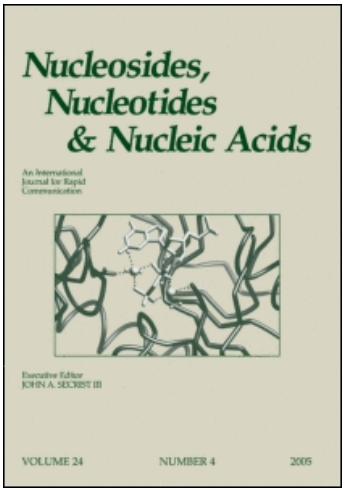

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OLIGONUCLEOTIDE ANALOGUES WITH DIALKYL SILYL INTERNUCLEOSIDE LINKAGES

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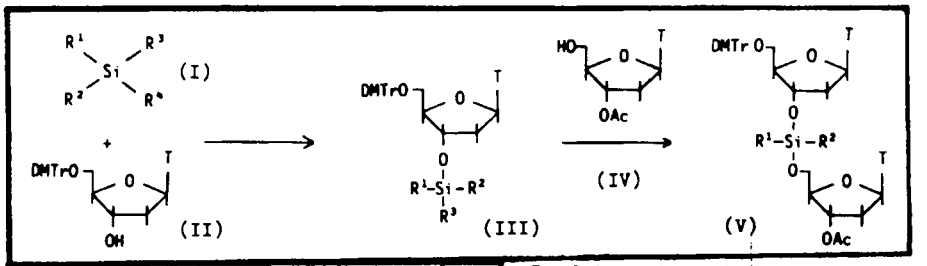
SUMMARY: Oligonucleotide analogues with dialkyl-silyl internucleoside linkages were prepared by "one pot" reactions starting from dialkyl-dichloro- resp. chloro-dialkylaminosilane derivatives.

Neutral oligonucleotide analogues, which penetrate cell walls, are sufficiently stable to degradation and have good hybridization properties inside cells, such as oligo-nucleoside-methyl phosphonates[1], may have an antiviral potential. Likewise, analogues with siloxane internucleoside bonds could be of interest. We, therefore, set out to study such compounds with dialkyl silyl linkages and report, here, routes to their preparation[2].

To 1,1-dichloro-sila-cyclohexane (Ia, Chart 1)[3] in abs. DMF/pyridine=8:1.2 we added 1 equiv. II, dissolved in abs. THF, at -78°C, through 1 h. After another 2 h at -78°C the solution of IIIa was further reacted with 0.9 equiv. of IV in abs. THF by warming up to room temperature overnight. Addition of saturated NaCl-solution and extraction of the product with CH_2Cl_2 yielded, after silicagel chromatography, 40% of Va, which, after detritylation (0.2% $ZnBr_2$ in abs. CH_3NO_2, 45 min, room temperature), was characterized by mass spectroscopy (FD: $(M+H)^+$=623; EI: characteristic fragments e.g. at m/z=397,381,355,339), UV and chromatographic behaviour. A sample of this compound was further deacetylated (conc. NH_3/THF=1:1, 2 h, room temperature) to give thymidin-3'-yl-(1,1-silacyclohexyl-)-5'-thymidine (FD-MS: $(M+H)^+$=581).

Since maximum flexibility of the backbone chain could be expected from dimethyl-sila-oligonucleotides, an analogue



	R_1	R_2	R_3	R_4
I a	cyclo-C_5H_{10}		Cl	Cl
b	CH_3	CH_3	Cl	Cl
c	CH_3	CH_3	$N(iso\text{-}C_3H_7)_2$	Cl
III a	cyclo-C_5H_{10}		Cl	-
b	CH_3	CH_3	$N(iso\text{-}C_3H_7)_2$	-
II a	cyclo-C_5H_{10}		-	-
b	CH_3	CH_3	-	-

of this structure was our next preparative target. Whereas Ib, through traces of moisture, gave series of oligosiloxane derivatives, the chloro-diisopropylamino-silane Ic[4] reacted with 1 equiv. II in THF/pyridine=10:4 at room temperature to IIIb. The latter, without isolation, was converted with 0.9 equiv. of IV to 51% Vb, which, after detritylation, was characterized by UV and mass spectroscopy, as above (FD: $(M+H)^+$=583).

Compounds V are, to our knowledge, the first examples of dialkyl-sila-oligonucleotide analogues[5]. The isolation of stable, proton-activable synthons III and solid-phase techniques (replacement of 3'-OAc by support anchor), which are under study, should enable us to prepare longer chains with sila-internucleoside linkages.

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