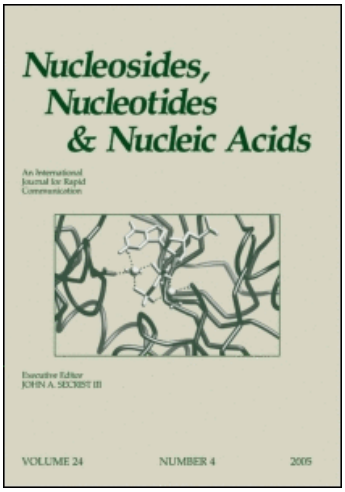


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# One-Pot Synthesis of an AZT Boranophosphate Conjugated with Tyrosine: A Potential Prodrug Candidate

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# One-Pot Synthesis of an AZT Boranophosphate Conjugated with Tyrosine: A Potential Prodrug Candidate

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## ABSTRACT

A one-pot synthesis of *P*-tyrosinyl(*P*-*O*)-5′-*P*-AZT boranophosphate **7** via a phosphoramidite method is described. The P-boranophosphate diastereomers were separated by RP-HPLC, and their structures were confirmed by NMR and MS.

*Key Words:* Nucleotide prodrug; Boranophosphate; AZT; Tyrosine.

Most anti-HIV drugs targeted at reverse transcriptase are 2′,3′-dideoxynucleoside (ddN) analogues. For example, 3′-azido-3′-deoxythymidine (AZT) was the first drug approved by the FDA for the treatment of HIV infection. In most cases, conversion of the nucleoside analogues to their 5′-monophosphates (ddNMPs) can be considered as the bottleneck in the overall metabolic pathway leading to the formation of the active 5′-triphosphate metabolites (ddNTP).[1] Therefore, prodrug approaches have been employed to design 2′,3′-dideoxynucleoside 5′-monophosphates that will deliver the 5′-monophosphate derivatives into the HIV-affected cells.

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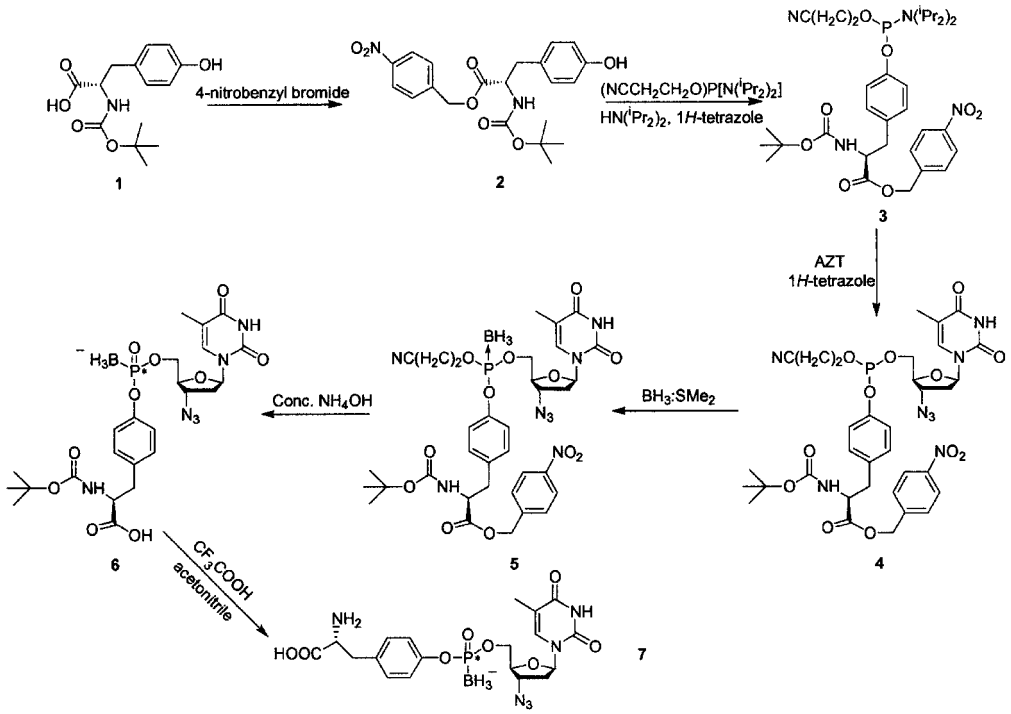
This process circumvents the initial nucleoside-kinase dependency step.[1] We propose to use nucleoside boranophosphate conjugated with tyrosine as a candidate for such a prodrug.

*P*-Tyrosinyl(*P*-*O*)-5′-*P*-AZT boranophosphate **7** was synthesized according to the following scheme using a phosphoramidite method. Commercially available tyrosine **1** was protected with a 4-nitrobenzyl group to give compound **2**. Phosphoramidite **3** was formed by phosphitylating compound **2** with *N*,*N*,*N*′,*N*′-tetraisopropylphosphane in the presence of 1*H*-tetrazole. After the reaction mixture was stirred for 40 min, AZT and another portion of 1*H*-tetrazole were added simultaneously to the mixture. The coupling reaction was completed in 15 min as monitored by $^{31}$P NMR, in which the singlet at 148 ppm for phosphoramidite **3** disappeared and two new singlets, corresponding to the diastereomers of phosphotriester **4**, appeared around 135 ppm. Phosphotriester **4** was then boronated with excess dimethyl sulfide-borane to yield AZT boranotriester **5**, which showed a characteristic broad peak centered at 116 ppm.[2] Compound **5** was then treated with concentrated $NH_4OH$, hydrolyzing the cyanoethyl and 4-nitrobenzyl groups to yield boranophosphate **6**. Further treatment of **6** with trifluoroacetic acid in acetonitrile afforded the title compound *P*-tyrosinyl(*P*-*O*)-5′-*P*-AZT boranophosphate **7**. The boron-modified P-diastereomers of **7** were separated in a 1:1 ratio by RP-HPLC on a $C_{18}$ column eluted with a 0.01 M solution of triethylammonium bicarbonate (TEAB) containing 15 to 25% acetonitrile; **7a** (19.0 min) and **7b** (19.8 min) were the faster and slower eluting diastereomers, respectively.





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In summary, we synthesized the first nucleoside boranophosphate conjugated with tyrosine by a one-pot reaction in good yield (from **2** to **7**, 42% yield). Introduction of a $BH_3$ group in such a conjugate is expected to confer on the conjugate good substrate properties[3] and to increase lipophilicity[3] and stability toward drug resistance,[4] relative to the unboronated prodrug.

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