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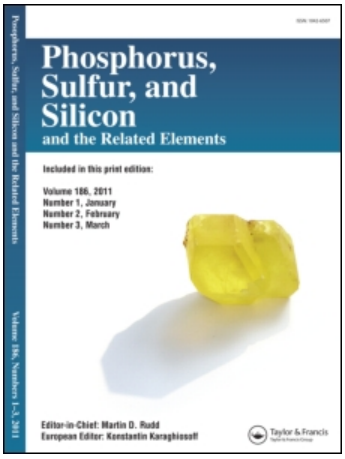

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A Simple and Efficient Procedure for the Synthesis of an Alendronate-Oligonucleotide Conjugate Via a Carbamate Linker

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A Simple and Efficient Procedure for the Synthesis of an Alendronate-Oligonucleotide Conjugate Via a Carbamate Linker

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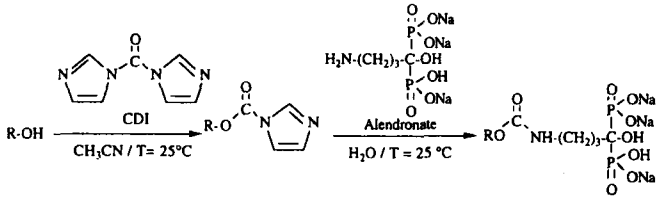
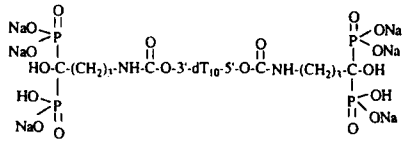
Alendronate, an aminobisphosphonate used clinically for the treatment of osteoporosis and others bones deseases is a synthetic analog of pyrophosphate in which the labile phosphoanhydride bond $(HO)_2P(O)$-**O**-$P(O)(OH)_2$ is replaced by a stable hydroxymethylene group $(HO)_2P(O)$-**C(OH)R**-$P(O)(OH)_2$. The most important action of this bisphosphonate is the inhibition of the bone resorption. The mechanism of action is not completely elucided. One hypothesis is that the bisphosphonate act by suppressing osteoclast activity [1]. Oligonucleotides are promising therapeutics too. For example, they are used for the enzyme inhibition or for the antisens strategy particulary in oncology [2] The pharmacological interest of these two moieties encouraged us to bind a bisphosphonate at the 5' OH of an oligonucleotide via a carbamate bond. In the first time, the synthesis conditions have been studied on model alcohol.



The key step of this synthesis is the activation of the alcoholic function by the 1,1'-carbonyldiimidazole (CDI) in dry dioxane to form an imidazole carbamate derivative. The coupling reaction was then carried with the sodium alendronate in water at controlled pH. This method has been used with success for the synthesis of the first alendronate-oligonucleotide conjugate and we hope new trends in biological applications.



T=Thymidine

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[1] H.A. Fleisch, *Ann. Med.*, **29**, 55 (1997).
[2] P.T.C. Ho, D.R. Parkinson, *Seminars in Oncology*, **24**, 187 (1997).