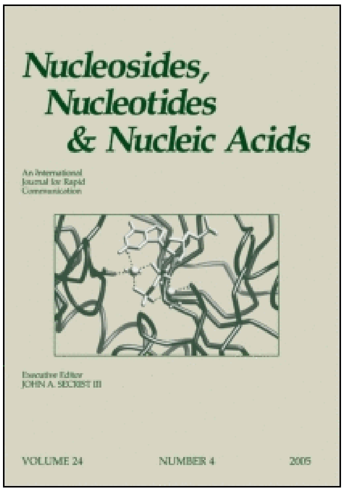


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of 3'-C-Substituted-2',3'-Dideoxynucleosldes as Potential Antcaids Agents

J. Fiandor[a]; D. M. Huryn[a]; B. Sluboski[a]; L. J. Todaro[a]; S. Tam[a]
[a] Roche Research Center, Hoffmann-La Roche Inc., Nutley, NJ

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'-Dideoxynucleosldes as Potential Antcaids 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

NUCLEOSIDES & NUCLEOTIDES, 8(5&6), 1107-1108 (1989)

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

J. Fiandor, D.M. Huryn, B. Sluboski, L.J. Todaro and S. Tam*

Roche Research Center, Hoffmann-La Roche Inc., Nutley, NJ

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-butyl-stannane under the conditions developed by G. Keck[1] 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**.

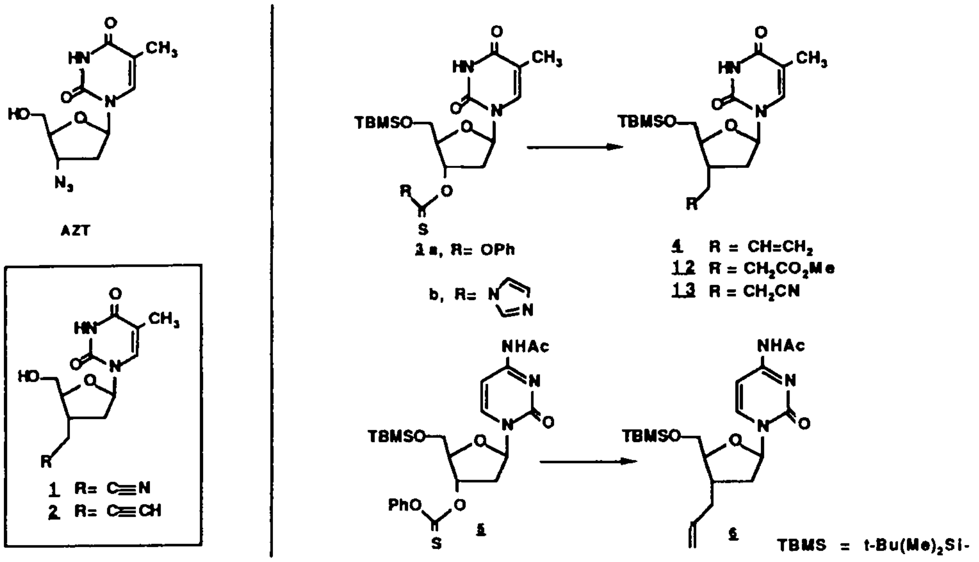
Since an allyl group is suitable for diverse structural manipulation, the efficient synthesis of a 3'-allyl substituted nucleoside, such as **4**, has allowed an easy access to many other structures in the series. Some examples of these transformations are shown below.

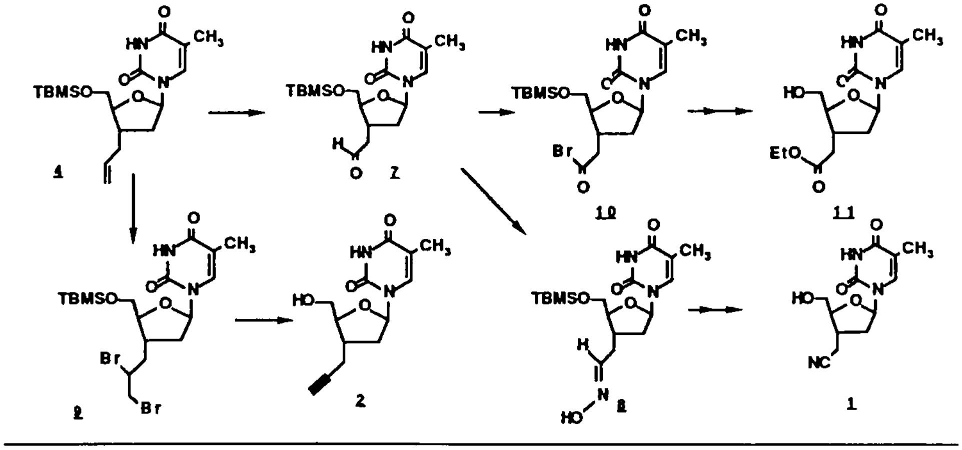
Reaction of the allyl compound **4** with osmium tetroxide/sodium periodate gave the aldehyde **7** in 57% yield. Compound **7** on treatment with hydroxylamine afforded a high yield of the crystalline oxime **8** which was readily converted to the cyano compound , **1** on reaction with carbonyldiimidazole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