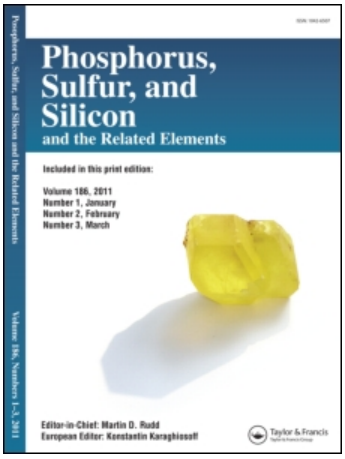

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Activation of Methylphosphonates and Their Thio- and Seleno Congeners with 1,3,5-Triazinyl Morpholinium Salts. Selenono-Selenolo Isomerization

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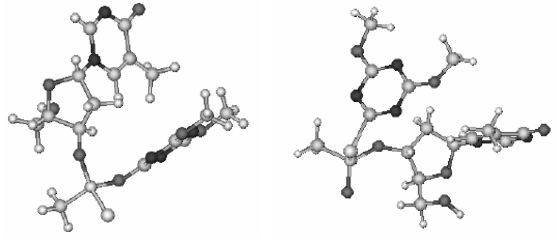
*The stereospecific activation of nucleoside 3′-O-methylphosphonoselenoates (**1**) with N-methyl-N-4,6-dimethoxy-1,3,5-triazinyl-yl morpholinium chloride resulted in formation of both O-activated (**5**) and Se-activated (**6**) 1,3,5-triazin-yl esters.*



5-S_P **6**-S_P

Keywords 1,3,5-triazines; 1,3,5-triazinyl salts; methylphosphonoselenoates; nucleotide analogues; phosphoroselenoates

INTRODUCTION

The *S(Se)-* or *O-* activations of diastereomerically pure nucleoside 3′-*O*-methanephosphonothio (seleno)ates (**1**, X=S, Se) provide monomers for the synthesis of dinucleoside (3′,5′)-methyl phosphonates (**2**) or methylphosphonothio(seleno)ates (**3**), respectively.[1,2] The concept of *active esters* and *superactive esters* as reactive intermediates in

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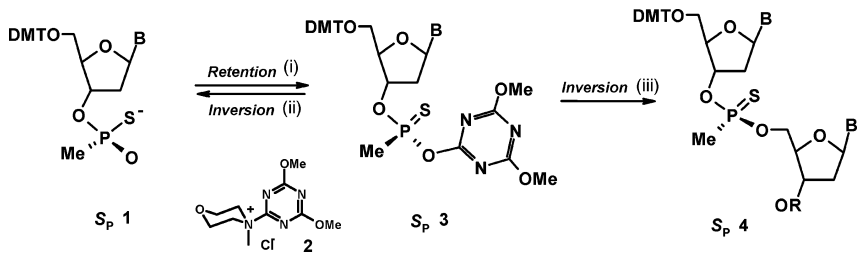


SCHEME 1 Reagents and reaction conditions: (i) 5′-O-DMT- thymidine and **2** (2 equiv) in THF, 30 min at RT. (ii) H_2O (20 equiv) and DBU (5 equiv), 30 min, (iii) **3** (1 equiv), overnight at RT, column chromatography.

acylation reactions has been widely used in synthesis of peptides,[3] amides,[4] or carboxylic acids[5] with very promising results obtained with triazine based coupling reagents.[6,7] Previously, this approach has been also used successfully in organophosphorus chemistry, where both P^{III} and P^{IV}compounds have been activated by several 1,2,4-triazoles[8] and hydroxybenzotriazoles.[9] In our search for methods of synthesis of chimeric oligonucleotides modified with *P*-methylphosphono- or phosphorothioates, we investigated bis(1,2,4-triazoyl) methylphosphonite[10] and bis(hydroxybenzotriazoyl) phosphorothioate[11] as phosphorylating agents, accordingly.

It seemed therefore attractive to confront the *"superactive ester"* approach for the synthesis of *P*-stereodefined chimeric oligonucleotides with methods evaluated previously. We found that chemoselective and stereospecific *O*-activation of nucleoside 3′-*O*-methylphosphonothioates (**1**) with *N*-methyl-*N*-4,6-dimethoxy-1,3,5-triazinyl-yl morpholinium chlorides (**2**) resulted in formation of active esters **3** which were used as monomers for stereoselective synthesis of dinucleoside (3′,5′)-methylphosphonothioates and have been convenient intermediates for interconversion of R_P-**1** into S_P-**1** (the stereochemical Walden cycle) monomers for stereoselective synthesis of **4** (Figure 1)[12] (Scheme 1).

The same strategy appeared to be promising for synthesis of chimeric oligonucleotides, modified with stereoregular dinucleoside (3′,5′)-methylphosphonoselenoates, useful tools for structural studies, because of the MAD effect, connected with the presence of selenium in the X-ray analyzed molecules,[13] and a diagnostic value of the P-Se coupling constants. However, in contrast to nucleoside 3′-*O*-methylphosphonothioates (**1**), exclusively*O*-activated with 1,3,5-triazin-yl-morpholinium chloride (**2**), the corresponding activation of nucleoside 3′-*O*-methylphosphonoselenoates[14] (**1**) was not selective,

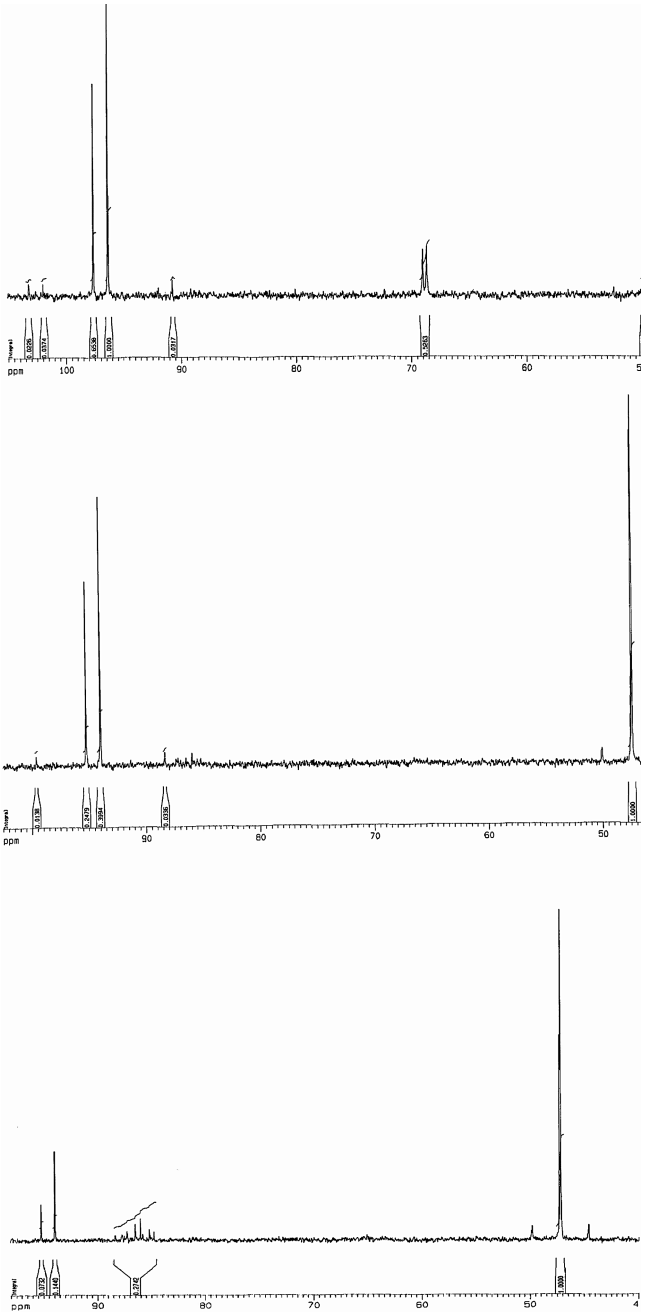
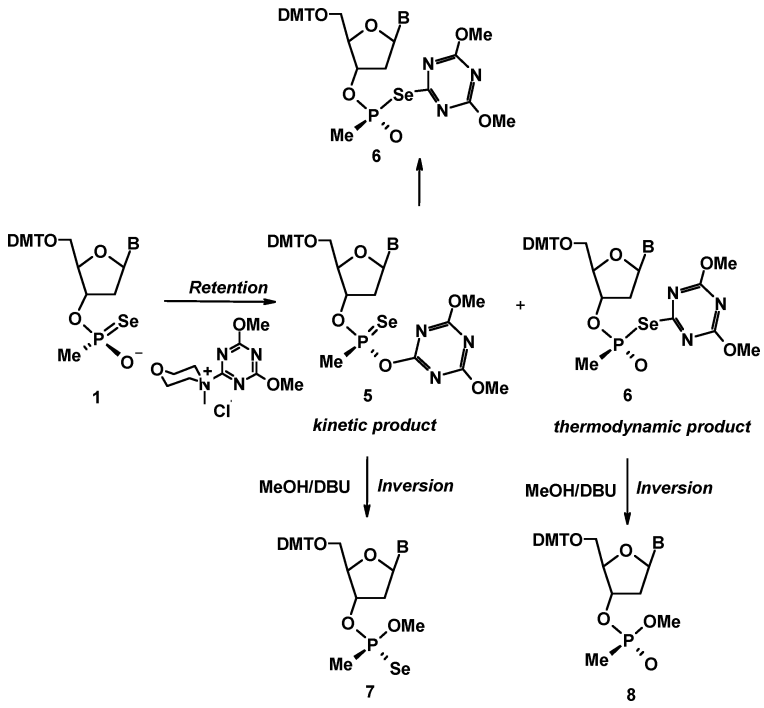


FIGURE 1



SCHEME 2

and we observed a formation of both *O*-activated (**5**) and *Se*-activated (**6**) 1,3,5-triazin-yl esters.

In the reported experiments (Scheme 2), followed by ^{31}P NMR (Figure 1), we found that *O*-activation was faster, and the protected 3′-*O*-(*O*-1,3,5-triazinyl) methylphosphonoselenoate **5** (δ: 97.64, 90.76 ppm, $J_{P-Se} = 911$ Hz) was a dominant isomer at the beginning of the reaction, when diastereomerically enriched methylphosphonoselenoate **1** (R_P:S_P (2:1) δ: 71.08, 70.62 ppm; $J_{P-Se} = 701$ Hz for both diast.) was activated with 3 equivalents of the corresponding the in situ generated 1,3,5-triazin-yl chloride 2. The amount of thymidine 3′-*O*-(*Se*-1,3,5-triazinyl) methylphosphonoselenolate 6 increased in due course of the activation (δ: 49.67 ppm, $J_{P\text{-}Se} = 425$ Hz; 49.59 ppm, $J_{P\text{-}Se} = 423$ Hz). After four h, there was a mixture of 1:1 ratio of the esters **5** and **6**, and after 72 h, only the ester **6** was observed.[15] The performed ab initio studies of the relative stabilities of esters **5** and **6** (Hyperchem 7.5, Amber 99; conjugate gradient $\Delta = 0.01$) confirmed that there existed only small differences in esters stabilities, decreasing in the following order S_P-6 > R_P-6 > S_P-5 > R_P-5. Therefore, the selenono-selenolo isomerization, observed during activation of **1** with **2** is a consequence of a

formation of the thermodynamically more stable products **6**, and preliminary formation of the kinetically favored esters **5**,[16] most probably catalyzed by amine chlorides present in the reaction mixture.[17]

In the presence of strong bases, e.g., DBU, both esters reacted in stereospecific way, affording the corresponding 5′-*O*-DMT-thymidine 3′-*O*-(*O*-methyl methanephosphono selenoates) (**7**), and 5′-*O*-DMT-thymidine 3′-*O*-methanephosphonates (**8**), respectively. Since we used diastereomerically enriched (1:2 R_P/S_P) methanephosphonoselenoates **1** in these experiments, this permitted us to assign the absolute configuration of the active esters **7** (Scheme 2) and stereoretention of the activations. The formation of *O*-methyl methylphosphonoselenoate **7** (δ: 100.1, 99.86 ppm; $J_{P-Se} = 876$ Hz) (and *O*-methyl methylphosphonate **8** (δ: 31.25, 31.18 ppm) in reactions of the corresponding esters **5** and **6** with methanol activated by DBU occurred with inversion of configuration.[18]

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[14] Into a solution of 1,2,4-triazole (5 mmol, 2.5 equiv) and Et_3N (6 mmol, 3 equiv) in THF (10 mL), cooled to 0°C, $MePCl_2$ (2.2 mmol, 1.1 equiv) was added, and a reaction mixture was stirred for 20 min. 5′-*O*-DMT-thymidine (2 mmol) dissolved in THF (10 mL) was added to this mixture dropwise, with stirring continued for

30 min. After this time, elemental Se was added, and the reaction mixture was left overnight. Hydrolysis (30 min) was performed with a mixture H_2O/Et_3N, followed by extraction of products with chloroform, and purification/separation of **1** *via* silica gel column chromatography with a mixture of $CHCl_3$ and EtOH (19:1, v/v) cont. 1% Et_3N as an eluent. Yield 80%.

[15] Diastereomerically enriched substrate **1** (R_P:S_P (2:1) δ: 71.08, 70.62 ppm; $J_{P\text{-}Se}$ = 701) and **2** (3 equiv.) were stirred at room temp. in dry MeCN. The reaction progress was followed by ^{31}P NMR. After the reaction was complete, and only the ester **6** (δ: 49.7 ppm, $J_{P\text{-}Se}$ = 425 Hz; 49.6 ppm, $J_{P\text{-}Se}$ = 423 Hz) was present, the reaction mixture was concentrated, washed with water, and purified by a silica gel column chromatography. Product **6** was eluted with 4% methanol in $CHCl_3$. Yield 67%.

[16] Similar results were observed in case of *O*,*O*-dimethyl phosphoroselenoates, when both *O*-triazinyl phosphoroselenoates (δ: 52.34. ppm, J_{P-Se} = 780 Hz) and *Se*-triazinyl selenolates (δ: 24.79 ppm, $J_{P\text{-}Se}$ = 488 Hz) were formed under similar conditions. Moreover, a mixture of both *O*-triazinyl and *S*-triazynyl isomers was also formed in a reaction of *O*,*O*-dimethyl phosphorothioate with 2 (δ: 53.8 ppm, and 32.97 ppm, respectively).

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