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. Dienes 5 and 6 and enynes 8 derived from adenosine were designed as putative substrates of the “hydrolytic activity” of AdoHcy hydrolase. Conceptually, enzyme-mediated addition of water

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DOI: 10.1081/NCN-120022634 1525-7770 (Print); 1532-2335 (Online)

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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 Ph3P=CHTs gave δ(E)-vinyl sulfone homonucleosides 1. Stannyldesulfonylation (Bu3SnH/AIBN/toluene) of 1 yielded separable mixtures of the vinyl δ(E and Z)-stannanes 2 and 3 (B = A).[5] Stille coupling[(PPh3)4Pd/THF] of vinyl δ(E)-stannane 2 (B = A) with ethyl (E)-3-iodopropenoate and deacetonization (TFA/H2O) gave dienoic ester 5 (δ’E/δ’E, s-trans; 75%), whereas reaction with ethyl (Z)-3-iodopropenoate gave the conjugated diene 6 (δ’E/δ’Z).[5] Analogous Pd-catalyzed coupling of δ’(Z)-stannane derived from uridine (3, B = U) with ethyl (Z)-3-iodopropenoate and deacetonization afforded 7 (δ’Z/δ’Z; 68%).

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/((PPh3)2PdCl2/Et2NH] of (E)-iodohomovinylic[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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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 (Me2SO-d6) δ 1.21 (t, J = 7.1 Hz, 3, CH3), 3.88 (q, J = 5.5 Hz, 1, H3'), 4.08–4.16 (m, 3, H2' & CH2), 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); 13C NMR (Me2SO-d6) δ 14.98, 60.65, 73.68 & 75.00 (C2' & C3'), 79.27 (C4'), 90.35 (Cl'), 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 (Cl) m/z 339 (MH+). Anal. Calcd for C15H18N2O7 (338.33): C, 53.25; H, 5.36; N, 8.28. Found: C, 53.62; H, 5.61; N, 8.01.
ACKNOWLEDGMENTS

Supported by an award from the American Heart Association, Florida/Puerto Rico Affiliate and MBRS RISE program R25 GM61347 (LNC).

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