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Stannylation Approach to the Synthesis of 2'- and 3'-Substituted Analogues of 2',3'-Didehydro-2',3'-dideoxynucleosides

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ABSTRACT

Three methods are described for the introduction of a tributylstannyl group to the sp²-carbon of 2',3'-didehydro-2',3'-dideoxy nucleosides (d44Ns). The resulting stannylated products serve as versatile intermediates for the synthesis of d4Ns having various types of carbon-substituent.

Key Words: 2',3'-Didehydro-2',3'-dideoxy nucleoside; Stannylation; Anionic migration; Desulfonylative-stannylation; Sulfoxide-metal exchange.

Although the discovery of potent anti-HIV activity of d4T has stimulated the synthesis and evaluation of 2',3'-didehydro-2',3'-dideoxynucleosides (d4Ns), there have been known only a narrow range of their analogues bearing a carbon-substituent at the 3'- or 2'-position.^[1] Since transformation of vinylstannanes to various

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carbon-substituents is well appreciated, we investigated three different methods to introduce SnBu₃ group to the 3'- or 2'-position of d4Ns.

Anionic O → C Stannyl Migration. [2] Transalkoxylation between Bu₃SnOMe and d4T gave the 5'-O-stannylated derivative 1 as evidenced by 119Sn and 1H NMR spectra in benzene-d₆. When 1 was treated with LTMP in the presence of HMPA, the 5'-O-SnBu₃ group underwent migration to the 3'-position, as a result of C3'-lithiation, to give 2 in 60% yield along with a small amount of 3 (9%). The observed highly unusual vinylic deprotonation in the presence of allylic protons (H-1' and H-4') could be due to the base moiety which acts as a Lewis base and thus directs the regiochemistry of lithiation.

Radical-mediated Desulfonvlative Stannvlation. The 3'-C-benzenesulfonvl d4A (4) was prepared from 9-(2,3-anhydro-β-D-ribofuranosyl)adenine^[4] in good overall yield. Radical-mediated ipso-substitution of the SO₂Ph group proceeded efficiently by reacting Bu₃SnH/AIBN in refluxing benzene containing Et₃N to yield 5 (76%). The presence of Et₃N in this reaction is crucial for the subsequent successful chromatographic isolation of 5.

Sulfoxide-metal Exchange Reaction. [5] For the introduction of SnBu₃ group to the 2'-position of d4U, sulfoxide-metal exchange was examined. Preparation of the substrate 6 was carried out by the reported O^2 , 2'-anhydro-bond cleavage with PhSH, [6] which was followed by oxidation. When 6 was reacted with EtMgBr, the

generated 2'-vinylmagnesium was found to undergo partial protonation with N^3 -H. By treating 6 initially with NaH, the desired 7 was isolated in 62% yield.

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