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SYNTHESIS OF A THYMIDINE DINUCLEOTIDE ANALOGUE CONTAINING AN INTERNUCLEOTIDE SILYL LINKAGE

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The synthesis of a silyl-linked analogue of a thymidine dinucleotide is described. The use of 5'-dimethoxytrityl and 3'-levulinyl protection allows mild and completely selective deprotection.

In recent years, considerable effort has been directed toward the synthesis of unnatural analogues of nucleosides and nucleotides (1). These are of interest as models of naturally occurring compounds, especially for studies of enzyme mechanisms (2). Also, many such analogues show interesting antiviral activity (3). Among these are the acyclic nucleoside analogues, which have shown activity against the herpes group of viruses (4-7). In the past, our group has been interested in the synthesis of novel internucleotide linkages (8), as have several other groups. Examples of phosphite (8a), phosphoramidate (8b,9), carbamate (10), phosphorothioate (2), carbonate (11), and methylphosphonate (12) linkages have been reported.

We wish to describe the synthesis of a nonionic nucleotide containing silicon in place of phosphorous. To our knowledge, this is the first example of such a "silylnucleotide"(13). We report the synthesis of the diphenylsilyl analogue of a fully protected 3',5'-linked thymidine dinucleotide by a simple, one-pot procedure. The choice of protecting groups is such that deprotection is mild and selective, allowing for the possibility of either chain extension or complete deprotection.

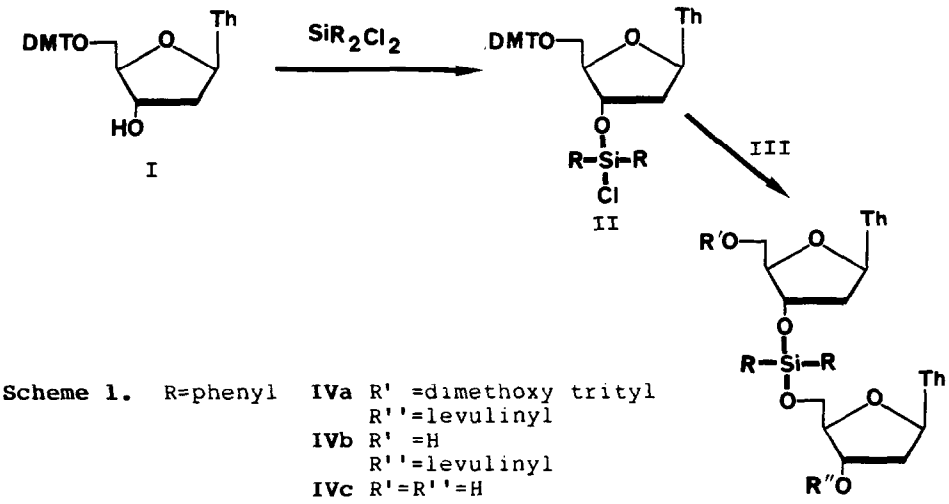
Our approach to the synthesis involved reacting dichlorodiphenylsilane with 5'-dimethoxytritylthymidine (**I**) to yield the nucleoside 3'-silyl chloride **II** (Scheme 1). This compound was not isolated, but reacted *in situ* with 3'-levulinyl thymidine (**III**, ref. 14) to yield the fully protected dimer **IVa.** The obvious drawback to this approach is the formation of symmetrically linked 3'-3' and 5'-5' dimers. Indeed, preliminary experiments showed the formation of a faster-moving tritylated material in addition to the desired product **IVa.** NMR showed this material did not contain a levulinyl group, and integration of signals indicated that this was the 3'-3'-linked dimer formed from the reaction

of **I** and **II**. In order to minimize this problem, a variety of conditions was tried, including the use of THF or DMF as solvent, pyridine or imidazole as base, $AgNO_3$ activation (15), and reduced temperatures. The following conditions gave the best result. Dichlorodiphenylsilane (252 ul, 1.2 mmol) was dissolved in anhydrous THF (10 ml) and anhydrous pyridine (2.4 ml, 30 mmol) in a sealed reaction vial at - 78°C. **I** (600 mg, 1.1 mmol) dissolved in THF (8 ml) in another sealed vial was added dropwise via syringe. THF (2 ml) was used to rinse vial and syringe. The addition took place over one hour, with rapid stirring. The reaction mixture was stirred at -78°C for two hours, as a white precipitate formed. **III** (3'-levulinyl thymidine (14), 340 mg, 1.0 mmol) was added in the same way, over ten minutes, and the reaction left to stir at room temperature overnight. The reaction mixture was extracted from brine with CH_2Cl_2, washed with water and coevaporated with toluene. The residue was taken up in CH_2Cl_2 and applied to a silica gel column (Et_2O:CH_2Cl_2:EtOH, 71:26:3), which yielded **IVa** (567 mg, 53%), which was precipitated from petroleum ether to give a fine white powder. A faster-moving material, tritylated but not levulinated, was also recovered (298 mg). NMR showed this to be the 3'-3' dimer described above.

During deprotection, **IVa** exhibited considerable sensitivity to acid and base. It was necessary to use the mildest deprotection conditions available. Fortunately, it was possible to remove the dimethoxytrityl group cleanly with $ZnBr_2$ (16). Thus, **IVa** (950 mg, .89 mmol) was added to $ZnBr_2$ (1M solution in nitromethane, 85 ml) at 0°C and stirred 45 minutes. The bright orange solution was poured into 1M NH_4OAc (600 ml) and extracted with chloroform. Washing with brine, drying with Na_2SO_4, coevaporation with toluene and silica gel column chromatography (CH_2Cl_2:MeOH, 9.5:.5) gave **IVb** (536 mg, 78%) as a white foam. A small amount of unreacted **IVa** was also recovered.

Hydrazine (17) was used to remove the levulinyl group. Although this reaction was also very clean, long reaction times led to decomposition. Thus, **IVb** (536 mg, .70 mmol) was added to hydrazine hydrate (.5M solution in pyridine:acetic acid, 3:2, 7 ml) and stirred at room temperature for 2.5 minutes. The reaction was stopped by addition of acetyl acetone (21 ml). Workup consisted of extraction from brine with CH_2Cl_2, washing with water, drying with sodium sulfate, and coevaporation with toluene. Purification on a silica gel column (CH_2Cl_2:MeOH:9.5:.5) gave **IVc** (314 mg, 67%) as a white glass. This material could not be crystallized from toluene, CH_2Cl_2, ethyl acetate, ethyl acetate:ether, or ethanol:water. It was finally foamed with acetone and triturated with ether to give a white powder (18). A very small amount of unreacted **IVb** was also isolated from the column.

The work described here has allowed us, for the first time, to synthesize a thymidine dimer containing a silyl internucleotide linkage. The choice of



Scheme 1. R=phenyl **IVa** R' =dimethoxy trityl
R''=levulinyl
IVb R' =H
R''=levulinyl
IVc R'=R''=H

Table 1. Physical data of isolated compounds.

compound	m.p.(°C)	max(min)nm	Rf
IVa	113-117	265(237)	.45[a], .16[b], .28[c]
IVb	83-85	264(235)	.38[a], .11[b], .14[c]
IVc	106-109	265(235)	.25[a], .03[b], .06[c]

a,CH_2Cl_2:MeOH, 9:1; b,Et_2O:CH_2Cl_2:EtOH, 71:26:3; c,EtOAc.

Table 2. Selected ^1H Resonances[a].

compound	H1'	$-OCH_3$	levulinyl-CH_3	Thymidine-CH_3
IVa	6.33, 6.48(dd)	3.77(s)	2.15(s)	1.37, 1.43(s)
IVb	6.13(t), 6.33(dd)	---	2.19(s)	1.88. 1.44(s)
IVc	6.18(t), 6.26(t)	---	---	1.72. 1.43(s)

[a] - ppm from TMS, in $CDCl_3$, except IIIc, in dmso-d6, dd=doublet of doublets, s=singlet, t=triplet.

protecting groups allows for full deprotection (**IVc**) or partial deprotection (**IVb**) and the possibility of chain extension.

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