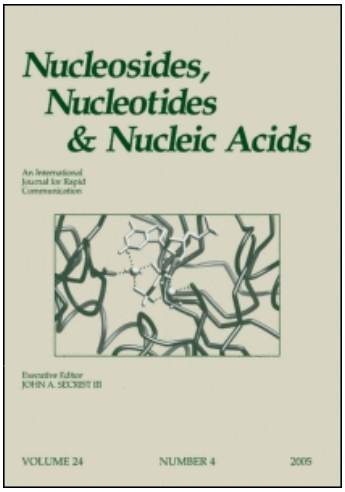

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

The Synthesis of αβ Imidothymidine Diphospate

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To cite this Article Davies, Lawrence C.(1989) 'The Synthesis of αβ Imidothymidine Diphospate', Nucleosides, Nucleotides and Nucleic Acids, 8: 5, 1053 — 1054
To link to this Article: DOI: 10.1080/07328318908054278
URL: http://dx.doi.org/10.1080/07328318908054278

NUCLEOSIDES & NUCLEOTIDES, 8(5&6), 1053-1054 (1989)

THE SYNTHESIS OF αβ IMIDOTHYMIDINE DIPHOSPATE

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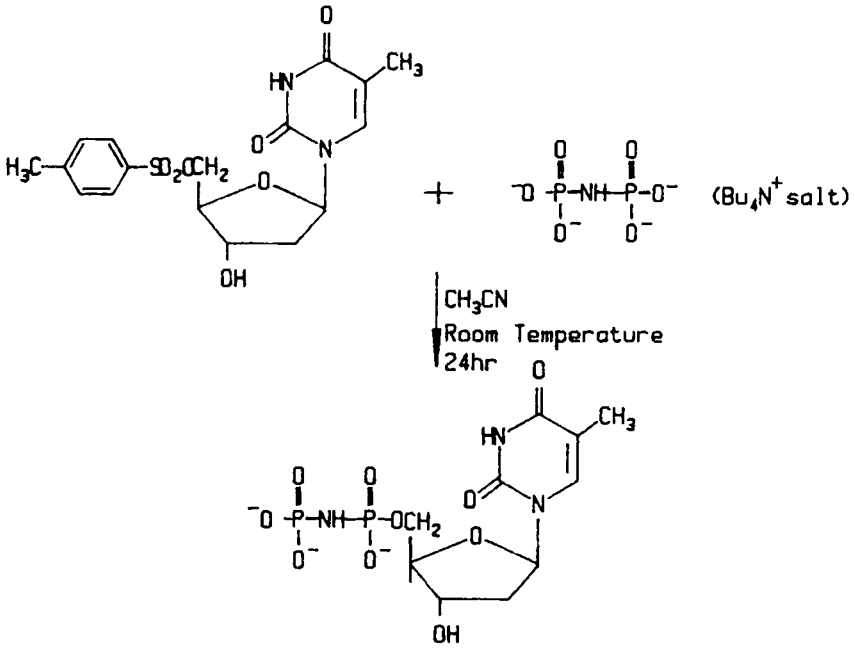
It has been shown by many workers that nucleotides containing an αβ methylene link have interesting biochemical properties compared to those containing an αβ oxo linkage.[1] In our laboratory αβ methylene thymidine triphosphate has been shown to be a more powerful inhibitor of thymidine kinase than thymidine triphosphate but a weaker inhibitor of ribonucleotide reductase and cytidine deaminase.[2] We have been interested in examining the properties of the αβ imido analogue. Several routes to prepare the unknown αβ imidothymidine triphosphate were unsuccessfully tried:

a) Reaction of 3'-O-Acetylthymidine with the tributylammonium salt of dicyclohexylcarbodiimide.

b) Reaction of 5'-O-tosylthymidine with the tributylammonium salt of imidodiphosphoric acid in hot dimethylacetamide.[3]

Dixit and Poulter[4] have developed milder conditions for the latter type of reaction which have proved successful in this case. Two equivalents of the tetrabutylammonium salt of imidodiphosphoric acid were reacted with 5'-O-tosylthymidine in dry acetonitrile for 24 hours. (Longer reaction times cause decomposition of the product). A large number of by-products are however produced. It has not been possible to purify the product to greater than about 80% purity by either ion-



exchange chromatography on DEAE-Sephadex using triethylammonium bicarbonate as buffer or on silica using a mixture of aqueous ammonia and n-propanol as eluant.

The ^{31}p nmr spectrum gives two singlets. Over a period of days the product decomposes to the phosphoramidate of thymidine monophosphate. Recently Ma, Babitt and Kenyon have published a synthesis of $\alpha\beta$ imidoadenosine diphosphate using the same procedure.[5]

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