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Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

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To cite this Article Fiandor, J. , Huryn, D. M. , Sluboski, B. , Todaro, L. J. and Tam, S.(1989) 'Synthesis of 3'-C-Substituted-2',3'-Dideoxynucleosides as Potential Anticancer Agents', *Nucleosides, Nucleotides and Nucleic Acids*, 8: 5, 1107 — 1108

To link to this Article: DOI: 10.1080/07328318908054299

URL: <http://dx.doi.org/10.1080/07328318908054299>

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SYNTHESIS OF 3'-C-SUBSTITUTED-2',3'-DIDEOXYNUCLEOSIDES AS POTENTIAL ANTI-AIDS AGENTS

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Abstract In this paper we report an efficient synthetic route to some novel 3'-C-substituted-2',3'-dideoxynucleosides. The critical 3'-C-C bond was constructed by an application of free radical methodology. This type of reaction was found to be stereoselective forming exclusively the 3'-"down" isomer. The stereochemical assignment at C-3' was confirmed by both nmr nOe experiments and single crystal X-ray analysis.

As part of our program on the development of anti-HIV agents, we have synthesized a new series of 2',3'-dideoxynucleosides. Our target structures are characterized by the presence of a carbon substituent at the C-3' position replacing the OH group. Representative examples of this novel series of nucleosides are compounds 1 and 2. These two compounds are of particular interest since the isosteric relationship of their carbon side chains at C-3' with an azido group make them close analogs of AZT, which is the only FDA approved drug for the treatment of AIDS to date.

In our synthesis, the critical 3'-C-C bond was formed by an application of free radical methodology. Thus, treatment of 3'-thiocarbonate 3a with allyl-tri-n-butylstannane under the conditions developed by G. Keck¹ was found to give 76% yield of 3'-allyl-substituted compound 4. This reaction was found to be stereoselective, and the stereochemical assignment at C-3' was inferred from nuclear Overhauser effect (nOe) experiments.

The same transformation can be carried out by reacting allyl tri-n-butylstannane with either the compound 3a or the imidazole thiocarbonyl compound, 3b, in degassed toluene solution containing α,α' -azobisisobutyronitrile (AIBN). After 3 hours at 80°C both reactions gave ~56% yield of compound 4.

The reaction was equally applicable for nucleosides with other bases. For example, under the thermal-initiated radical reaction conditions, 3'-allyl-2',3'-dideoxycytidine (6), was obtained in 40% yield from the 3'-thiocarbonate 5.

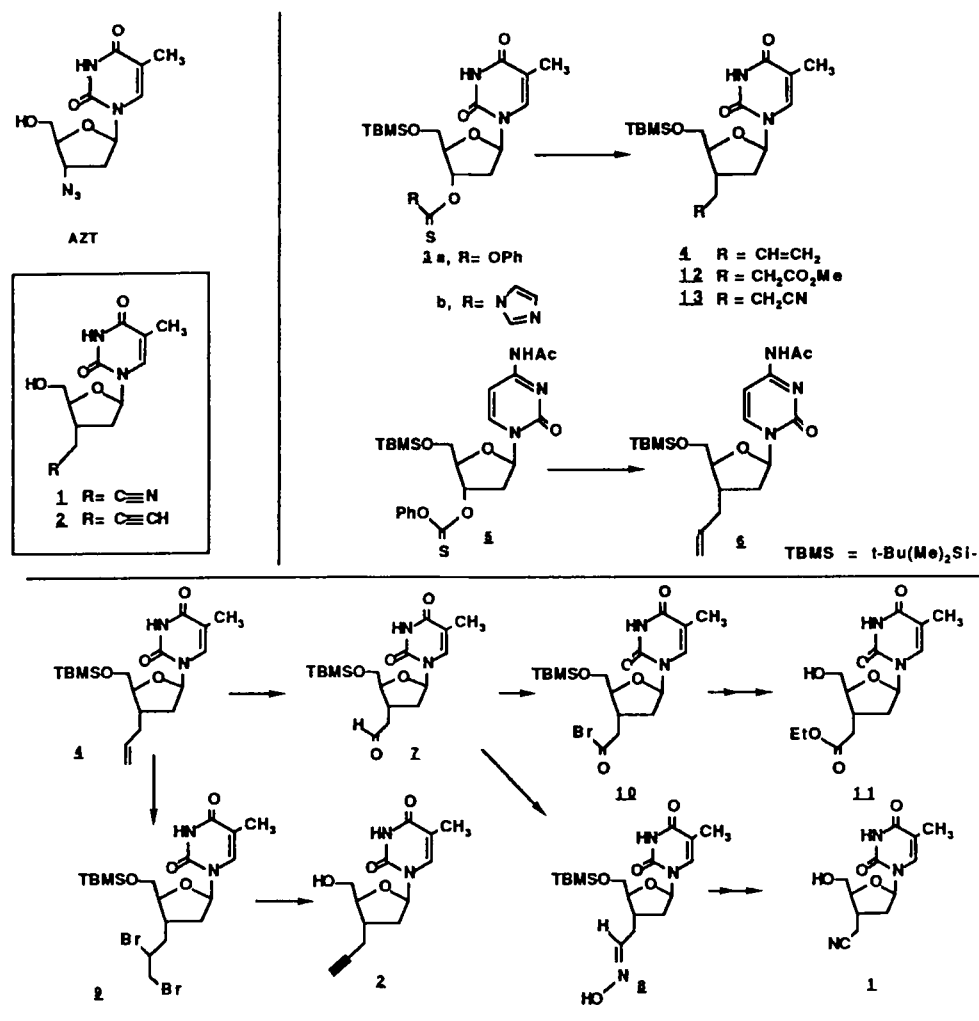
Since an allyl group is suitable for diverse structural manipulation, the efficient synthesis of a 3'-allyl substituted nucleoside, such as 4, has allowed an easy access to many other structures in the series. Some examples of these transformations are shown below.

Reaction of the allyl compound 4 with osmium tetroxide/sodium periodate gave the aldehyde 7 in 57% yield. Compound 7 on treatment with hydroxylamine afforded a high yield of the crystalline oxime 8 which was readily converted to the cyano compound, 1 on reaction with carbonyldiimidazole (97% yield).

Single crystal X-ray analysis of the oxime derivative 8 confirmed our stereochemical assignment.

For the synthesis of the propargyl compound 2, the allyl compound 4 was first converted into the dibromide 9 by reaction with bromine in carbon tetrabromide. Treatment of 9 with Na/DMSO then afforded the desired product 2 in 43% yield.

The aldehyde 7 is another useful synthetic intermediate. For example reaction of aldehyde 7 with N-bromosuccinimide gave the acid bromide 10 which on subsequent treatment with ethanol formed the ethyl ester 11 in 64% yield.



In addition to the successful use of allyl-tri-n-butylstannane, another type of free radical methodology was found to be equally applicable to nucleosides. Thus, reaction of compound 3 with either methyl acrylate or acrylonitrile under the thermal-initiated radical reaction conditions gave the expected products, 12 and 13, respectively, in 40-50% yield.

The 5'-silyl protecting groups in all of the examples given above were readily removed by conventional methods, such as Bu_4NF .

REFERENCE

1. G.E. Keck and J.B. Yates, *J. Amer. Chem. Soc.*, **1982**, *104*, 5829.