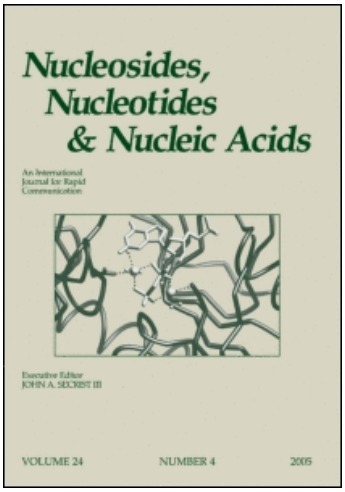


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Phosphoramidite Chemistry for the Synthesis of *cyclo*Sal-Pro-Nucleotides

Florence Mugnier[a]; Chris Meier[a]
[a] Institut für Organische Chemie, Universität Hamburg, Hamburg, Germany

To cite this Article Mugnier, Florence and Meier, Chris(1999) 'Phosphoramidite Chemistry for the Synthesis of *cyclo*Sal-Pro-Nucleotides', Nucleosides, Nucleotides and Nucleic Acids, 18: 4, 941 — 942
To link to this Article: DOI: 10.1080/15257779908041605
URL: http://dx.doi.org/10.1080/15257779908041605

NUCLEOSIDES & NUCLEOTIDES, 18(4&5), 941-942 (1999)

PHOSPHORAMIDITE CHEMISTRY FOR THE SYNTHESIS OF *CYCLO*SAL-PRO-NUCLEOTIDES

Florence Mugnier and Chris Meier*

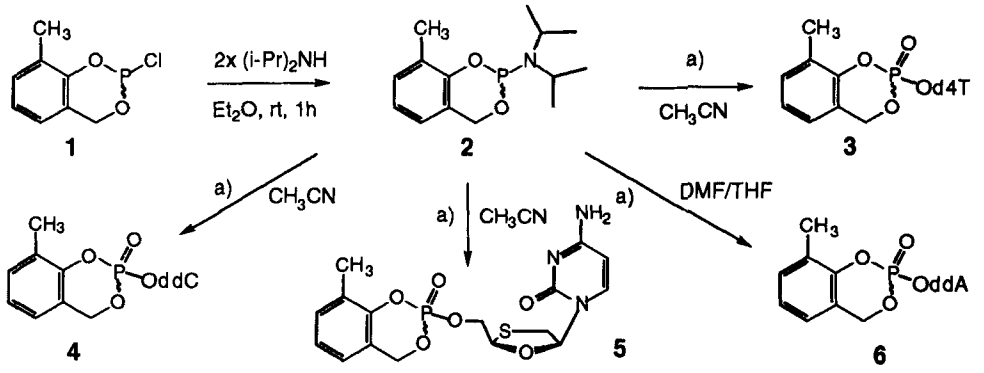
Institut für Organische Chemie, Universität Hamburg, Martin-Luther-King-Platz 6, D-20146 Hamburg, Germany

Abstract: An alternative synthesis of 3-methyl-*cyclo*Sal-nucleotides **3-6** using phosphoramidite chemistry is described. This protocol clearly shows advantages for the *cyclo*Sal-introduction into cytosine containing nucleoside analogues.

Previously, we reported the synthesis and the biological evaluation of different *cyclo*Sal-pro-nucleotides[1]. This concept has been developed to release nucleotides from lipophilic precursors by chemical hydrolysis. The mechanism involves a tandem-reaction. The *cyclo*Sal-concept was successfully applied to the antiviral nucleoside analogues d4T, AZT, ddA, d4A, F-ddA and ACV. For the preparation of the *cyclo*Sal-phosphotriesters, we always used cyclic chlorophosphanes as **1**. The advantage of phosphorus(III)-chlorides of type **1** is their high reactivity. However, this high reactivity could be contra productive if further functional groups are present in the parent nucleosides. This was observed in the case of adenine's exocyclic amino group. Nevertheless, by changing the solvent and the reaction temperature good regioselectivities were obtained. However, guanine-bearing nucleosides need no precautions when chlorophosphanes were used. In contrast, cytosine nucleoside caused considerable problems with chlorophosphane **1**, e.g. the *cyclo*Sal-modification of 3TC resulted in very low yields of the corresponding phosphotriester. Therefore, we studied the use of the phosphoramidite **2** of 3-methyl-salicyl alcohol. This compound was easily accessible by reacting the corresponding chlorophosphane **1** with two equivalents of di-*i*-propylamine in diethyl ether. Phosphoramidite **2** was thereafter isolated by simple filtration and evaporation of the solvent and could be used without further purification.

Here we describe the reaction of **2** with d4T, ddC, 3TC and ddA (Scheme). The reactions were performed using different weak acids as catalysts, reaction temperatures and times.

Scheme: Synthesis of 3-methyl-*cyclo*Sal-nucleotides using phosphoramidite **2**



a) i) acid catalysts, different temp.; ii) TBHP

Table: Reaction conditions and yields of the 3-methyl-*cyclo*Sal-nucleotides **3-6**

entry	nucleoside	solvent	catalyst	eq. cat.	time	temp.	yield
1	d4T	CH_3CN	1H-tetrazole	4	2.5h	0 °C	**3**, 80%
2	d4T	CH_3CN	PyH^+Cl^-	4	2.5h	0 °C	**3**, 80%
3	d4T	CH_3CN	ImH^+Tf^-	4	2.5h	rt	**3**, 90%
4	ddC	CH_3CN	$PyH^+BF_4^-$	4	0.75h	rt	**4**, 72%
5	ddC	CH_3CN	ImH^+Tf^-	4	0.7h	0 °C	**4**, 70%
6	ddC	CH_3CN	PyH^+Cl^-	4	0.5h	rt	**4**, 75%
7	3TC	CH_3CN	PyH^+Cl^-	4	0.5h	rt	**5**, 80%
8	ddA	DMF/THF 2:1	PyH^+Cl^-	4	0.5h	rt	**6**, 11%

The oxidation of the intermediate phosphites was carried out by addition of *t*-butylhydroperoxide (TBHP). Using amidite **2**, the synthesis of d4T phosphotriester **3** lead to very high yields which were higher than with the corresponding chlorophosphane **1** (Table). Surprisingly, the very cheap and easy to handle pyridinium chloride as acid catalyst lead also to very good yields. The same was observed for the ddC triester **4**. Most importantly, the reaction of 3TC with phosphoramidite **2** and PyH^+Cl^- gave *cyclo*Sal-triester **5** in good yield. With chlorophosphane **1** only very low yields of **5** and the N,O-di-*cyclo*Sal-derivative were isolated. Here, the phosphoramidite method clearly has an advantage. However, the reactions of **2** with ddA gave only very poor yields of phosphotriester **6**. Most probably this is due to the solvent mixture DMF/THF 2:1 because even the d4T reaction failed to yield the *cyclo*Sal-triester **3** in this solvent. The use of acetonitrile is not possible because of low solubility of ddA in this solvent.

1) Meier, C.; Lorey, M.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **1998**, *41*, 1417-1427; Meier, C.; De Clercq, E.; Balzarini, J. *Eur. J. Org. Chem.* **1998**, 837-846.