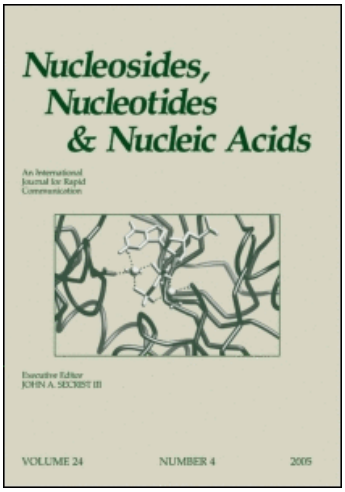

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N,O-Selectivity in the Synthesis of 3-Me-*Cyclo*Sal-ddAMP

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N,O-SELECTIVITY IN THE SYNTHESIS OF 3-ME-*CYCLO*SAL-DDAMP

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ABSTRACT: The factors influencing the *N,O*-regioselectivity during preparation of 3-Me-*cycloSal*-ddAMP were studied.

Recently we described the synthesis of *cyclo*Sal-pro-nucleotides of the antivirally active nucleoside analogue 2',3'-dideoxyadenosine **1** (ddA)[1]. The preparation of these *cyclo*Sal-derivatives was performed using the *N*-unprotected ddA as starting material because of possible problems during the deprotection of the base-labile phosphotriesters and the acid-labile purine dideoxynucleoside. In principle, phosphotriester **2** was synthesized using chlorophosphane **3** as published before[1,2]. However, the free amino group of the heterocycle can also react with this reactive phosphane **3** and consequently would increase the number of the reaction products: In addition to title compound **2**, also the *N-cyclo*Sal-**4** and the *N,O*-bis(*cyclo*Sal)-derivative **5** are possible (Scheme 1). In this work, we present the results of a systematic variation of the reaction conditions for synthesis of **3-methyl-*cyclo*saligenyl-ddAMP** (3-Me-*cyclo*Sal-ddAMP) **2**.

In fact, in all reactions we obtained triester **2** and the *N,O*-bis(*cyclo*Sal)-phosphotriester **5**. In contrast, the *N-cyclo*Sal-phosphotriester **4** was never observed. After isolation of **2** and **5**, the chemical shifts of ^{31}P-NMR resonances could be used of their identification. Therefor, we used the integration of the ^{31}P-NMR signals of **2** and **5** for the following reaction optimization as analytical tool. Thus, the influence of the solvent and the reaction temperature to yield **2** was studied. As solvents CH_3CN, DMF and mixtures of DMF/THF were used and the temperature was varied from 0°C to -78°C. As summarized in the Table, it was indeed possible to obtain phosphotriester **2** as the major product.

Acetonitrile as solvent was unsuitable because of low solubility of ddA **1**. Therefore, an incomplete reaction of the nucleoside with chlorophosphane **3** was observed and a product ratio in favor of the undesired **5** instead of 3-Me-*cyclo*Sal ddAMP **2** was obtained (2:1).

Scheme 1: Possible products of the 3-Me-*cyclo*Sal-ddAMP synthesis

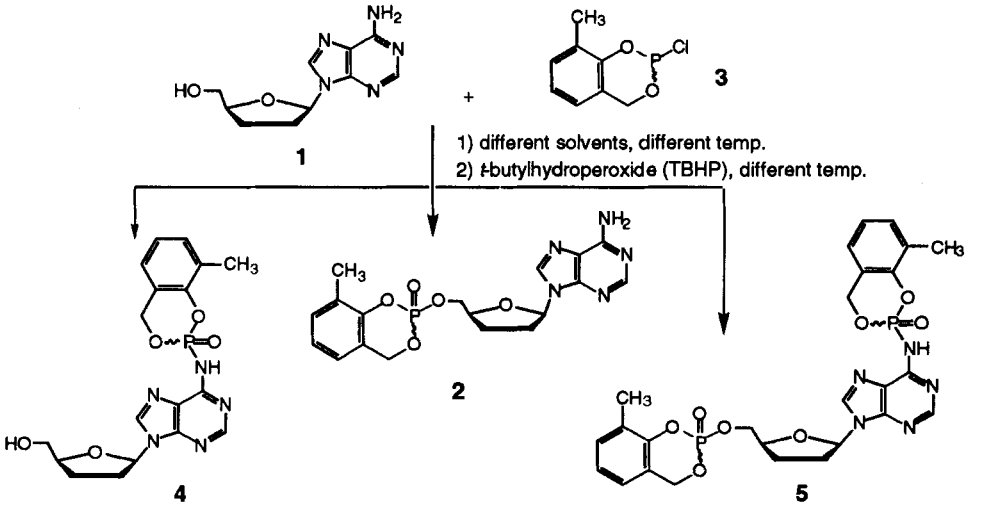

Table 1: Product ratios obtained under different reaction conditions

entry	solvent	$T_{phosphitylation}$	$T_{oxidation}$	product ratio (**2** : **5**)
1	CH_3CN	0°C	0°C	1 : 2
2	DMF/THF 1:1	0°C	-40°C	3 : 1
3	DMF/THF 2:1	0°C	-40°C	6 : 1
4	DMF/THF 2:1	-40°C	-40°C	9 : 1
5	DMF/THF 2:1	-78°C	-78°C	8.5 : 1
6	DMF	-40°C	-40°C	2.5 : 1

Best results were observed with a mixture of DMF/THF 2:1 (v/v) due to a homogenous phase reaction. Furthermore, the low melting point of DMF and THF allowed a lowering of the reaction temperature. In addition to the solvent effect, the temperature plays an important role for the *N,O*-regioselectivity. First experiments at 0°C gave only a 3:1-ratio of compound **2** to compound **5**. The best *O*-selectivity was obtained at -40°C during phosphitylating reaction as well as during oxidation (9:1 ratio). Using pure DMF as solvent or lowering of the temperature to -78°C did not result in a further improvement of the product ratio in favor of 3-Me-*cyclo*Sal-ddAMP **2**. The fact that we never isolated the *N-cyclo*Sal-triester showed that the *O*-phosphitylation seems to proceed far faster than the *N*-phosphitylation. However, further phosphitylation leading to **5** could not be totally suppressed. The chemical yield of **2** using optimal reaction conditions was 56 %.

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