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Hartmut Seliger^a; Georg Feger^a

^a Univ. Ulm, Sektion Polymere, Ulm, F.R. Germany

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OLIGONUCLEOTIDE ANALOGUES WITH DIALKYL SILYL INTERNUCLEOSIDE LINKAGES

Hartmut Seliger* and Georg Feger

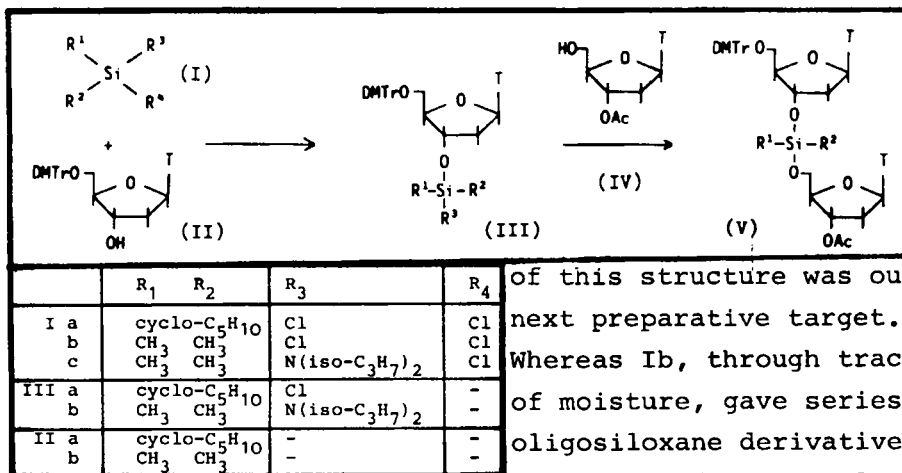
Univ. Ulm, Sektion Polymere, Oberer Eselsberg, D 7900 Ulm, F.R. Germany

SUMMARY: Oligonucleotide analogues with dialkyl-silyl internucleoside linkages were prepared by "one pot" reactions starting from dialkyl-dichloro- resp. chloro-dialkylamino-silane 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 phosphonates¹, 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 preparation².

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 CH₂Cl₂ yielded, after silicagel chromatography, 40% of Va, which, after detritylation (0.2% ZnBr₂ in abs. CH₃NO₂, 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. NH₃/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



of this structure was our next preparative target. Whereas Ib, through traces of moisture, gave series of oligosiloxane derivatives, the chloro-diisopropylamino-silane Ic⁴ 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 de-tritylation, 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 analogues⁵. 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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