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Biomimetic Seleninates and Selenonates

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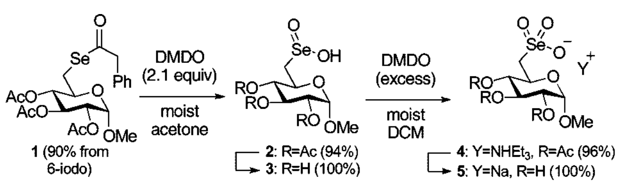
Aliphatic seleninic ($RSeO_2H$) and selenonic ($RSeO_3H$) acids and their salts may be viewed as isosteres[1] of the biologically ubiquitous anionic O-phosphate,[2] O-sulfate,[3] and carboxylate[4,5] groups and can be predicted to resist the action of most enzymes that operate in the biosynthesis or subsequent processing of those bioanions. While sometimes considered too unstable[6] or too toxic[7] for medicinal chemistry use, seleninates and selenonates nevertheless exhibit unique reactivity that can potentially be channeled for an assortment of bioorganic applications, including studies of enzyme action and inhibition, enzyme structure and mechanism, and biomimetic chemical ligation. We report a mild and efficient method for the preparation of pyranose-, nucleoside-, amino acid-, and polyhydric-based seleninates and selenonates, as well as some unusual coupling reactions with nucleophilic functionality that is commonly found in proteins and enzyme active sites.

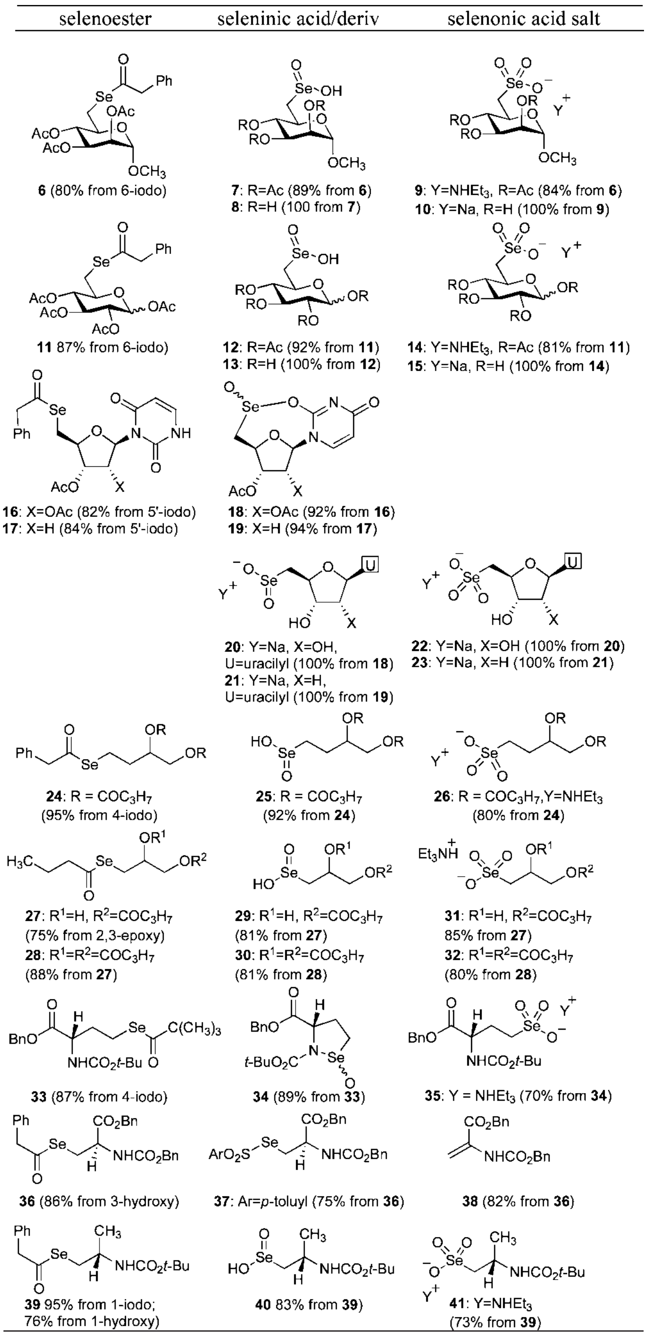
Selenoesters such as the *gluco*-pyranoside-based **1** (eq 1) are readily prepared by displacement reaction of the corresponding primary iodide with a selenocarboxylate anion generated in situ from the carboxylic acid and Woollins' reagent.[8] Clean oxidation of **1** to the seleninic acid occurred in the presence of stoichiometric amounts of dimethyldioxirane (DMDO);[9] the product **2** crystallized from solution and was characterized by mass spectrometry, ^{1}H, ^{13}C, and ^{77}Se NMR spectroscopy, and X-ray crystallography. The acetates were cleaved quantitatively with methoxide to afford triol **3** without affecting the seleninate functionality. Oxidation of **2** with excess DMDO led to the selenonate, which was conveniently isolated by chromatography as its triethylammonium salt **4**. Alternatively, **4** was prepared directly from **1** by DMDO oxidation in 81% yield; deacetylation with methoxide gave selenonate triol sodium salt **5** quantitatively.[10] Fewer than a dozen aliphatic selenonic acids have been previously reported and very little is known about their chemistry.



(1)

By using comparable transformations, a variety of polyfunctional selenoesters were converted to seleninates and selenonates (Table 1). The *manno*-pyranoside (**6**) and *gluco*-pyranose (**11**) systems gave respective seleninates (**8** and **13**) and selenonates (**10** and **15**) that superficially resemble the corresponding 6-*O*-phosphates.[11] Uridine (**16**) and 2′-deoxyuridine (**17**) substrates gave initially upon oxidation the cyclic seleninic esters **18** and **19**, but these rings were readily opened during subsequent deacetylation. Nucleoside seleninates **20** and **21** and selenonates **22** and **23** may be thought of as truncated 5′-*O*-phosphate analogues.[12] The mono- and di-*O*-acylated butanediol and propanediol seleninates (**25**, **29**, and **30**)

Table 1. Synthesis of Seleninates and Selenonates from Selenoesters



and selenonates (**26**, **31**, and **32**) resemble lysophospholipids, although they are monobasic. The selenoglutamate **35** was prepared

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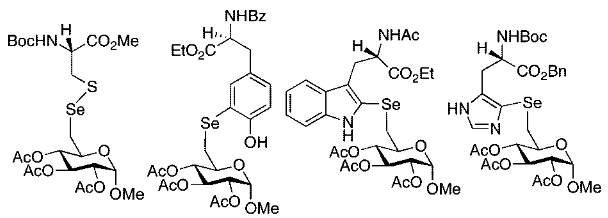
from a protected homoserine by Mitsunobu substitution followed by DMDO oxidation; cyclized seleninamide **34** was isolated as the intermediate.

In contrast to the homoserine substrate, serine-derived selenoester **36** gave a seleninic acid that was not isolable, but instead eliminated H_2SeO_2 within minutes by retro-ene reaction to give the dehydroalanine derivative **38**.[13] Following treatment of the presumed seleninic acid intermediate with *p*-toluenesulfonylhydrazide,[14] however, the trapped stable redox product selenolsulfonate **37** was isolated in good yield. The alaninol-derived system **39**, by comparison, oxidized smoothly to seleninate **40** without elimination, and further oxidation to selenonate **41** was also uneventful.

Seleninic acids react with mercaptans to give the selenosulfide.[15] With seleninate **2**, 1.0 equiv of *N*-Boc-cysteine methyl ester reacted in CH_2Cl_2 solution within 1 min at 23 °C to give the coupled product **42** in good yield.[16] A number of enzyme active sites contain a cysteine sulfhydryl,[17] so given the appropriate seleninate-containing substrate mimic, this reaction is a potential avenue for

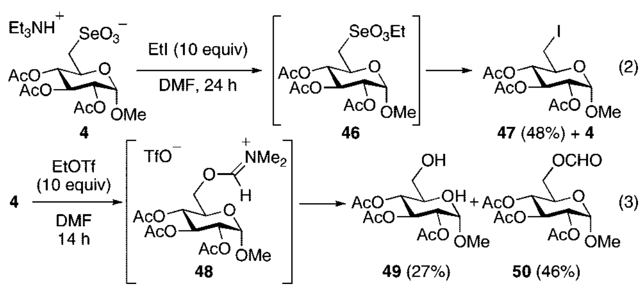


42 (81% from **2**) **43** (30% from **2**) **44** (60% from **2**) **45** (56% from **2**)

irreversible inhibition by covalent attachment.

Other electron-rich protein side-chain residues couple with the seleninic electrophile. *N*-Benzoyltyrosine ethyl ester (1.0 equiv, 24 h, CH_2Cl_2, 37 °C) reacted slowly with **2** to afford the ortho selenylated product **43**.[18] Likewise, *N*-acetyltryptophan ethyl ester gave the 2-selenylated indole derivative **44**,[19] and *N*-Boc-histidine benzyl ester was selenylated on the imidazole ring (**45**).[20] These three solution reactions are significantly slower than the sulfhydryl coupling, but might occur with appropriately positioned residues in an enzyme active site.

An attempt to convert selenonate **4** into its ethyl ester (eq 2)[21] led unexpectedly to the 1° iodide **47**, evidently by way of displacement of $EtOSeO_2^-$ from **46**. Reaction of **4** with EtOTf in DMF solution (eq 3) gave products (**49** and **50**) that may have arisen by hydrolysis of iminium intermediate **48**, wherein the amide carbonyl has displaced $EtOSeO_2^-$. The susceptibility of selenonates to S_N2 cleavage at the C−Se bond has not been explored previously,[22] but represents another mode of potential covalent attachment to an active site nucleophile.



The stability of many, but not all, of the new seleninates, can be attributed to the slow rate of selenoxy retro-ene elimination expected for systems with a β-oxygen substituent.[23] For others (**25**, **40**), the stability of the resulting alkene would seem to be insufficient to favor the elimination (compare the selenocysteine systems, which eliminate readily). The stability of the selenonates may derive from the ability of their C−Se bonds (1°, electron-poor, *beta*-branched) to withstand both S_N1 and S_N2 pathways for cleavage.

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Supporting Information Available: Experimental details for new compounds, and the crystal structure of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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