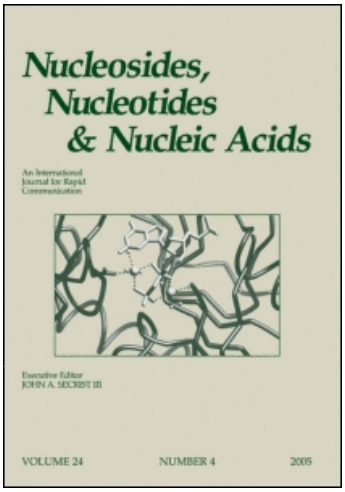

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A New Protecting Group for the 5'-Hydroxyl Group Having O-S Single Bond Oxidatively Cleavable Under Mild Conditions

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A NEW PROTECTING GROUP FOR THE 5′-HYDROXYL GROUP HAVING O–S SINGLE BOND OXIDATIVELY CLEAVABLE UNDER MILD CONDITIONS

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▫ *We developed a new protecting group, i.e., cis-[4-[[(4-methoxytrityl)sulfenyl]oxy]tetrahydrofuran-3-yl]oxycarbonyl (MTFOC), which could be removed under neutral conditions involving the oxidative removal of the MMTrS group followed by the self-cyclization of the resulting intermediate. The introduction of the protecting group into the 5′-hydroxyl group of a thymidine derivative and its deprotection were studied.*

Keywords MTFOC Group, Protected Protecting Group, Oligodeoxynucleotide Synthesis

INTRODUCTION

Recently, we have reported 2-[[*N*-(tritylthio)methylamino)]methyl]benzoyl (MAB) and 2-[(4-methoxytritylthio)oxymethyl]benzoyl (MOB) as protected protecting groups, especially, demonstrating the utility of the former in the synthesis of a tetrathymidylate.[1] It turned out that the protecting group could be removed *via* a two-step deprotection mechanism. The first step is the removal of the MMTrS group. The second step involves the self-cyclization of the resulting 2-hydroxymethylbenzoyl intermediate to liberate the free 5′-OH group. However, this self-cyclization required rather long periods of time for its complete removal under neutral conditions. Although we could accelerate the reaction by use of

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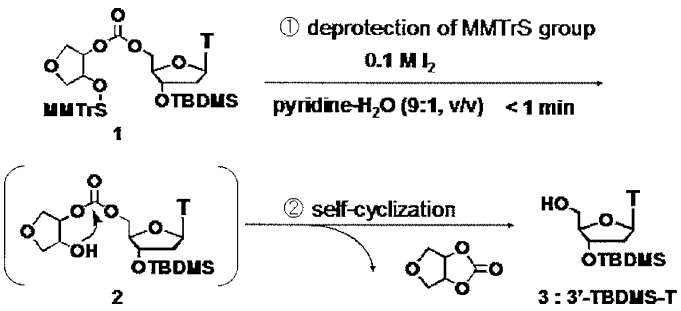


FIGURE 1 A new protecting group having the MMTrS group and its deprotection mechanism.

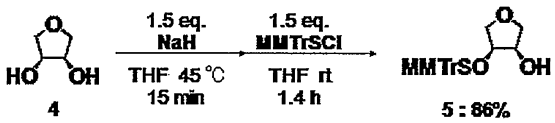
base treatments such as 0.2 M *N*,*N*-diisopropylethylamine (DIEA)/CH_3CN-H_2O (9:1, v/v), these weakly alkaline conditions were still intolerable for the synthesis of longer oligodeoxynucleotides.

In order to improve these problems, we designed *cis*-[4-[[(4-methoxytrityl)sulfenyl]oxy]tetrahydrofuran-3-yl]oxycarbonyl (MTFOC) as a new protecting group. In this study, a 5′-*O*-protected thymidine derivative **1** was synthesized to see if the MTFOC group can be removed by a two-step procedure. It was expected that the cyclization of a *cis*-[4-hydroxytetrahydrofuran-3-yl]oxycarbonate intermediate **2**, which would be formed by removal of the MMTrS group, would be very fast because of the neighboring group effect of the nucleophilic hydroxyl group of **2** on the attack to the carbonyl group. To the best of our knowledge, this study is the first example that used the carbonate structure with a *cis*-diol skeleton as the backbone structure of the protected protecting group (Figure 1).

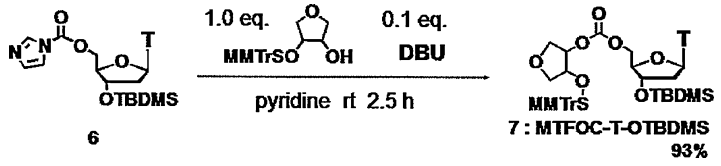
RESULTS AND DISCUSSION

The key compound, *cis*-4-[[(4-Methoxytrityl)sulfenyl]oxy]tetrahydrofuran-3-ol (**2**:MTFOH), was synthesized, as shown in Scheme 1. Treatment of the starting material **4** with NaH followed by the in situ reaction with MMTrSCl gave the desired MTFOH **5** as an enantiomeric mixture in good yield.

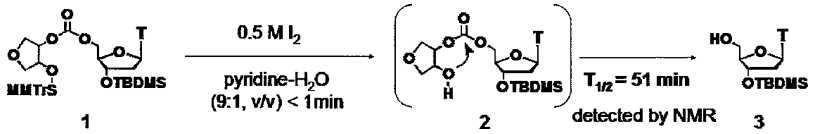
The reaction of 3′-*O*-(*t*-butyldimethylsilyl)thymidine with 1.5 equiv of 1, 1′-carbonyldiimidazole in pyridine gave the 5′-*O*-[(imidazol-1-yl)carbonyl]thymidine derivative **6**, which was obtained as an amorphous solid. The condensation of **6** with 1.0 equiv of MTFOH in pyridine in the presence of a catalytic amount (0.1 equiv) of DBU at room temperature for 2.5 h gave 5′-*O*-MTFOC-3′-*O*-(*t*-butyldimethylsilyl)thymidine (MTFOC-T-OTBDMS) in 93% yield, as shown in Scheme 2.



SCHEME 1



SCHEME 2



SCHEME 3

The self-cyclization of the intermediate **2** is considered to be the rate-determining step of the deprotection. Therefore, we determined the kinetics of the cyclization. The kinetic analysis was carried out by use of NMR spectroscopy. As shown in Scheme 3, the starting material (7.14 μmol) was dissolved in 1.0 mL of a 0.5 M iodine solution in pyridine-d_5:D_2O (9:1, v/v), and an aliquot (700 μl) was taken and checked by NMR.

It was found that the MMTrS group was removed within 1 min to give the intermediate **2**, which was gradually converted to 3′-*O*-TBDMS-T (**8**) according to the pseudo-first order kinetics with $T_{1/2}$ = 51 min. For comparison, the kinetics of cyclization of the previously reported 2-hydroxylmethylbenzoyl intermediate[1] was also determined under the same conditions. As the result, the $T_{1/2}$ value of this reaction was determined to be 164 h, which was much longer than that of the intermediate **2**.

CONCLUSION

We demonstrated for the first time the usefulness of the tetrahydrofuran skeleton as a key structural component of new protecting groups. Although we need to improve the second step reaction since it took rather long periods of time, the strategy for development of the MTFOC group described would provide new insight into the chemical synthesis of oligodeoxynucleotides.[2] Further study in this direction is strongly indicated and will be reported in due course.

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