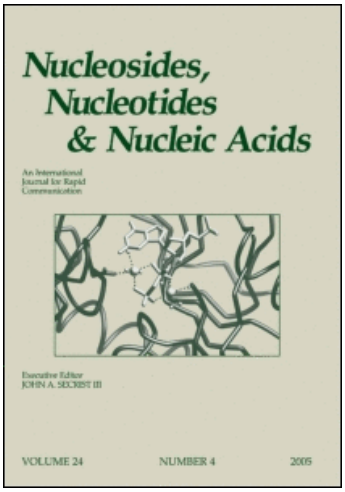

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Synthesis of the *t*BuSATE Pronucleotide of AZT by Two Different Synthetic Approaches

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SYNTHESIS OF THE *t*BuSATE PRONUCLEOTIDE OF AZT BY TWO DIFFERENT SYNTHETIC APPROACHES

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ABSTRACT A large scale synthesis of the *t*BuSATE pronucleotide of AZT was required for *in vivo* studies. A comparative synthesis of this derivative by phosphoramidite and monophosphate approaches is reported.

INTRODUCTION

We have previously demonstrated that mononucleoside phosphotriester derivatives of AZT incorporating *S*-acyl-2-thioethyl (SATE) groups are promising new kinds of esterase-labile mononucleotide prodrugs (pronucleotides).[1] Among the SATE transient phosphate protections, the *S*-pivaloyl-2-thioethyl (tBuSATE) group (Fig.) appeared as the most appropriate for *in vivo* experiments in regard to its high resistance against enzymatic hydrolysis.[2] *In vivo* studies of the *t*BuSATE pronucleotide of AZT needed large quantities of this derivative. In this respect, we decided to compare two different synthetic approaches using P(III) and P(V) intermediates.

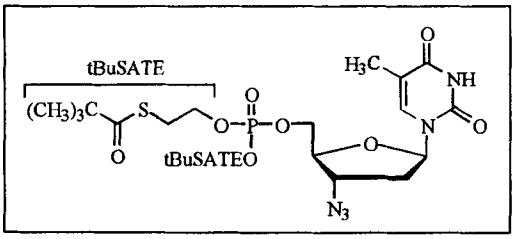
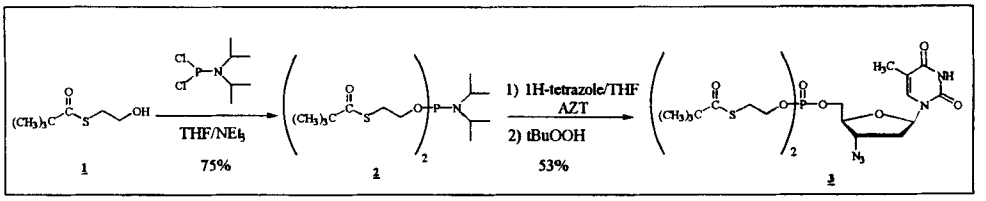


Figure : *Structure of the tBuSATE pronucleotide of AZT*

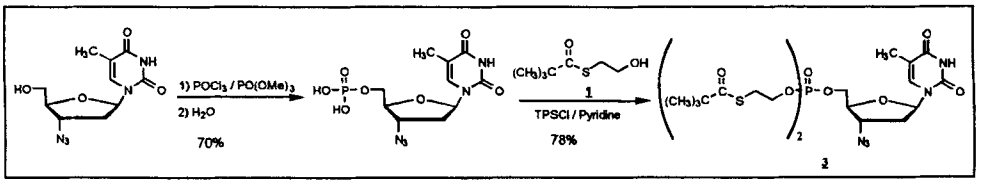
SYNTHESIS

The phosphoramidite method (Scheme 1) used a common procedure for the synthesis of SATE pronucleotides.[1] The key step involved coupling of AZT with the phosphoramidite **2**, which incorporated the two *t*BuSATE groups, followed by *in situ* oxidation.

On the other hand, monophosphate approach (Scheme 2) required the preliminary synthesis of 5'-monophosphate (AZTMP). Then, the mononucleotide was activated by TPSCl and coupled with the thioester precursor **1**.



Scheme 1 : *The phosphoramidite approach*



Scheme 2 : *The monophosphate approach*

RESULTS AND CONCLUSION

In the case of a large scale synthesis, the phosphoramidite approach did not seem to be effective due to the strictly anhydrous conditions required and the concomitant formation of by-products.

The monophosphate approach appeared to be more appropriate. The reaction of AZTMP with *S*-pivaloyl-2-thioethanol **1** gave a single product (the target pronucleotide **3**) which was easily purified by silica gel column chromatography.

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