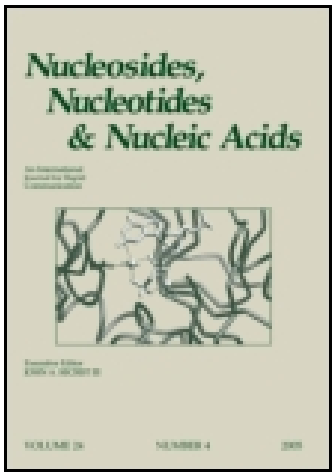

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OXIDATIVE TRANSFORMATIONS OF NUCLEOSIDE FLUORENEMETHYL H-PHOSPHONOSELENOATE DIESTERS

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OXIDATIVE TRANSFORMATIONS OF NUCLEOSIDE FLUORENEMETHYL H-PHOSPHONOSELENOATE DIESTERS

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▫ *9-Fluorenemethyl H-phosphonoselenoate monoester has been used to produce thymidine 3′-O-phosphoroselenoate monoester from which various P(V) derivatives containing multiple modifications at phosphorus were obtained; e.g., thymidine 3′-O-phosphoroselenofluoridate, 3′-O-phosphoroselenothioate, or 3′-O-phosphorodiselenoate monoesters.*

INTRODUCTION

We have previously reported on the use of 9-fluorenemethyl H-phosphonoselenoate monoester as a useful reagent for transferring of an H-phosphonoselenoate moiety[1] to nucleosides. In this article, we expand the uses of 9-fluorenemethyl H-phosphonoselenoate monoester by performing several oxidative transformations on the intermediate nucleoside fluorenemethyl H-phosphonoselenoate diester **1** prior to the removal of the fluorenemethyl protecting group. This gives access to several novel phosphoroselenoate monoesters.

RESULTS AND DISCUSSION

The nucleoside fluorenemethyl H-phosphonoselenoate diester **1** is easily available through previously published procedures.[1] The most basic oxidative transformation is oxidation of **1** into the corresponding phosphoroselenoate diester **3**. By performing this reaction using standard protocol developed for H-phosphonate diesters[2] a significant deselenization occurred, even with equimolar

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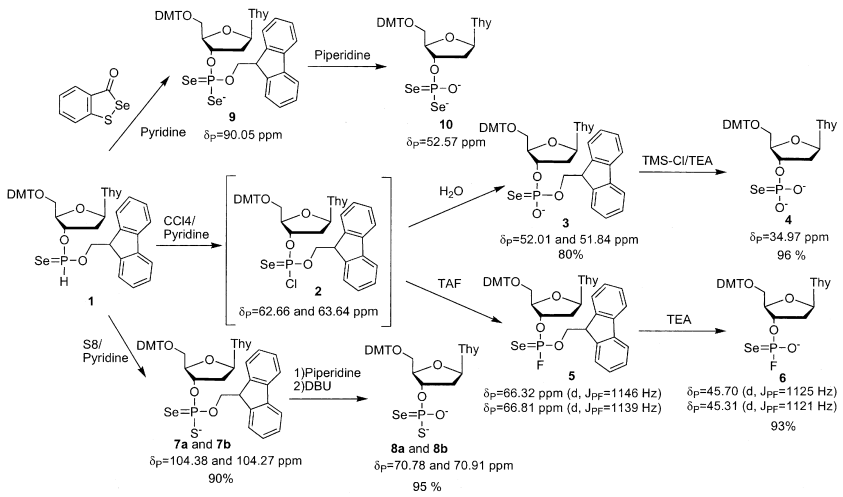
amounts of iodine used. However, when the reaction was run in MeCN with iodine (1 eq), pyridine (20 eq), and water (60 eq), the deselenization of the product could be almost completely suppressed. Changing from iodine to carbon tetrachloride as an oxidizing agent simplified further the synthetic protocol. The reaction with CCl4 (10 eq), pyridine (20 eq), and water (60 eq) in MeCN resulted in clean and fast (15 min) formation of the desired phosphoroselenochloridate **2**, which upon hydrolysis afforded product **3** in isolated yield of 80%.

Deprotection of diester **3** to produce monoester **4** using the protocol developed for the sulfur analogue[3] that involved treatment with aqueous ammonia was accompanied by severe side products formation. It was found that the cleanest deprotection of **3** could be achieved by using TMS-Cl (10 eq) and TEA (20 eq) in pyridine (10 min). Under such conditions, **4** was the only observable product and it was isolated in 96% yield by precipitation from diethyl ether. The obtained phosphoroselenoate monoester **4** was, however, unstable in aqueous solution and loses selenium within hours, in contrast to the corresponding diesters of type **3**, which were much more stable (Scheme 1).

The intermediate phosphoroselenochloridate **2** can also be treated with 1 eq triethylammonium trishydrofluoride (TAF) to produce fast (5 min) and quantitatively (^{31}P NMR) the corresponding phosphoroselenofluoridate **5**. Crude **5** could easily be deprotected using TEA (10 eq) in pyridine and the monoester **6** was isolated in 93% yield.

The diastereoisomers of **1** could easily be separated by flash column chromatography and their sulfurization gave rise to novel phosphate monoester analogues, phosphoroselenothioates, with a chiral phosphorus center. Sulfurization of **1** with elemental sulfur (3 eq) and pyridine (20 eq) in MeCN was uneventful and



SCHEME 1 Oxidative transformations of nucleoside fluorenemethyl H-phosphonoselenoate diesters.

yielded within 20 min the diesters **7a** and **7b** essentially quantitatively (^{31}P NMR; isolated yields ca 90%).

The deprotection of diesters **7a** and **7b** using aqueous conditions turned out to be a difficult task. Changing to anhydrous conditions with thiophenol and triethyl amine gave the desired monoesters **8a** and **8b**, but the reaction was slow (2 h) and side products were formed over time. However, using piperidine (20 eq) in pyridine furnished clean formation of the desired products. The produced ammonium salts of **8a** and **8b** were somewhat unstable, but titration of the salts with DBU stabilized the products sufficiently to permit their isolation and characterization. These monoesters were, however, even more prone to degradation than phosphoroselenoate **4** and in the presence of air or moisture, compound **8** decomposed within hours.

Selenization of **1** turned out to be less straightforward than sulfurization because using elemental selenium and pyridine in MeCN gave slow conversion and some by-products formation. Changing to KSeCN as a selenizing agent gave a somewhat faster reaction, but formation of side products was not completely suppressed. Attempts to use triphenyl phosphine selenide or triphenyl phosphoroselenoates gave no formation of the desired product. The best results were obtained with selenization of **1** with 1.1 eq of 3*H*-1,2-benzothiaselenol-3-one[4] (BTSe) and 20 eq of pyridine in MeCN. This gave clean and fast (5 min) formation of diselenoate **9**, which upon treatment with piperidine (20 eq) afforded monoester **10** (^{31}P NMR). Unfortunately, phosphorodiselenoate **10** was too unstable to allow its isolation and more detailed characterization.

CONCLUSION

Nucleoside 9-fluorenemethyl H-phosphonoselenoate monoester **1** was found to be a convenient starting material for the preparation of various P(V) derivatives with multiple modifications at the phosphorus center. By oxidative transformations of **1**, several novel selenium-containing nucleotide analogues have been synthesized.

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