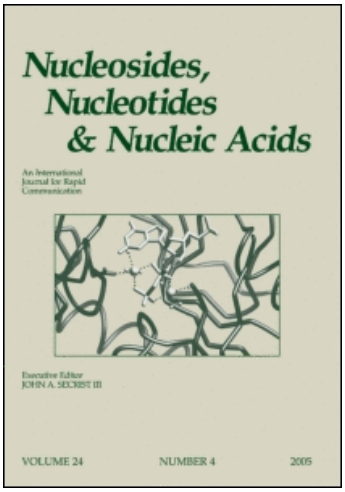

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Facile Synthesis of Base-Labile 2'-Deoxyribonucleosides: An Improved Synthesis of 2'-Deoxy-5-aza-Cytidine

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FACILE SYNTHESIS OF BASE-LABILE 2'-DEOXYRIBONUCLEOSIDES: AN IMPROVED SYNTHESIS OF 2'-DEOXY-5-AZA-CYTIDINE

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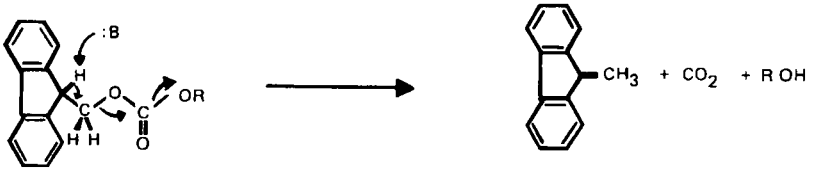
Abstract: The use of the Fmoc group for the protection of the hydroxy functions of the sugar moiety gave an improved overall yield of 2'-deoxy-5-azacytidine (6β), due to the mildly-basic conditions required for its removal from the protected nucleoside.

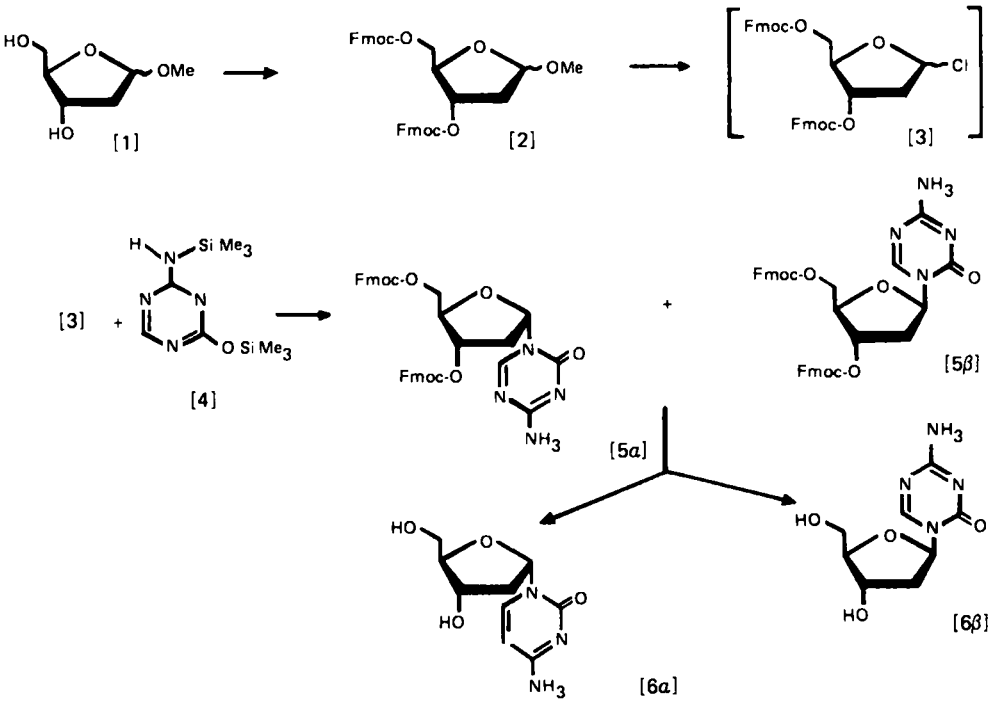
Recent reports describing the role of 2'-deoxy-5-azacytidine (6β) in the regulation of gene expression through the inhibition of DNA methylation[1] have generated renewed interest in this nucleoside. 2'-deoxy-5-azacytidine was first synthesized in 1964 by a multistep procedure described by Pliml and Sorm[2]. More recently, improved yields were obtained by a direct glycosylation procedure of silylated 5-aza-cytosine, or *via* a total synthesis, using glycosyl isocyanates as intermediates.

Our attempts at the synthesis of 2'-deoxy-5-azacytidine *via* the glycosylation procedure described by Piskala[3], using the toluoyl group for protection of the sugar moiety, were largely unsuccessful, due to the hydrolysis of the product during the final deprotection procedure.

The use of the 9-fluorenylmethoxycarbonyl group (Fmoc) enabled us to overcome this problem. When used for the protection of hydroxyl groups, it may be conveniently removed by the action of triethylamine in dry pyridine *via* a β-elimination reaction.



The fully-deprotected crystalline product (6β) was obtained from (5α,β) by the action of 15 equivalents of triethylamine in dry pyridine after one hour at room temperature in a 36% yield[4].



The use of the Fmoc group in nucleoside synthesis represents a significant improvement of the existing methodology. Our procedure should be applicable to the synthesis of numerous other nucleosides analogues, unobtainable by the standard route.

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