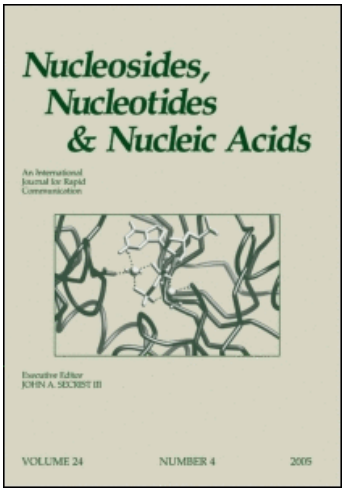

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SYNTHESIS OF NOVEL BRANCHED NUCLEOSIDE DIMERS CONTAINING A 1,2,3-TRIAZOLYL LINKAGE

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Abstract. Three branched nucleoside dimers containing a 1,2,3-triazole linkage have been synthesized using 1,3-dipolar cycloaddition of N-3 or C-5 acetylene nucleosides with 3'-azido-3'-deoxythymidine.

Introduction. The synthesis of oligonucleotides with modified internucleoside phosphate linkages have recently emerged as an important goal in the antisense field. The ability of these oligonucleotides to interfere specifically with mRNA targets constitutes a promising and powerful approach for the control of cellular and viral gene expression.[1] Ongoing synthetic studies into this broad class of compounds have focused on the chemical modification of the backbone, sugar and base functionalities of natural DNA and have resulted in significant progress toward establishing oligonucleotides as viable therapeutic agents.[2] These modifications basically address two main problems associated with *in vivo* application of natural oligonucleotides i) their low stability towards cellular nucleases and ii) poor cell penetration due to their polyanionic structure. Among the various nucleosidic linkages so far proposed, the oxime linkage (MMI) seems to show interesting properties.[2] In addition, pyrimidine analogs with extended aromatic and hydrophobic faces have previously been shown to stabilize DNA/DNA and DNA/RNA helices. 5-Heteroaryluridines have recently been shown to possess helix stabilizing properties relative to the 5-propynyl modification.[3]

We were interested in the influence of substituted 1,2,3-triazole located at the N-3 position of uracil, thymine acyclonucleosides[4] and nucleoside analogs (3' and 5'-azidothymidine) on

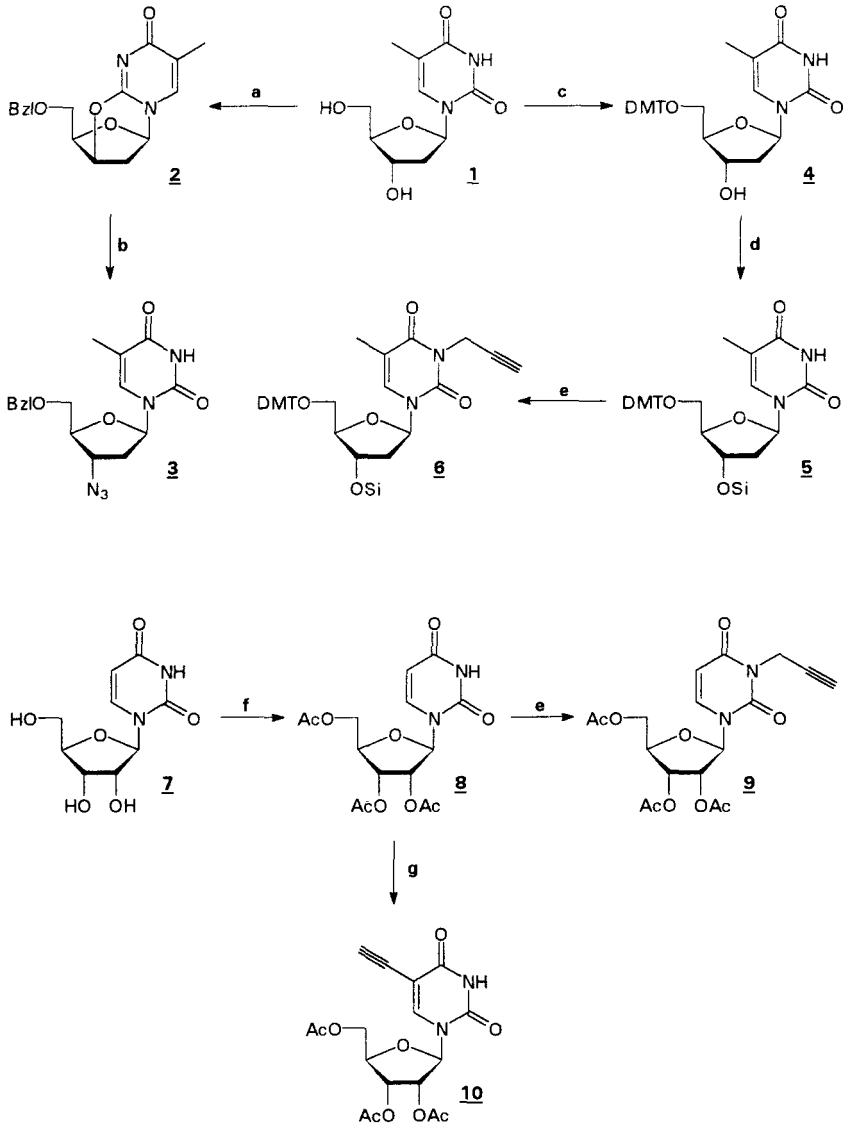
HIV replication.[5] Probably, these N-3 triazoles can alter base-base interaction at several levels and, in particular in their capacity to act as chain terminators.[6] Furthermore nucleoside dimers containing N-3 substituted AZT as one of the components have been prepared and evaluated for their anti HIV activities.[7]

First we determine the extent to which larger substituents are tolerated at the N-3 or C-5 position of these branched nucleosides. Secondly, in order to evaluate the influence of polarity and/or basicity of the modified backbone structure on RNA binding affinity, branched nucleosides of type 11–16 containing a triazole ring were synthesized.[8]

Results and Discussion. The general strategy developed should allow an easy access to the target branched dimers 11 -16 using 1,3-dipolar cycloaddition reaction. The synthesis is outlined in scheme 1 and 2. Thymidine 1 was converted in two steps to compound 5. After considerable trial, it was found that optimum success could be achieved via the alkylation of the N-3 using propargyl bromide to yield 6 in 95%. The same reaction conditions were applied to prepare compound 9 (80% from uridine 7) (Scheme 1). To introduce the ethynyl group in position C-5 of uridine 7, we took advantage of the methodology described by Yamamoto et al.[9] to yield 10 in 70% (Scheme 1).

The second building block will contain the azido group in position C-3'. Treatment of thymidine 1 under Mitsunobu[10] reaction gave the 2,3'-anhydro compound 2, which is reacted with NaN_3/DMF/140°C to provide protected AZT 3 in good yield (Scheme 1).

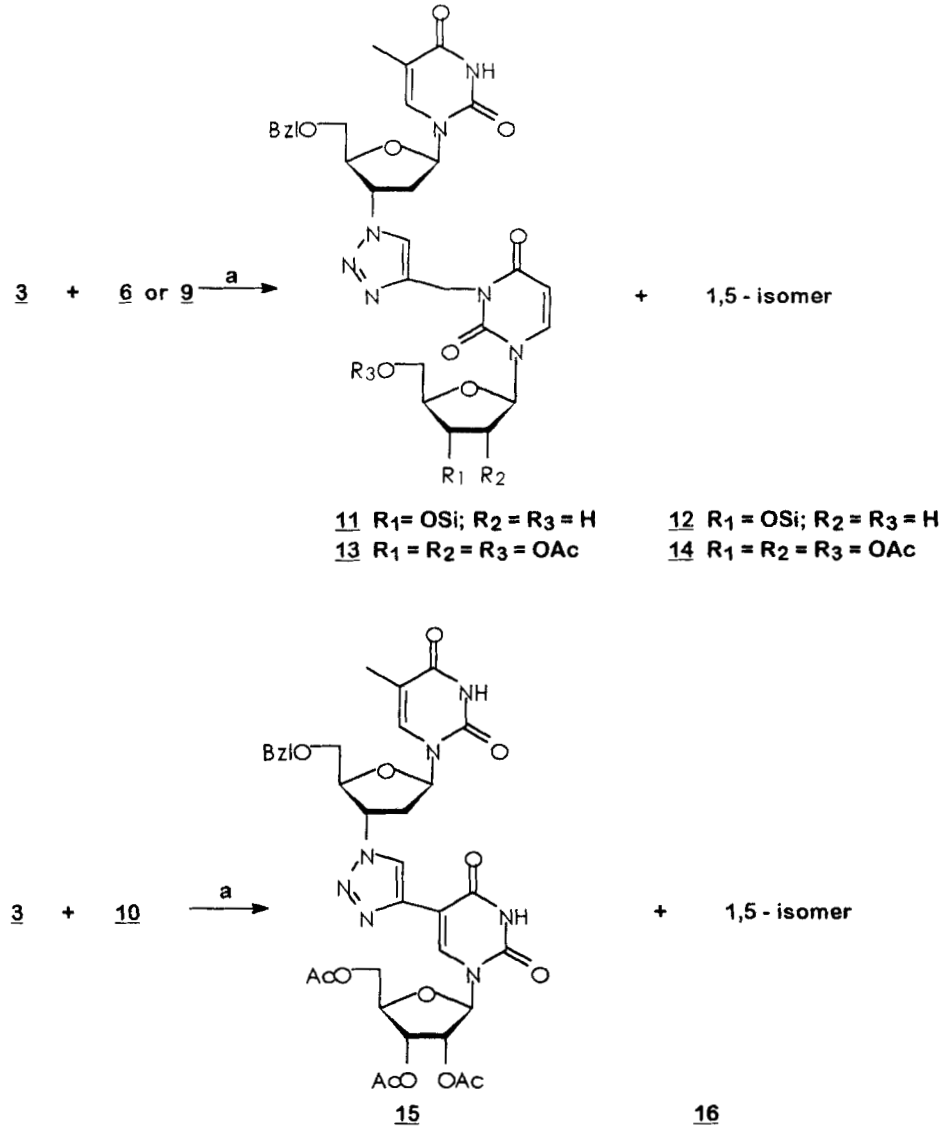
Having protected AZT 3 and propargyl derivatives 6 and 10 in hand, we began a detailed study of the ability of these synthons to be coupled into nucleoside dimers (Scheme 2). The 1,3-dipolar cycloaddition reaction of the azide 3 (2 eq) with propargyl derivatives 6, 9, and 10 (1 eq) in dry toluene under reflux afforded a mixture of the two possible 4- and 5-substituted isomers (11 and 12), (13 and 14), (15 and 16). The coupling reaction was further optimized by adding a catalytic amount of Lewis acid e.g. $ZnCl_2$, resulting in complete consumption of acytelene derivatives 6, 9 and 10, improvement of the yield and decreased reaction time to 12-24 h. The excess of protected AZT was easily recovered and could be used in subsequent reactions. The separation of the two isomers was achieved by preparative TLC (chromatotron, Harrison Research) using a step gradient (MeOH in CH_2Cl_2 ; 0 $\rightarrow$ 2,5 %). It is noteworthy that reaction of 3 with 6 under cycloaddition conditions was resulted in a mixture of protected and deprotected isomers at position C5'



Scheme 1

Bzl = Benzoyl; Si = *tert.*-Butyldimethylsilyl; Ac = Acetyl; DMT = Dimethoxytrityl

a: Mitsunobu reaction; **b**: NaN_3, DMF; **c**: DMTCl, pyridine, DMAP; **d**: TBDMSCl, imidazole, DMF; **e**: propargyl bromide, K_2CO_3, DMF; **f**: AcCl, pyridine, DMAP; **g**: ref. 9



Scheme 2

Bzl = Benzoyl; Si = *tert.*-Butyldimethylsilyl; Ac = Acetyl; DMT = Dimethoxytrityl
a: toluene, 100°C

Table 1. Analytical data of 11–16.

Compound	$H_{1'T}$	$H_{1'U}$	H_{5Tr}	H_{4Tr}	R_f	Ratio	Yield
11	6.51	6.14	7.82		0.26	56%	35%
12	6.29	6.24		7.43	0.19	44%	
13	6.35	5.97	7.99		0.39*	85%	45%
14	6.50	5.90		7.90	0.35	15%	
15	5.88	6.30	8.86		0.25	60%	60%
16	6.36	6.02		7.68	0.20	40%	

* After two migrations (CH_2Cl_2/MeOH 95/5)

of the lower nucleoside. In order to assure an easy workup the mixture was treated with trichloroaceticacid / MeOH / dichloromethane to completely remove the protecting group (DMTr). This was resulted in the formation of only two isomers 11 and 12.

It is well known that addition of azido derivatives to unsymmetric derivatives is determined by steric and electron withdrawing groups at the 4-position and electron releasing groups at the 5-position. On the other hand, the sterically less hindered isomer tends to be the major product[11]. Structures of new branched nucleoside dimers were determined on the basis of the corresponding analytical and spectroscopic data. Full assignment of all proton resonances was achieved by COSY and ROESY experiments (Table 1). As seen from table 1, due to the effect of the adjacent sugar the triazolic proton in the 4-substituted isomers 11, 13 and 15 appeared at lower field than in the 5-substituted derivatives 12, 14 and 16. These differences in the chemical shifts between the isomers are in agreement with literature data[11].

Conclusion. In summary, various synthetic routes for the preparation of the N-3 or C-5 triazolyl branched nucleoside dimers has been accomplished. The simplicity of this procedure encouraged us to extend the methodology to the preparation of other modified dimers. These modified nucleosides may be of interest as potential candidates for nucleoside based therapeutics.

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