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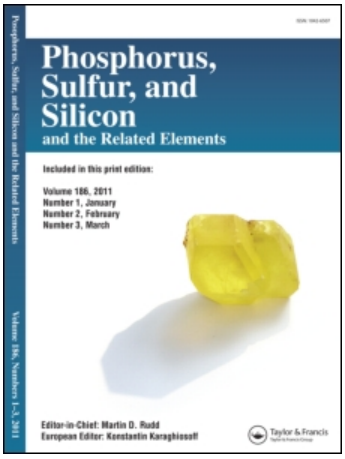

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Mixed Phosphorus-Carboxylic Anhydrides as Synthons for Stereoselective Synthesis of [RP]-Dinucleoside (3',5')-Methanephosphonates

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The use of 5'-*O*-DMT-nucleoside 3'-*O*-(*O*-2,4,6-trimethylbenzoyl methane-phosphonothioate)s (mixed anhydrides) **(3)** as intermediates for the preparation of [Rp]-dinucleoside (3',5')-methanephosphonothioates **(7)** and -methanephosphonates **(8)** is discussed.

Keywords: Dinucleoside ; (3′,5′)-methanephosphonates; dinucleoside ; (3′,5′)-methanephosphonothioates; mixed anhydrides; nucleoside 3'-*O*-methanephosphonothioates

1. INTRODUCTION

Oligo(nucleoside methanephosphonate)s (PMe-Oligos, **1**) belong to the first generation of analogues of oligonucleotides being considered as selective inhibitors of protein biosynthesis (*antisense oligomers*).[1] It has been recently demonstrated that *chimeric oligonucleotides* consisting of flanking [R_P]-dinucleoside (3',5')-methanephosphonates **(2)** at 3'- and 5'-ends of oligomers having phosphate or phosphorothioate internucleotide linkages form duplexes with complementary oligoribonucleotides which are acceptable as the substrates for RNAse-H.[2] However, only these *chimeric oligomers* which have incorporated [R_P]-dinucleoside (3',5')-methanephosphonates have had acceptable binding avidity towards complementary RNA, whereas these oligomers built up from diastereomeric mixtures of dinucleoside methanephosphonates, or from those of [S_P]-configuration exhibited much lower avidity towards the same RNA matrix [3] Since only [R_P]-**2** are of interest for preparation of these *stereodefined chimeric antisense oligomers*, the opposite diastereomers [S_P]-**2** are useless.

Recently we reported the novel approach to the stereocontrolled and stereoselective synthesis of [R_P]-**2** based upon the utilization of both diastereomerically pure 5'-*O*-DMT-nucleoside 3'-*O*-methanephosphonoanilidothioates,[4] and 5'-*O*-DMT-nucleoside 3'-(*O*-alkyl methanephosphonothioate)s [5] for the exclusive synthesis of [Rp]-**2**.

In this paper we present alternative approach , in which the phosphorylating properties of 5'-*O*-DMT nucleoside 3'-*O*-(*O*-2,4,6-trimethylbenzoyl methanephosphonothioate)s **(3)** towards 5'-OH nucleosides has been studied.

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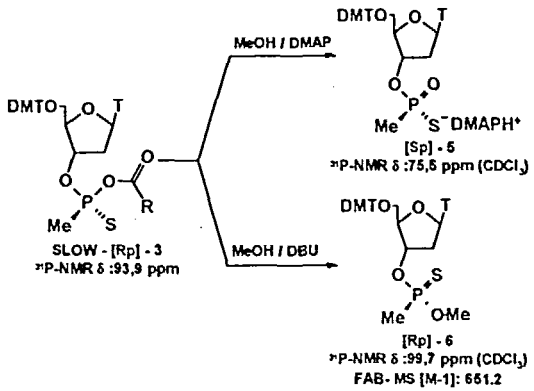
2. RESULTS AND DISCUSSION

5'-*O*-DMT-nucleoside 3'-*O*-(*O*-2,4,6-trimethylbenzoyl methanephosphonothioate)s **(3)** have been prepared from separated into diastereomers 5'-O-DMT-nucleoside 3'-O-methanephosphonoanilidothioates **(4)**, which were converted to methanephosphonothioates **(5)**, followed by chemoselective O-benzoylation, according to the earlier described procedures.[5] Their reactivity towards alcohols have been studied (scheme 1).



Scheme 1

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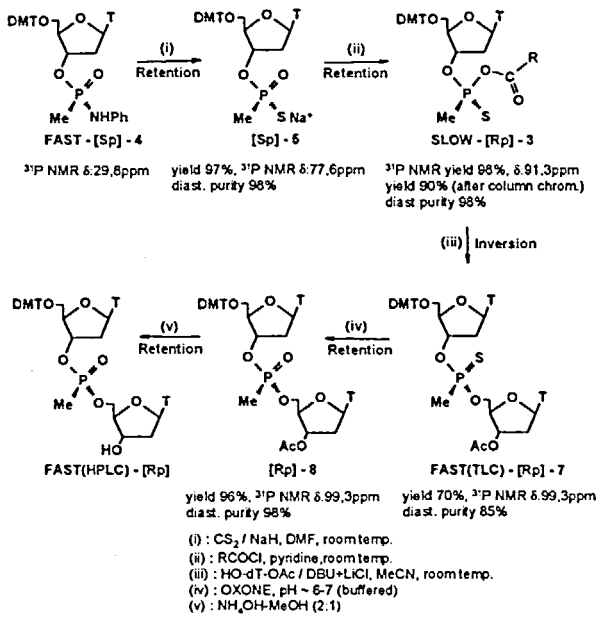
When diastereomerically pure SLOW-[Rp]-5'-*O*-DMT-thymidine 3'-*O*-(*O*-2,4,6-trimethylbenzoyl methanephosphonothioate) **3** was treated with methanol in the presence of DMAP in MeCN, the only product observed was [Sp]-5'-*O*-DMT-thymidine 3'-*O*-methanephosphonothioate **(5)** (^{31}P NMR δ 75.5 ppm) with the retained absolute configuration at the phosphorus center. In contrast, when stronger base DBU was used as activator instead of DMAP, diastereomerically pure 5'-*O*-DMT-thymidine 3'-*O*-(*O*-methyl methanephosphonothioate) **(6)** was obtained in very good yield (^{31}P NMR 99.7 ; MS FAB$^-$ [M-H] 651.2, yield 95%). Thus nucleophilic substitution at the phosphorus atom in **3** in the presence of DBU proceeds regio- and chemoselectively with the inversion of configuration. The same compound [Rp]-**3** was used as the substrate for the preparation of fully protected [Rp]-dithymidilyl (3'5')-methanephosphonothioate **(7)**(scheme 2).



Scheme 2

Reaction of [Rp]-**3** with 3'-*O*-acetylthymidine in the presence of 4 equivalents of DBU in acetonitrile solution at ambient temperature was completed within 24

hours, and [Rp] 5'-*O*-DMT thymidylyl 3'-*O*-acetylthymidine (3',5')-methanephosphonothioate **(7)** was isolated by silica gel column chromatography in 70% yield. The second product of the opposite configuration, [Sp]-**7** (about15%) was also obtained. When the opposite isomer [Sp]-**3** has been used as the substrate for the condensation , the major product was identified as [Sp]-**7**. Thus the reaction between 5'-*O*-DMT nucleoside 3'-*O*-(*O*-2,4,6-trimethylbenzoyl methanephosphonothioate)s **(3)** and 5'-*O*-nucleosides proceeds in the presence of DBU with predominant inversion of configuration at the phosphorus center. The diastereomerically pure product [Rp]-**7** has been further converted into [Rp]-5'-*O*-DMT thymidylyl 3'-*O*-acetylthymidine (3',5')-methanephosphonate **(8)** by means of stereoretentive oxidation with oxone.[6] After the standard selective 3'-deprotection it was compared by means of HPLC with the authentic sample of [Rp,Sp]-**8,** obtained *via* methanephosphonamidite method.

The above synthesis of **7,** followed by the stereospecific oxidation gives additional opportunity for the utilization of the mixed anhydrides **3** as substrates for the preparation of diastereomerically pure [Rp]-dinucleoside (3',5')-methanephosphonates.

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