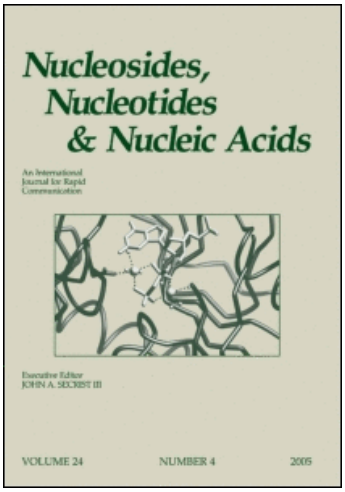

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Oligonucleotides with Reactive Dialdehyde Groups as Novel Affinity Reagents

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OLIGONUCLEOTIDES WITH REACTIVE DIALDEHYDE GROUPS AS NOVEL AFFINITY REAGENTS

S.N.Mikhailov[1*], B.S.Ermolinsky[1], E.V.Efimtseva[1], M.G.Brevnov[2], O.M.Gritsenko[2], E.S.Gromova[2], A.Van Aerschot[3], P.Herdewijn[3]

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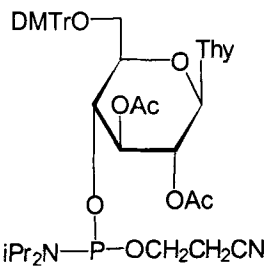
ABSTRACT: The preparation of ON derivatives with regiospecifically incorporated dialdehyde reactive groups and their successful use as affinity labels was described.

Recently we have developed for the first time the preparation of oligodeoxynucleotide (ON) derivatives with regiospecifically incorporated additional diol groups which was further oxidized to dialdehyde reactive groups[1]. For this purpose three phosporamidite blocks **1-3** were prepared.



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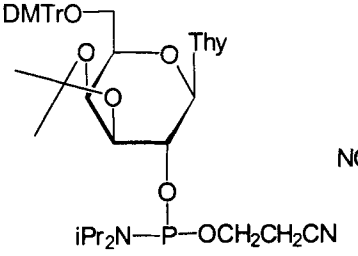

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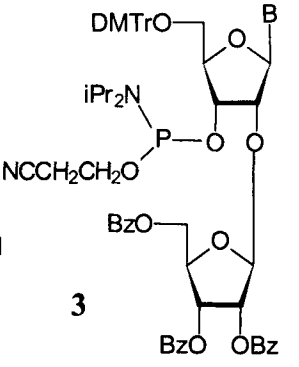

3

In order to investigate the periodate oxidation reaction in detail three model dinucleoside phosphate, containing 1-(β-D-glucopyranosyl)thymine, 1-(β-D-galactopyranosyl)thymine and 2′-*O*-β-D-ribofuranosyluridine were synthesized. The

oxidation of the trans diol group in the first dimer using 10 fold excess of sodium periodate proceeded too slowly at 20° C (estimated half time of 10 hr) to be applied on ON level. The oxidation of 3',4'-cis hydroxyl group in the second dimer was complete in 1.5 hr. In the last case of disaccharide derivative the oxidation proceeded even more readily in 10 min. The amidite **2** was used successfully in standard automated ON synthesis. The acid labile isopropylidene group was removed from ONs with 80% acetic acid (2 hr at room temperature). During this time 40-50% of the isopropylidene groups were cleaved without visible depurinisation. Further periodate oxidation yielded ON derivatives with dialdehyde groups. It was shown that modified ONs and their natural complements still formed DNA duplexes which were used for affinity labeling of *Eco*RII or *Mva*I restriction-modification enzymes[1].

Another possibility for regioselective incorporation of reactive dialdehyde groups consists in the preparation of ON derivatives containing disaccharide nucleoside analogue. We developed a general method for their stereospecific synthesis starting from readily available 3',5'-*O*-blocked *N*-acylribonucleosides which were reacted with a slight excess of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in the presence of tin tetrachloride[2]. Starting from amidite **3** several sets of ON derivatives were prepared[3]. Additional diol groups of ribose moiety in these ONs were readily oxidized with sodium periodate to dialdehyde groups.

The developed methodology is of general importance and such ON analogues may be used as selective inhibitors for other enzymes interacting with nucleic acids.

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