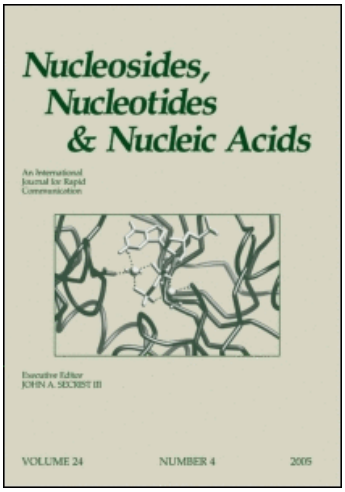

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SYNTHESIS OF 5′-ETHYNYL-2′-DEOXYNUCLEOSIDE ANALOGUES AS BUILDING BLOCK FOR ANTISENSE OLIGONUCLEOTIDE

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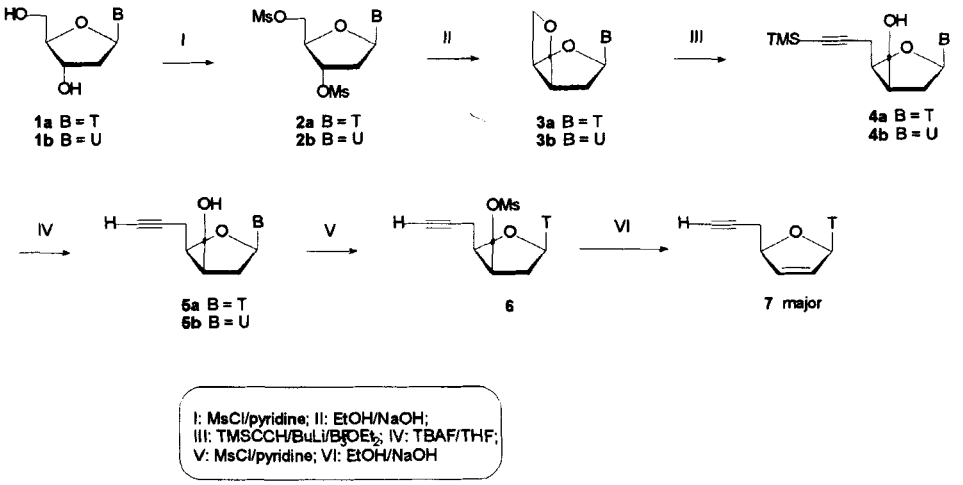
ABSTRACT: New nucleosides and nucleoside analogue dimers were prepared using 5′-ethynyl-2′-deoxynucleoside as starting material.

Nucleosides incorporating acetylenic function have attracted considerable attention as antitumor and antiviral agents[1]. The introduction of an acetylenic function at the 5′-position of the carbohydrate moiety had limited success due to the lack of a general synthetic method[2]. The present work deals with the enantioselective synthesis of 2′-deoxythymidine and 2′-deoxyuridine derivatives, where the hydroxy substituent at the 5′-position of the sugar moiety is replaced by an ethynyl group.

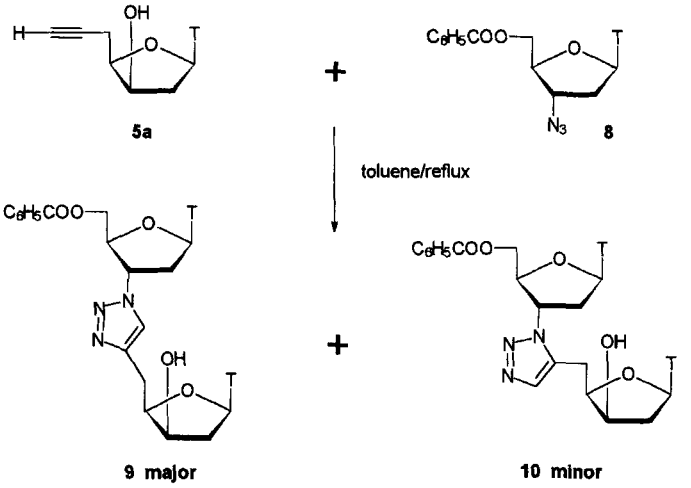
In continuation of our research program on the chemistry of 1,2,3-triazole[3,4] we were looking for an efficient and direct method of C-C bond formation at the C5′-position of deoxynucleosides[5]. The synthetic route is summarized in schemes 1,2.

Recently 1,3 dipolar cycloaddition was used to build the 1,2,3-triazole ring of branched nucleoside dimers[4,5]. Thus, cycloaddition of protected AZT, **8** (2 eq) with 5′-ethynyl nucleoside **5a** (1 eq), in dry toluene under reflux, afforded a mixture of the two possible 4- and 5-substituted isomers **9** (major) and **10** (minor). Structures of new nucleosides and nucleotide dimers were determined on the basis of their corresponding analytical and spectroscopic data.

We have used a relatively direct and easy way to synthesise 5′-ethynyl nucleoside. The latter should be a suitable intermediate for the preparation of modified nucleoside with



Scheme 1



Scheme 2

potential antitumor and antiviral activities (e.g. **5a,b** and **7**) and also of new oligonucleotides with modified backbone (e.g. **9** and **10**).

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