = 11.5 Hz, 1, H8′), 6.06 (dd, *J* = 9.0, 11,2 Hz, 1, H5′), 7.08 ("t", *J* = 11.7 Hz, 1, H7′), 7.33 ("t", *J* = 11.5 Hz, 1, H6′), 7.66 (d, *J* = 8.1 Hz, 1, H6), 11.40 (br s, 1, NH); ^{13}C NMR (Me_2SO-d_6) δ 14.98, 60.65, 73.68 & 75.00 (C2′ & C3′), 79.27 (C4′), 90.35 (C1′), 102.90 (C5), 120.13 (C8′), 127.14 (C6′), 138.40 & 139.47 (C5′ & C6), 142.15 (C7′), 151.45 (C2), 163.95 (C4), 166.35 (C9′); MS (CI) *m/z* 339 (MH^+). Anal. Calcd for $C_{15}H_{18}N_2O_7$ (338.33): C, 53.25; H, 5.36; N, 8.28. Found: C, 53.62; H, 5.61; N, 8.01.

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