BIOMIMETIC ENZYME INHIBITORS

by

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written under the direction of
Professor Spencer Knapp
and approved by

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New Brunswick, New Jersey
May, 2010
ABSTRACT OF THE DISSERTATION

Biomimetic Enzyme Inhibitors

by Mohannad Abdo

Dissertation Director:
Professor Spencer Knapp

Synthetic biomimetic compounds play crucial roles in virtually all aspects of biology and medicine. Their continual development contributes towards understanding and manipulating the normal action of enzymes and other proteins as well as in the development of new drugs. Herein, the novel synthesis of biomimetic enzyme inhibitors, including GlcNAc-thiazolines, GlcNAc-thiolsulfonates, and seleninates, selenonates, and various other organoselenium compounds, is reported. Evaluation of these biomimetics against N-acetyl-β-hexosaminidases, protein tyrosine phosphatases, and some nucleoside processing enzymes is described. Evidence toward elucidation of several reaction mechanisms linked to the synthesis and inhibition of these compounds is also presented.
Dedication

To my loving parents Afaf and Mohammad, my siblings, Diya, Ahmad, and Rania, and grandmother Sabha
Acknowledgement

Reminiscing upon the hours, days, years of research dedicated to producing this dissertation, I think of the most important people that smoothed the difficult path I embarked upon. Although words cannot begin to describe all that they have done for me, I would like to express my gratitude towards them.

Professor Spencer Knapp, as a mentor and remarkable scientist you have never ceased to help me in all the areas which formed the basis of my studies and research. Your patience and willingness to set me in the right direction was nothing short of phenomenal, and without your guidance and daily accessibility this dissertation would have never been possible.

I extend my endless thanks to Professors Heinz Roth, Daniel Seidel, and Dr. Benjamin Amorelli for their beneficial discussions regarding my research and the defense of my dissertation. Additionally, I would like to acknowledge my fellow colleagues in the “Knapp Group” for developing my expertise in the laboratory, engaging in many helpful discussions, and creating a fun working environment.

My love goes to my family. My parents Afaf and Mohammad have been with me every step of the way with their constant words of hope, encouragement and wisdom; I am proud to be their son. My three siblings Diya, Ahmad, and Rania have managed to impact my life in ways I cannot even begin to imagine. Their much needed words of comfort have encouraged me to push through the obstacles. I have always looked to them as my role models, and they never ceased to provide me with the strength I needed.
Finally, whenever I think of success, the glimmer in the eyes of my
grandmother Sabha is resonant in my mind. From my elementary levels of
success she has always believed in me and despite her lack of presence, her
compassion and faith runs in me on a daily basis. I hope to have her strength
and perseverance with me in my future endeavors.
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<td>$K_i$</td>
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<td>mass spectrometer</td>
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<td>NAG</td>
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<td><em>yersinia</em> protein tyrosine phosphatase</td>
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The Quest for Biomimetic Enzyme Inhibitors

Biomimetic chemistry entails the synthesis of unnatural compounds with the purpose of mimicking the structures and functions of compounds found in biological systems. Typically, natural substrates have high affinity for their biological targets, but they may still possess undesirable characteristics regarding bioavailability, metabolic stability, selectivity, and toxicity. Artificially engineered mimics, therefore, represent a possible avenue to work around one or more of these issues.

One of the most commonly used strategies to address the issue of undesirable characteristics in natural substrates and further understand biomimetic chemistry involves the concept of bioisosterism. This concept entails the replacement of the natural active substrate with another compound by exchanging one group of atoms for another. The resulting compound still retains many of the desirable properties of the original compound, but is aimed to minimize or eliminate the undesirable ones.

The construction of an effective bioisosteric replacement is not a simple process; it requires consideration of the groups to be exchanged within the natural substrate and their intended replacement. Ideally, these two groups should be comparable with respect to relevant properties such as size, shape, electronics, lipophilicity, solubility, chemical reactivity, in addition to other important characteristics. Considering all of the aforementioned factors at once when planning for a replacement may prove to be impossible; however, one
should try to carefully balance and weigh all the various properties to allow the new compound to be successful.\(^3\)

Biomimetics are crucial to virtually all aspects of biology and medicine. They can fool enzymes that recognize their natural substrates, bind to them, and alter their usual progression of processing substrates into products. The importance of understanding and manipulating the normal action of enzymes and other proteins necessitates continual development of new structures with the potential to interact abnormally with them. This importance is most apparent in the pharmaceutical industry where design of biomimetics is one of the most common methods for developing successful drugs.
References

Enzyme Inhibitors Derived From GlcNAc-Thiazoline

1.1 Background

1.1.1 N-acetyl-β-hexosaminidases

Retaining N-acetyl-β-hexosaminidases (NAGases) are a class of glycosyl hydrolases that are responsible for the removal of 2-acetamido-2-deoxy-D-glucopyranosyl (GlcNAc) and -galactopyranosyl (GalNAc) residues from glycoconjugates (Figure 1.1.1). Humans have three NAGases: N-acetylhexosaminidase A (Hex A), N-acetylhexosaminidase B (Hex B), and O-GlcNAcase (OGA). Hex A and Hex B are members of family 20 of glycoside hydrolases that are normally localized within the lysosome. They catalyze the cleavage of β-O-linked GalNAc (O-GalNAc) residues from glycoconjugates. O-GlcNAcase is a member of family 84 of glycoside hydrolases that is critical in the post-translational modification of nucleocytoplasmic proteins. It catalyzes the cleavage of β-O-linked GlcNAc (O-GlcNAc) modified serine and threonine residues.1-4

![Diagram of GlcNAc and GalNAc hydrolysis](image)

Figure 1.1.1. Hydrolysis of GlcNAc and GalNAc residues from glycoconjugates
The dynamic modification of lysosomal, cytoplasmic, and nuclear proteins by O-GlcNAc/O-GalNAc residues is an important signaling mechanism that shares characteristics with phosphorylation. "O-GlcNAc and -GalNAc-ylation" functions in diverse cellular processes including nutrient sensing, modifying protein target activity, and controlling gene expression and protein degradation. Unusual patterns of O-GlcNAc and -GalNAc-ylation have been linked to insulin resistance, cancer, Alzheimer’s, and to several neurodegenerative disorders such as Tay-Sachs and Sandhoff diseases.

1.1.2 Proposed catalytic mechanism of NAGases

A number of retaining NAGases, including the bacterial enzyme from Streptomyces plicatus (SpHex), and the human enzymes OGA and Hex A and Hex B, are believed to utilize substrate-assisted catalysis. The first step entails a cyclization that proceeds via the attack of the 2-acetamido carbonyl oxygen on the anomeric center to form a covalent bicyclic oxazolinium intermediate. This step is facilitated by the respective polarization of the 2-acetamido group and the aglycon by a basic carboxyl group and an acidic carboxyl group in the active site of the enzyme. The second step involves the ring opening of the oxazolinium intermediate by a general base-catalyzed attack of a water molecule on the anomeric center and general acidic catalysis facilitating the departure of the amide group (Figure 1.1.2).
1.1.3 GlcNAc-thiazoline as a NAGase inhibitor and pharmacological chaperone

Small molecule inhibitors of the NAGases have received a great deal of attention as tools for elucidating their role in biological processes as well as in developing therapeutic interventions with minimal side effects. One of those inhibitors, GlcNAc-thiazoline 1-1-1, has enjoyed extensive use in studies over the past decade. It is an excellent example of an effective bioisosteric replacement derived from the transition state of the NAGases catalytic cycle. In contrast to the NAG-oxazoline intermediate 1-1-2, which is too hydrolytically unstable for use as an inhibitor, GlcNAc-thiazoline 1-1-1 is a much more stable mimic that exerts a powerful inhibitory effect on jack bean NAGase,\textsuperscript{23} SpHex,\textsuperscript{23-24} OGA,\textsuperscript{20} Hex A and Hex B.\textsuperscript{19,20,24} (Figure 1.1.3).
1.2  **GlcNAc-thiazoline conformations**\(^{25}\)

1.2.1  **Inhibitor conformations**

The details of the relationship between inhibitor conformation and binding are important for understanding the interactions of substrate with enzyme, and for the design of new inhibitors.\(^{26}\) With regards to the latter, an inhibitor with some degree of conformational flexibility may be desirable as it allows for the molecule to adopt the most favorable conformation for binding to the active site. This conformational mobility can also prove advantageous as the inhibitor retains the chance to inhibit mutant forms of the target microorganisms.\(^{27}\)

Recent protein crystallographic studies have revealed that GlcNAc-thiazoline **1-1-1** binds in NAGase active sites\(^{19,21-23,28,29}\) in the *pseudo*-chair (\(^{4}C_{1}\)) conformation, suggesting that this is the specific conformation that most closely matches the transition state in Figure 1.1.2. However, the conformation of GlcNAc-thiazoline **1-1-1** in solution remained to be fully described.
1.2.2 NOE measurements of GlcNAc-thiazoline

We have examined the conformational properties of GlcNAc-thiazoline 1-1-1 in solution by nuclear overhauser effect (NOE) measurements. Attempts to cool methanolic solutions of GlcNAc-thiazoline 1-1-1 to -78 °C in order to freeze out individual contributing conformations and to identify them by $^1$H NMR spectroscopy were unsuccessful. However, NOE studies on GlcNAc-thiazoline 1-1-1 in methanol-d$_4$ solution revealed a number of proton–proton through-space contacts that can be attributed to one or more of the four conformations shown in Figure 1.2.1. The diagnostic H ··· H contacts for each conformation are also displayed in Figure 1.2.1 (dashed arrows).

![Diagram of GlcNAc-thiazoline conformations](image)

**Figure 1.2.1.** Four GlcNAc-thiazoline 1-1-1 conformations. Dashed arrows represent diagnostic NOE signals observed

Table 1.2.1 summarizes the qualitative NOE enhancements observed upon irradiation at each of eight proton signals. The H-2/H-3 and H-5/Me NOEs are
(among these four possibilities) uniquely due to the $^0$S$_2$ conformation, and the intensity of these signals indicates that this is indeed the major contributing conformation in methanol solution. Additionally, the weaker NOEs observed for H-2/H-4 and H-3/H-5 can be uniquely attributed to the $^4$C$_1$ conformation. Furthermore, a very weak H-1/H-4 NOE is observed, and this is unique (again, among these four possibilities) to the $^1$S$_3$ conformation. Thus, a small contribution by the $^1$S$_3$ is indicated. The absence of an H-1/H-6 NOE suggests, however, that the contribution of the $^1$C$_4$ conformation is negligible.

Table 1.2.1. Qualitative Individual NOEs for GlcNAc-thiazoline 1-1-1$^{a,b}$

<table>
<thead>
<tr>
<th>Proton $hv\rightarrow$</th>
<th>H-1</th>
<th>H-2</th>
<th>H-3</th>
<th>H-4</th>
<th>H-5</th>
<th>H-6</th>
<th>H-6'</th>
<th>CH$_3$</th>
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<td>6</td>
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<tr>
<td>CH$_3$</td>
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</tr>
</tbody>
</table>

$^a$ Observed for MeOH-d$_4$ solution of GlcNAc-thiazoline 1-1-1 at 25 °C

$^b$ Key: ****, strong NOE observed; ***, medium NOE; **, weak NOE; *, very weak NOE; blank, no NOE; –, selfsame proton.

1.2.3 Summary of GlcNAc-thiazoline conformations

GlcNAc-thiazoline 1-1-1 is conformationally mobile in solution, existing simultaneously in a pyranose pseudo-chair and two pseudo-(twist boats) – $^4$C$_1$, $^0$S$_2$, and $^1$S$_3$, respectively – each detectable by NOE studies. The energy difference among them are likely on the order 1 – 2 kcal/mol according to calculations by Prof. Paul Rablen at Swarthmore College.$^{25}$
1.3 Tautomeric modification of GlcNAc-thiazoline$^{30}$

1.3.1 Selectivity of GlcNAc-thiazolines for OGA vs. human Hex

To help sort out the mechanisms and effects of protein “O-GlcNAc-ylation,” a significant effort has been directed toward the development of inhibitors of OGA that do not simultaneously inhibit the mechanistically related human Hex A and Hex B. In comparison to the latter, OGA tolerates inhibitor groups larger than acetamido –CH$_3$, or its equivalent, in the acetamido binding pocket, and thus provides an avenue for potential optimization of inhibitor selectivity, efficacy, solubility, transport, and metabolic stability. GlcNAc-thiazoline is a nanomolar but non-selective inhibitor of OGA, Hex A, and Hex B. By increasing the size of the thiazoline ring substituent from methyl to ethyl, propyl, and butyl, Vocadlo and coworkers were able to increase the selectivity for inhibition of OGA, but at the expense of inhibition activity (Figure 1.3.1)$^{20,31}$.

\[
\begin{align*}
1-1-1 & : K_I = 70 \text{ nM vs OGA} & \text{Selectivity vs Hex} = 1 \\
1-3-1 & : K_I = 120 \text{ nM} & \text{Selectivity} = 270 \\
1-3-2 & : K_I = 230 \text{ nM} & \text{Selectivity} = 1500 \\
1-3-3 & : K_I = 1500 \text{ nM} & \text{Selectivity} = 3100 \\
\end{align*}
\]

Figure 1.3.1. Selectivity of GlcNAc-thiazolines for OGA vs human Hex
Analogous steric-based selectivity improvements to other OGA inhibitors have also been realized.\textsuperscript{32-38} On the other hand, inhibitors that possess functionalized acetamido mimics could provide an expanded array of options for biochemical and medicinal chemistry studies (Figure 1.3.2).\textsuperscript{39}

![Figure 1.3.2](image)

**Figure 1.3.2.** Modification of Glc-NAc-thiazoline 1-1-1 on the methyl group

### 1.3.2 Tautomeric deuteration of GlcNAc-thiazoline

To prepare a new series of methyl-modified GlcNAc-thiazolines 1-3-4 the previously unrecognized propensity of GlcNAc-thiazolines to undergo buffer- and acylation-induced imine-to-enamine conversion was exploited. The methyl protons of GlcNAc-thiazoline triacetate 1-3-6, which is available on multigram scale by treatment of commercial glucosamine pentaacetate 1-3-5 with $P_4S_{10}$ (Scheme 1.3.1),\textsuperscript{40} exchange with deuterium in certain solvents in the presence of acid. As this reaction could also be used to prepare tritiated 1-1-1, the deuteration was optimized as follows. Treatment of GlcNAc-thiazoline triacetate 1-3-6 with 2.4 equiv of pyridine, 1.2 equiv of triflic acid, and 100 equiv of $D_2O$ in
acetonitrile solution for 8 h at 23 °C and then extractive workup gave the trideuterated GlcNAc-thiazoline 1-3-8. No C-deuteration was detected in the absence of the buffer components pyridine and triflic acid. Standard deacetylation then led to the corresponding triol 1-3-9 without significant loss of deuterium, according to integration of the methyl signal in the 1H NMR spectrum. Alternatively, triol 1-1-1 was directly trideuterated by treatment with the same buffer system, and 1-3-9 was separated from the buffer components by partitioning between 1-butanol and saturated aqueous sodium bicarbonate (93% yield, 95% D3). In polar solvents at acidic pH, GlcNAc-thiazoline triacetate 1-3-6 hydrolyzes to the acetamido mercaptan, and thioconjugates can then be prepared by various S-alkylation and arylation reactions.41 Hydrolysis of 1-3-8 led analogously to the trideuteroacetamido mercaptan 1-3-10; however, ~5% of the deuterium was lost in the process. The transformations in Scheme 1.3.1 are consistent with acid-promoted tautomerization of GlcNAc-thiazoline triacetate 1-3-6 to give the enamine 1-3-7; reprotonation leads to sequential replacement of all three methyl H’s.
1.3.1 Tautomeric deuteration of GlcNAc-thiazoline

Scheme 1.3.1. Tautomeric deuteration of GlcNAc-thiazoline

1.3.3 Tautomeric halogenation and displacement reactions

Would other electrophiles react with 1-3-7? Treatment of GlcNAc-thiazoline triacetate 1-3-6 with the same buffer, but in the presence of 3.2 equiv of N-chlorosuccinimide (NCS) or N-bromosuccinimide (NBS), gave the trichloride 1-3-13 or tribromide 1-3-14, respectively (Scheme 1.3.2). The dichloride 1-3-11 or dibromide 1-3-12 could be obtained (along with the trihalogenated products) by reducing the amount of NCS or NBS to 2.2 equiv. The monochloride or monobromide could not be prepared selectively, evidently because the second and third chlorinations/brominations are faster than the first. Fluorination, however, could be effectively stopped after one substitution: exposure of
GlcNAC-thiazoline triacetate 1-3-6 to buffer and 1.5 equiv of Selectfluor\(^{42}\) gave 1-3-15 in high yield. Standard deacetylation led to the fluoro thiazoline triol 1-3-16.

\[
\text{Scheme 1.3.2. Tautomeric halogenation of GlcNAC-thiazoline}
\]

Efforts to iodinate GlcNAC-thiazoline have been undertaken by my colleague Kehinde Ajayi. He has demonstrated that iodination of GlcNAC-thiazoline triacetate 1-3-6 could also be stopped after a mono-substitution (Scheme 1.3.3). The product 1-3-17 proved to be unstable to storage, but could be isolated and characterized, and subsequently treated with nucleophiles. Thus, substitution of iodo by azido led to 1-3-18, and, following deacetylation, to 1-3-19. Replacement of iodo with acetoxy and S-acetylthio was also successful, and the
resulting thiazolines 1-3-20 and 1-3-22 were deacetylated (the latter in the presence of iodomethane) to afford 1-3-21 and 1-3-23, respectively.

Scheme 1.3.3. Tautomeric iodination and displacement reactions

1.3.4 GlcNAc-thiazole acylations

The ease of tautomerization of GlcNAc-thiazoline triacetate 1-3-6 suggested that an N-acyl-enamine might also be accessible (Scheme 1.3.4). Reaction of GlcNAc-thiazoline triacetate 1-3-6 with 1 equiv of TFAA indeed gave the enamine 1-3-24. In methanol solution, 1-3-24 reverted to GlcNac-thiazoline triacetate 1-3-6, and when treated with methoxide, 1-3-24 gave GlcNAc-
thiazoline triol 1-1-1. Upon acylation of GlcNAc-thiazoline triacetate 1-3-6 with 2.1 equiv of TFAA, the C-acylated product 1-3-25 formed in good yield, presumably through 1-3-24 as an intermediate. Deacetylation gave keto triol 1-3-26, as confirmed by peracetylation to 1-3-27. Both 1-3-24 and 1-3-27 exist as pseudo-chair conformers in solution, according to the vicinal proton $J$ values.

Scheme 1.3.4. GlcNAc-thiazoline acylations

1.3.5 Radical trifluoromethylation

Would monohalogenated GlcNAc-thiazolines be obtained from enamine 1-3-24? During attempts to brominate enamine 1-3-24 with $N$-bromsuccinamide,
we discovered a new trifluoromethylation reaction (Scheme 1.3.5). Treatment of enamine 1-3-24 with benzoyl peroxide and a low power UV light source gave the 2,2,2-trifluoroethyl thiazoline 1-3-28. This product shows the diagnostic five-bond coupling between the thiazoline methylene H's (−CH₂CF₃) and the pyranose H-2. $^{19}$F NMR analysis ($\delta$ –63.9, t, $J = 10.3$ Hz) supports this structure, as do the spectra of the deacetylated product 1-3-29. Treatment of 1-3-29 with excess sodium methoxide in refluxing methanol gave the orthoester 1-3-30.

Scheme 1.3.5. Radical trifluoromethylation
A radical chain mechanism (Scheme 1.3.6) accounts for the formation of 1-3-28. The initiating radical can add to the C=C of 1-3-24, leading to a tertiary thiazolidine radical (I), fragmentation of which would give the trifluoroacetyl radical and a thiazoline product. The trifluoroacetyl radical likely fragments further to provide carbon monoxide and the trifluoromethyl radical. Addition of trifluoromethyl radical to 1-3-24 again leads to a thiazolidinyl radical (II), and then the chain is propagated by another fragmentation, giving 1-3-28 as well as more trifluoromethyl radical.

Scheme 1.3.6. Proposed mechanism for radical trifluoromethylation

1.3.6 Radical addition of thiomethane

The trifluoromethylation mechanism is supported by the successful trapping of the thiazolidine radical by methyl mercaptan (Scheme 1.3.7).
Exposure of enamine 1-3-24 to the radical initiating conditions, but in the presence of excess mercaptan, led to the formation of thioether adduct 1-3-31 as an inseparable 9:1 mixture of stereoisomers (respective anomeric H’s at 5.94 and 6.21 ppm). Kinetic hydrogen atom abstraction likely occurs preferentially from the less hindered beta face, and is faster than loss of CF₃CO·, accounting for the formation of product still bearing this group. Deacetylation of thioether adduct 1-3-31 gave triol 1-3-32, but as a 1:4 mixture of isomers (respective H-1’s at 5.77 and 5.98 ppm). The change in isomeric composition upon basic hydrolysis reflects thiazolidine ring opening to an imine mercaptide intermediate, which recloses to give the thermodynamic mixture of isomers of 1-3-32.

Scheme 1.3.7. Radical addition of methyl mercaptan
1.3.7 Inhibition studies of modified GlcNAc-thiazolines toward OGA vs. human Hex

Recent biological analysis, carried out in the laboratory of Prof. John A. Hanover at the National Institutes of Health, showed the selective inhibition of human recombinant O-GlcNAcase by the new modified GlcNAc-thiazolines, relative to their inhibition of human placental β-hexosaminidase (Figure 1.3.3). \(^{49}\) While all seven new compounds show somewhat reduced inhibition relative to the parent GlcNAc-thiazoline triol 1-1-1, the azide 1-3-19 and the fluoride 1-3-16 exhibit excellent selectivity for the O-GlcNAcase, and 1-3-19 retains nearly all of the inhibitory activity of GlcNAc-thiazoline triol 1-1-1. These two highly selective and potent GlcNAc-thiazolines differ significantly from previously characterized selective O-GlcNAcase inhibitors. The fluorine and azide derivatives may prove useful for developing reagents for imaging, labeling, and interfering with O-GlcNAc cycling in living cells and tissues.
Figure 1.3.3. Inhibition by modified GlcNAc-thiazoline of OGA in comparison to human placental Hex
1.4 α-GlcNAc-thiolsulfonates

1.4.1 OGA two splice variants

Human OGA exists as two splice variants (Figure 1.4.1): a full-length isoform (hIOGA) that is better characterized, and a shorter nuclear-localized variant (hsOGA) that has not been well characterized. The short nuclear variant of OGA has the identical catalytic domain as the full length enzyme however it lacks the C-terminal region considered to be a histone acetyltrasferase (HAT) domain. Furthermore, it has 15 amino acids at its C-terminus different from those in long OGA.

![Figure 1.4.1. Schematic protein structures of long and short OGA](image)

To better understand the roles played by the two OGA isoforms, one requires an inhibitor with differential inhibition characteristics towards the two splice variants. Some selectivity may prove useful in identifying key differences between them and their catalytic mechanisms and activity. In an effort to develop a selective inhibitor, an α-GlcNAc-thiolsulfonate glycomimic was prepared. The thiolsulfonate was designed as a competitive and potential suicide inhibitor with
respect to enzyme-substrate covalent bond formation as it could deliver an electrophilic anomeric sulfur atom of the substrate to the active site (Figure 1.4.2).

![Diagram of enzyme-substrate interaction](image)

**Figure 1.4.2.** Possible modes of OGA inhibition

### 1.4.2 Synthesis of α-GlCNAC-thiolsulfonates

β-Anomeric thiolsulfonates have been prepared with anomeric selectivity and in moderate to good yield. The synthesis of β-gluco-methane- and benzenethiolsulfonates was first reported by Davis et al., who treated the corresponding acetate and benzyl-protected α-bromoglucose, with sodium methane- and benzenethiosulfonate.\(^{53}\) Davis\(^ {53-55}\) and others\(^ {56-57}\) later described these thiolsulfonates as reactive intermediates for the preparation of the derived mixed disulfide mono- and disaccharides, glycoproteins, and sulfenamides.
These anomeric thiol sulfonates clearly identify the anomeric C-S divalent sulfur as the most reactive atom towards nucleophiles derived from mercaptans, alcohols, and amines.

\(\alpha\)-GlcNAc-thiol sulfonate 1-4-3 was prepared by acidic hydrolysis of GlcNAc-thiazoline triacetate 1-3-6 to \(\alpha\)-GlcNAc-mercaptan 1-4-1, and then nucleophilic displacement of tosyl bromide (Scheme 1.4.1). Using tosyl bromide as the electrophile gave significantly higher yields than the corresponding commercially available tosyl chloride. Reactions of 1-4-1 with tosyl chloride gave almost exclusively the known symmetrical \(\alpha\)-GlcNAc-disulfide. Attempted deprotection of 1-4-2 with sodium methoxide in methanol provided the acetamido thiol sulfonate triol 1-4-3 in excellent yield. This thiol sulfonate, however, was base sensitive so limited reaction time and immediate chromatography was necessary.

**Scheme 1.4.1.** Preparation of \(\alpha\)-GlcNAc-thiol sulfonate 1-4-3
1.4.3 Selective inhibition of α-GlcNAc-thiolsulfonates toward OGA isoforms

Recent biological analysis of α-GlcNAc-thiolsulfonate 1-4-3, carried out in the laboratory of Prof. John A. Hanover at the National Institutes of Health, showed differential inhibition characteristics of this new inhibitor toward the OGA isoforms. Enzyme assays revealed that the inhibition of long OGA by α-GlcNAc-thiolsulfonate 1-4-3 at low concentrations was about 4-fold less than that of short OGA, indicating some degree of selectivity (Figure 1.4.3).

![Graph](image)

**Figure 1.4.3.** Analysis of inhibition of hsOGA and hIOGA by α-GlcNAc-thiolsulfonate 1-4-3

Furthermore, these assays indicated that α-GlcNAc-thiolsulfonate 1-4-3 acted as a purely competitive inhibitor of short OGA but showed a mixed-type inhibition for
long OGA. This mixed inhibition resulted from a combination of competitive inhibition similar to that observed for the short isoform and a second nonspecific component.

Upon the incubation of long OGA with a saturating solution of $\alpha$-GlcNAc-thiolsulfonate $1\text{-}4\text{-}3$ at $37^\circ C$, a modification of the enzyme was observed. Comparable modification did not occur in short OGA, indicating a possible covalent modification at a site apart from the active site of OGA. Thiolsulfonate modification has been reported to occur at cysteine residues through the formation of disulfide linkages.$^{54,61}$ Glycosyl thiolsulfonates have been used by Davis and coworkers as reagents for protein pseudo-glycosylation at cysteine.$^{54,61}$ The feasibility of disulfide bond formation with $\alpha$-GlcNAc-thiolsulfonate $1\text{-}4\text{-}3$ and cysteine residues was modeled by conjugating $\alpha$-GlcNAc-thiolsulfonate $1\text{-}4\text{-}3$ with an $N$-$C$-protected cysteine (Scheme 1.4.2).

![Scheme 1.4.2. Coupling of $\alpha$-GlcNAc-thiolsulfonate $1\text{-}4\text{-}3$ with an $N$-$C$-protected cysteine](image)

Long OGA is known to have two free cysteines, positions 166 and 878,$^{62}$ that are possible modification sites. The later cysteine residue is absent in short OGA. Indeed, alkylation of the free sulfhydryls in cysteine residues of long OGA
with N-ethylmaleimide completely blocked modification by α-GlcNAc-thiolsulfonate 1-4-3. Furthermore, the treatment of the modified long OGA with dithiothreitol reversed the modification, suggesting the presence of a reducible α-GlcNAc-protein disulfide bond. On the bases of the aforementioned inhibition studies, the presumed GlcNAc disulfide modification by α-GlcNAc-thiolsulfonate 1-4-3 likely occurs in the C-terminal HAT domain; the region that features the free cysteine at 878 that is absent in short OGA.

The modification of OGA with thiol-linked GlcNAc abolishes almost all of its enzymatic activity. The amount of effective enzyme decreased as the time of preincubation of long OGA with α-GlcNAc-thiolsulfonate 1-4-3 increased. Furthermore, thiol-GlcNAc-modified long OGA is completely insensitive to cleavage by caspase. Long OGA is known to be a substrate for caspase 3, and its cleavage sites are speculated to reside in the N-terminal and middle domain. Complete caspase 3 resistance of modified long OGA suggests a dramatic change in the conformation or steric properties of the latter, rendering the cleavage sites inaccessible. It is presently unclear whether the modification of long OGA with S-GlcNAc occurs while the inhibitor is bound to the active site or occurs independent of the active site binding event. However, the results suggest that a change in the conformation of the enzyme upon remote modification drastically alters the active site architecture, resulting in a complete blockage of a substrate access. The covalent attachment of an α-S-GlcNAc unit to long OGA accounts for the irreversible and time-dependent irreversible inhibition of catalysis.
How might the $\alpha$-GlcNAc-thiolsulfonate 1-4-3 competitively inhibit an enzyme that specifically processes $\beta$-linked substrates? One hypothesis is that $\alpha$-GlcNAc-thiolsulfonate 1-4-3 assumes the $^1S_3$ twist boat conformation of the bound substrate. In this conformation, the sulfonyl oxygens might be in position to act as H-bond acceptors from the general acid residue and/or other donor residues in the active site (Figure 1.4.4). Support for this idea is found in the studies of Sivapriya et al, who showed that a sulfone inhibitor of $\alpha$-mannosidase binds much better than the corresponding sulfide.

![Inhibitor in $^1S_3$ conformation](image1)

![Bound substrate in $^1S_3$ conformation from Sivapriya et al](image2)

**Figure 1.4.4.** A proposal for the mode of binding of $\alpha$-GlcNAc-thiolsulfonate 1-4-3 by OGA

After all, and as shown in section 1.2, small molecule inhibitors (like GlcNAc-thiazoline 1-1-1) could be conformationally mobile in solution but bind only in the conformation that most closely resembles the hypothetical bound substrate transition state.
1.5 References


2.1 Seleninates and selenonates as bioisosteres

2.1.1 Biological anionic functionality

Anionic functionality such as $O$-phosphate, $O$-sulfate, and carboxylate exists prominently in Nature, residing notably in numerous biological substrates that activate an assortment of catalytic cycles that engage directly or indirectly in various physical processes and in the etiology of many disease states. For instance, lysophosphatidic acid (LPA$^1$) is a natural substrate that features an $O$-phosphate functionality in its structure. It is a simple and potent signaling molecule with diverse physiological actions, including proliferative and/or morphological effects, and has been proposed to be involved in neurogenesis, myelination, angiogenesis, wound healing, and cancer progression.$^2$ Other examples include $N$-acetylneuraminic acid,$^3$ D-glucono-1,5-lactone 6-$O$-phosphate,$^4$ lipoic acid,$^5$ heparin,$^6$ and 2'-deoxythymidine 6'-$O$-phosphate$^7$ (Figure 2.1.1).
In an effort to explore the role of biological substrates in nature, including complex catalytic cycles, extensive research has been conducted in the synthesis of isosteric replacements for the O-phosphate, O-sulfate, and carboxylate groups. For example, tetrazoles, amides, and phosphonates have been developed as isosteres for the carboxylates.\(^8\) Phosphorothioates and phosphonates have been used as replacements for O-phosphates, and sulfonates and thiosulfonates as substitutes for O-sulfates\(^9,\)\(^10\) (Figure 2.1.2).
Figure 2.1.2. Anionic bioisosteres of O-phosphate, O-sulfate, and carboxylate groups

2.1.2 Organoselenium bioisosteres

Organoselenium compounds\textsuperscript{11} have been found or induced in Nature\textsuperscript{12} and have been studied in the laboratory in all four oxidation states: selenol, selenenic, seleninic, and selenonic\textsuperscript{13} (Figure 2.1.1). They are important as reagents and intermediates in organic synthesis,\textsuperscript{14} as heavy-atom versions of oligonucleotides\textsuperscript{15} and proteins\textsuperscript{16} for crystallographic study, as human metabolites,\textsuperscript{17} as cancer-preventative agents\textsuperscript{18} and other medicinals,\textsuperscript{19} and as potential substrates for biomimetic studies.\textsuperscript{20}
Seleninic and selenonic acids and their salts may be viewed as isosteres\(^{21}\) of the biologically ubiquitous anionic O-phosphate,\(^{22}\) O-sulfate,\(^{23}\) and carboxylate\(^{24,25}\) groups (Table 2.1.2), and can be predicted to resist the action of most enzymes that operate in the biosynthesis or subsequent processing of those bio-anions. While sometimes considered too unstable\(^{26}\) or too toxic\(^{27}\) 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. A mild and efficient method for the preparation of aliphatic seleninates and selenonates is, therefore, very desirable.
2.2 Aliphatic seleninic and selenonic acids

2.2.1 Synthesis of aliphatic seleninic and selenonic acids

Efforts to introduce the selenium atom into organic structures were undertaken by my colleague Dr. Etzer Darout. By exploiting the superior nucleophilicity of seleno-nucleophiles relative to their corresponding thio reagents, he has demonstrated the introduction of selenocarboxylates into various substrates including carbohydrates, nucleosides, and amino acids.

Selenocarboxylates are generated in situ using Woollins’s reagent. Woollins’s reagent is a selenium analogue of Lawesson’s reagent (Figure 2.2.1) and its preparation entails treating pentaphenylpentacyclophosphine with 10 equiv of selenium powder in refluxing toluene. The resulting solid is collected by filtration and stored in a desiccator at 23 °C.

Figure 2.2.1. Structures of Woollins’s and Lawesson’s reagents

A heterogeneous suspension of Woollins’ reagent in toluene converts a carboxylic acid to a solution of the corresponding selenocarboxylic acid, which may be used directly for a variety of substitution reactions (Scheme 2.2.1).
Scheme 2.2.1. Synthesis of selenocarboxylic acids

Pyranose-, nucleoside-, polyhydric-, and amino acid-based aliphatic seleninates and selenonates were prepared efficiently by the oxidation of their corresponding selenoester precursors. Selenoesters were readily prepared by displacement reaction of the corresponding primary halides or by Mitsunobu substitution with a selenocarboxylate anion generated in situ (Scheme 2.2.2).

Scheme 2.2.2. Synthesis of aliphatic seleninates and selenonates
2.2.2 Pyranose-based seleninic and selenonic acids

The gluco-pyranoside-based selenoester 2-2-2 was readily prepared by displacement reaction of the corresponding primary iodide 2-2-1 with 2-phenylselenocarboxylate anion generated \textit{in situ} from phenylacetic acid and Woollins’s reagent. Clean oxidation of 2-2-2 to the seleninic acid 2-2-3 occurred in the presence of stoichiometric amounts of dimethyldioxirane (DMDO);\textsuperscript{31} the product 2-2-3 crystallized from solution and was characterized by mass spectrometry, \textsuperscript{1}H, \textsuperscript{13}C, and \textsuperscript{77}Se NMR spectroscopy, and X-ray crystallography (Figure 2.2.2). The acetates were cleaved quantitatively with methoxide to afford triol 2-2-4 without affecting the seleninate functionality (Scheme 2.2.3).

\textbf{Scheme 2.2.3.} Synthesis of gluco-pyranoside based seleninate
Oxidation of seleninic acid 2-2-3 with excess DMDO led to the selenonate, which was conveniently isolated by chromatography as its triethylammonium salt 2-2-5. Alternatively, selenonate 2-2-5 was prepared directly from selenoester 2-2-2 by DMDO oxidation in 81% yield; deacetylation with methoxide gave selenonate triol sodium salt 2-2-6 quantitatively (Scheme 2.2.4). Fewer than a dozen aliphatic selenonic acids have been previously reported and very little is known about their chemistry.
Scheme 2.2.4. Oxidation of seleninate to selenonate

By using analogous oxidations, other pyranose-based selenoesters were converted to seleninates and selenonates (Scheme 2.2.5). The manno-pyranoside selenoester 2-2-8 and gluco-pyranose selenoester 2-2-14 systems gave respective seleninates 2-2-10 and 2-2-16 and selenonates 2-2-12 and 2-2-18 that superficially resemble the corresponding 6-O-phosphates.33
Furthermore, mimics of naturally occurring GlcNAc derivatives were prepared.\textsuperscript{34} The $\alpha$-GlcNAc chloride 2-2-19 gave its corresponding selenoester 2-2-20.

\textbf{Scheme 2.2.5.} Additional pyranose-based seleninates and selenonates
Oxidation and deacetylation of the selenoester 2-2-20 gave its respective seleninate 2-2-22 and selenonate 2-2-24 (scheme 2.2.6).

![Scheme 2.2.6. Synthesis of α-GlcNAc seleninates and selenonates](image)

On the other hand, the β-GlcNAc iodide 2-2-27, prepared from its respective alcohol 2-2-26, gave the β-GlcNAc selenoester 2-2-28. Oxidation of selenoester 2-2-28 led cleanly after deprotection to the seleninate 2-2-30. Further oxidation led to the selenonate 2-2-31 however; its corresponding deacetylated product 2-2-32 was not isolated as it proved to be unstable (scheme 2.2.7).
Scheme 2.2.7. Synthesis of β-GlcNAc seleninates and selenonates

2.2.3 Nucleoside-based seleninic and selenonic acids

Uridine 2-2-35 and 2’-deoxyuridine 2-2-36 selenoester systems were prepared from their corresponding iodides 2-2-33 and 2-2-34 respectively. The oxidation of selenoesters 2-2-35 and 2-2-36 gave initially upon oxidation the cyclic seleninic esters 2-2-37 and 2-2-38, but these rings were readily opened during subsequent deacetylation. Nucleoside seleninates 2-2-39 and 2-2-40 and selenonates 2-2-41 and 2-2-42 may be thought of as truncated 5’-O-phosphate analogues.35
Scheme 2.2.8. Synthesis of nucleoside seleninates and selenonates

2.2.4 Polyhydric-based seleninic and selenonic acids

The mono- and di-O-acylated butanediol and propanediol seleninates (2-2-46, 2-2-51, and 2-2-52) and selenonates (2-2-47, 2-2-53, and 2-2-54) were prepared from their respective 4-iodobutane-1,2-diol-1,2-acetonide 2-2-43 and glycidyl butyrate 2-2-48. These biomimetic seleninates and selenonates resemble lysophospholipids, although they are monobasic\(^1\) (Scheme 2.2.9).
2.2.5 Amino acid-based seleninic and selenonic acids

The selenoglutamate 2-2-58 was prepared from a protected homoserine by a displacement of iodide followed by DMDO oxidation; cyclized seleninamide 2-2-57 was isolated as the intermediate (Scheme 2.210).

Scheme 2.2.9. Synthesis of polyhydric seleninates and selenonates

Scheme 2.2.10. Synthesis of selenoglutamate mimics
In contrast to the homoserine substrate, serine derived selenoester 2-2-60 gave a seleninic acid that was not isolable (2-2-61), but instead eliminated \( \text{H}_2\text{SeO}_2 \) within minutes by retro-ene reaction to give the dehydroalanine derivative 2-2-62.\(^{36}\) Following treatment of the presumed seleninic acid intermediate with \( p \)-toluenesulfonylhydrazide,\(^{37}\) however, the trapped stable redox product selenosulfonate 2-2-63 was isolated in good yield. The alaninol derived system 2-2-66, by comparison, oxidized smoothly to seleninate 2-2-67 without elimination, and further oxidation to the selenonate 2-2-68 was also uneventful (Scheme 2-2-11).

**Scheme 2.2.11.** Synthesis of additional amino acid-based seleninates and selenonates
2.2.6 Seleninate and selenonate linking reactions of active site functionality

Seleninic acids can couple with thiols over a wide pH range to give a redox product, the mixed selenosulfide (RSeSR'). With gluco-pyranoside-based seleninate 2-2-3, 1.0 equiv of N-Boc-cysteine methyl ester reacted in dichloromethane solution within 1 min at 23 °C to give the coupled product 2-2-69 in good yield (Scheme 2.2.12). A number of enzyme active sites contain a cysteine sulfhydryl, so given the appropriate seleninate-containing substrate mimic, this reaction is a potential avenue for irreversible inhibition by covalent attachment. A partial list of enzymes with active site cysteine includes thymidylate synthase, monoamine oxidase, ribonucleotide reductase, protein tyrosine phosphatase, and the cysteine proteases.

Scheme 2.2.11. Redox coupling of N-Boc-cysteine methyl ester with seleninate 2-2-3

Other electron-rich protein side-chain residues couple with the seleninic electrophile. N-benzoyltyrosine ethyl ester (1.0 equiv, 24 h, CH$_2$Cl$_2$, 37 °C)
reacted slowly with 2-2-3 to afford the ortho selenylated product 2-2-70. Likewise, \(N\)-acetyltryptophan ethyl ester gave the 2-selenylated indole derivative 2-2-71, and \(N\)-Boc-histidine benzyl ester was selenylated on the imidazole ring (2-2-72). These three solution reactions are significantly slower than the sulfhydryl coupling, but might occur with appropriately positioned residues in an enzyme active site (Figure 2.2.3).

![Figure 2.2.3. Coupling of seleninate 2-2-3 with protein side chain functionality](image)

Selenonates, on the other hand, are susceptible to \(S_N2\) cleavage at the C–Se bond. An attempt to convert selenonate 2-2-5 into its ethyl ester led unexpectedly to the \(1^\circ\) iodide 2-2-1, evidently by way of displacement of EtOSeO\(_2^-\) from 2-2-73. Reaction of selenonate 2-2-5 with ethyl triflate in DMF solution gave products (2-2-75 and 2-2-76) that may have arisen by hydrolysis of iminium intermediate 2-2-74, wherein the amide carbonyl has displaced EtOSeO\(_2^-\) (Scheme 2.2.12).
Scheme 2.2.12. Novel C–Se bond cleavage reaction of selenonate 2-2-5

When selenonate 2-2-5 was allowed to stir with trifluoroacetic acid in dichloromethane solution, products 2-2-75 and 2-2-78 were obtained, evidently by formation of oxonium intermediate 2-2-77. Intermediate 2-2-77 may have arisen by participation of the gluco-pyranoside C₄ acetyl group to displace SeO₂ (Scheme 2.2.13). The susceptibility of selenonates to Sₙ² cleavage at the C–Se bond has not been explored previously,₄₄ but represents another mode of potential covalent attachment to an active site nucleophile.

Scheme 2.2.13. Reaction of selenonate 2-2-5 with trifluoroacetic acid and water
2.3 Case study: tyrosine and naphthalene seleninates as inhibitors of protein tyrosine phosphatases (PTPs)\textsuperscript{45}

2.3.1 PTPs

Protein tyrosine phosphorylation is a major post-translational mechanism for cellular signaling in response to growth factors, hormones, and cytokines. The extent and duration of tyrosine phosphorylation are tightly regulated by the activities of protein tyrosine kinases and protein tyrosine phosphatases (PTPs). Similar to the kinases, the PTPs constitute a large family of enzymes\textsuperscript{46} and they catalyze the removal of phosphate groups from phosphorylated tyrosine residues on proteins (Figure 2.3.1). Malfunction in PTP activity has been associated with human diseases, including cancer, diabetes and obesity, and autoimmune disorders. Among various promising approaches, the development of small molecule modulators of PTP activity could aid in the study of PTP function in complex signaling cascades.\textsuperscript{47}

![Figure 2.3.1. Hydrolysis of phosphates from tyrosine residues](image-url)
2.3.2 Catalytic mechanism of PTPs

The PTP family shares a conserved active site that recognizes phosphotyrosine (pTyr) and uses a common catalytic mechanism that features a highly nucleophilic cysteine residue.\textsuperscript{47} Catalysis proceeds through a two-step mechanism that involves the production of a cysteinyl-phosphate intermediate (Figure 2.3.2). The first step entails the nucleophilic attack on the phosphate by the sulfur atom of the thiolate ion of the essential cysteine residue. This is coupled with protonation of the tyrosine leaving group of the substrate by a conserved aspartic acid residue. The second step involves the hydrolysis of the phospho-enzyme intermediate with a water molecule mediated by a glutamine and an aspartic acid residue.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{p131}
\caption{General catalytic mechanism of PTPs}
\end{figure}
2.3.3 Synthesis of tyrosine-based seleninic acid

Considering the potential bioisosteric match of seleninates for the ubiquitous O-phosphate, and their unique coupling with thiols, homologated tyrosine seleninates could be an ideal target for possible PTP inhibitors (Figure 2.3.3).

![Figure 2.3.3. Possible PTP seleninate inhibitors](image)

Seleninic acid 2-3-3 was prepared from the homotyrosine derivative 48 2-3-1 by selenocarboxylate Mitsunobu conversion 30 (78% yield) to the selenoester 2-3-2 and then reaction of 2-3-2 with DMDO in wet acetone solution at 23 °C. Seleninate 2-3-3 was formed (88%) without any overoxidation to the selenonate. The product was purified by silica chromatography and was stable for days stored neat at 23 °C, or in methanol or DMSO solution. The reaction in wet dichloromethane of 2-3-3 (1 equiv) with the sulfhydryl of a model Cys derivative gave the selenosulfide 2-3-4 in 82% yield, thus demonstrating the feasibility of coupling 2-3-3 with the PTP active site Cys residue (Scheme 2.3.1).
Scheme 2.3.1. Synthesis of homotyrosine seleninate and its redox coupling with

\( \text{N-Boc-cysteine methyl ester} \)

2.3.4 Inhibition studies of tyrosine-based seleninic acid

Recent biological analysis, carried out in the laboratory of Prof. Zhong-Yin Zhang at the Indiana University School of Medicine, showed that incubation of 2-3-3 with the Yersinia PTP, YopH, resulted in a time- and concentration-dependent loss of phosphatase activity (Figure 2.3.4 A). Similar results were obtained with the mammalian enzyme PTP1B as well as the dual specificity phosphatases VHR and VHX. Inactivation of the PTPs by 2-3-3 appeared to be irreversible, as extensive dialysis and/or buffer exchange of the reaction mixture failed to restore enzyme activity. Analysis of the pseudo-first-order rate constant as a function of inhibitor concentration showed that 2-3-3 mediated YopH inactivation displayed saturation kinetics (Figure 2.3.4 B), yielding values for the binding constant \( K_i \) and the inactivation rate constant \( k_i \) of 44.5 \( \pm \) 8.8 \( \mu \)M and 0.243 \( \pm \) 0.009 min\(^{-1}\), respectively.
Figure 2.3.4. Kinetic analysis of YopH inactivation by 2-3-3 at 25 °C and pH 6. (A) Time and concentration dependence of inhibitor 2-3-3 mediated YopH inactivation. (B) Concentration dependence of the pseudo-first-order rate constants $K_{obs}$ for 2-3-3 mediated YopH inactivation.

These results suggest that 2-2-3 is an active site-directed affinity agent whose mode of action involves at least two steps: binding to the PTP active site, followed by covalent modification of active site residue(s). In further support of this idea, the active site-directed competitive YopH inhibitors arsenate and $p$-nitrocatechol sulfate were each able to partially protect YopH from 2-3-3 mediated inactivation.45

To directly demonstrate that inhibitor 2-3-3 inactivates the PTPs by covalent modification, YopH treated with or without 2-3-3 was analyzed using mass spectrometry (Figure 2.3.5). The mass of unmodified YopH PTP domain (residues 163-468) measured by an electrospray ion trap mass spectrometer was 33 512 Da, which is in close agreement with the theoretical value (33 513
Da). YopH treated with 2-3-3 showed an altered mass of 33 884 Da. This corresponds to a mass difference of 372 Da, consistent with the formation of a mixed selenosulfide covalent adduct between YopH and 2-3-3 (the theoretical mass shift is 371 Da). Although a selenosulfide bond is normally readily cleaved by DTT in buffer solution, the selenosulfide linkage in the modified YopH is comparatively stable, inasmuch as mM concentrations of DTT failed to reactivate the inhibitor 2-3-3 treated enzyme. Thus, the (PTP)S-\text{SeR}' bond is probably protected from DTT by being buried in the active site. Finally, 2-3-3 failed to modify the catalytically inactive mutant YopH/C403S, consistent with formation of the covalent adduct between YopH and 2-3-3 at the active site Cys403 explicitly.

![Mass spectrometry analysis of YopH inactivation by 2-3-3.](image)

**Figure 2.3.5.** Mass spectrometry analysis of YopH inactivation by 2-3-3. Deconvoluted ESI mass spectra of YopH treated with (bottom) or without (top) seleninate 2-3-3.
To further define the details of PTP inactivation by 2-3-3, a 2.3 Å crystal structure of PTP1B · 2-3-3 complex was obtained. The final model for the PTP1B · 2-3-3 complex includes PTP1B residues 2-283 and all non-H atoms in 2-2-3. The overall structure of PTP1B · 2-3-3 is similar to the previously determined ligand-free PTP1B structure. The major difference between these two structures is the electron density in the PTP active site corresponding to 2-3-3, which is covalently attached to PTP1B via a selenosulfide bond between Cys215 Sγ and the selenium atom in 2-3-3 (Figure 2.3.6). The bond length for the S-Se linkage is 2.2 Å, in good agreement with the theoretical value (2.1 Å). The structural data provide direct evidence that inhibitor 2-3-3 specifically inactivates the PTPs by forming a mixed selenosulfide with the active site Cys residue.

Figure 2.3.6. Crystal structure of PTP1B · 2-3-3
In addition to revealing the nature of covalent linkage between PTP1B and 2-2-3, the structure also identifies additional non-covalent interactions between the active site of PTP1B and 2-3-3. As shown in the crystal structure, inhibitor 2-3-3 is inserted into the active site pocket that is capped by the P-loop (β8-R5, residues 215-221). At the center of the P-loop lies the catalytic Cys215 which forms a covalent bond with the selenium atom in 2-3-3. The highly flexible WPD loop adopts an open conformation in the PTP1B·2-3-3 structure. The selenium atom makes two polar interactions with the main-chain nitrogens of Gly220 and Arg221. It is also within van der Waals contacts with main-chain carbon atoms of Ile219, Gly220, and Arg221 as well as the side chain of Arg221 (Figure 2.3.7). An H-bond exists between the carbonyl oxygen in the methyl ester and the side chain of Gln262. The phenyl ring of 2-3-3 is engaged in extensive hydrophobic interactions with the residues lining the active site cavity, including Tyr46, Ser216, Ala217, and Arg221. Hydrophobic interactions are also observed between the benzylic methylene next to the selenium and the side chain of Arg221, while the carbonyl carbon and the methyl group in the methyl ester interacts with the side chains of Tyr46 and Val49, respectively. Finally, the tert-butyl group in 2-3-3 also makes contacts with Tyr46. These non-covalent interactions likely contribute to the efficient PTP inactivation by 2-3-3.
2.3.5 Development of probes for profiling PTP activity and selectivity

Although PTPs share a common catalytic mechanism, they have distinct and often unique biological functions in vivo. In order to establish these functional roles, extensive research has been conducted in the development of selective and specific chemical probes. This process involves identifying a suitable PTP inhibitor, and later, tethering it to an easily visualized probe.

Recent work in the development of PTP inhibitors has revealed that the binding of substrates/inhibitors involve two components. The first component, which is highly conserved within the entire PTP family, entails the recognition of the “phenyl phosphate” moiety within the catalytic pocket. The second, which is arguably different among various PTPs, involves the interactions of the non “phenyl phosphate” residues within, and surrounding, the catalytic pocket.
Recent chemical probes based on the modification of the “phenyl phosphate” moiety have been prepared. The synthesis of α-bromobenzyl phosphonate have been reported by Zhang et al.\textsuperscript{53} This specific irreversible inhibitor, prepared from its corresponding 4-cyanobenzyl bromide, was afterwards conjugated with rhodamine and biotin tags for visualization and purification.\textsuperscript{52,53} Although the probe was not selective, it was very specific and arguably useful to the global monitoring of the entire PTP family’s activity.

In an effort to identify potent selective PTP inhibitors, many variations surrounding the “phenyl phosphate” core have been synthesized. By utilizing peptide leads from peptidyl phosphotyrosyl containing substrates\textsuperscript{56-59} Zhang et al. developed the constrained naphthoyl carboxylates and naphthoyl phosphonates with the aid of some screening or computer pharmacore-based methods.\textsuperscript{55} Szczepankiewicz, developed a link fragment strategy where a benzoic acid core\textsuperscript{60} was linked to various different ligands.\textsuperscript{61} Others, have prepared indole-,\textsuperscript{60} coumarin-,\textsuperscript{62} and bicyclic and tricyclic thiophene\textsuperscript{63} inhibitors (Figure 2.3.8).

\textbf{Figure 2.3.8.} Examples of rigid polycyclic PTP inhibitors
In an attempt to generate new scaffolds of selective inhibitors 2,6-disubstituted seleninate naphthalenes have been prepared. These seleninate naphthalenes can easily be tethered to various visualization tags if they prove to be good candidates (Scheme 2.3.2).

Scheme 2.3.2. Naphthoyl seleninates as PTP inhibitors and probes

2.3.6 Synthesis of naphthalene-based seleninic acids

2,6-Disubstituted naphthalenes have been prepared from their corresponding commercial amino naphthoic acid 2-3-5. Through diazotization followed by potassium selenocyanate, 2-3-5 was converted into its respective selenocyanate derivative 2-3-6. Esterification of 2-3-6 to 2-3-7, followed by stoichiometric DMDO oxidation led to the first naphthalene seleninate 2-3-8 derivative (Scheme 2.3.3).
Scheme 2.3.3. Synthesis of naphthalene seleninate 2-3-8

By comparable transformations other naphthalene seleninates have been prepared. Coupling of selenocyanates 2-3-5 with L-phenylalanine ethyl ester hydrochloride and L-alanine ethyl ester hydrochloride led to their corresponding selenocyanates 2-3-9 and 2-3-10. Oxidation of selenocyanates 2-3-9 and 2-3-10 led to the seleninates 2-3-11 and 2-3-12 (Scheme 2.3.4).

Scheme 2.3.4. Synthesis of additional naphthalene seleninates
2.3.7 Inhibition studies of naphthalene-based seleninic acids

Recent biological analysis, carried out in the laboratory of Prof. Zhong-Yin Zhang at the Indiana University School of Medicine, showed the potent inhibition of naphthalene seleninates $2\text{-}3\text{-}8$, $2\text{-}3\text{-}11$, and $2\text{-}3\text{-}12$ towards the mammalian enzyme PTP1B, bacterial enzyme YopH, and the dual specificity phosphatase VHR (Table 2.3.1). While these seleninates provide excellent catalytic efficiency comparable to that of the tyrosine seleninate $2\text{-}3\text{-}3$, no clear selectivity trend has been observed.\textsuperscript{66}

**Table 2.3.1.** Kinetic constants for seleninic-acid mediated PTP inactivation, at pH 7 and 25 °C\textsuperscript{a}

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Compound</th>
<th>$K_i$, mM</th>
<th>$k_i$, min\textsuperscript{-1}</th>
<th>$k_i/K_i$, M\textsuperscript{-1} min\textsuperscript{-1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTP1B</td>
<td>$2\text{-}3\text{-}11$</td>
<td>9±4</td>
<td>21±8</td>
<td>2.3 x 10\textsuperscript{3}</td>
</tr>
<tr>
<td></td>
<td>$2\text{-}3\text{-}12$</td>
<td>3.8±1.6</td>
<td>10±3</td>
<td>2.6 x 10\textsuperscript{3}</td>
</tr>
<tr>
<td></td>
<td>$2\text{-}3\text{-}8$</td>
<td>16.5±3.2</td>
<td>29±4</td>
<td>4.46 x 10\textsuperscript{3}</td>
</tr>
<tr>
<td></td>
<td>$2\text{-}3\text{-}3$</td>
<td>0.43±0.10</td>
<td>0.36±0.04</td>
<td>0.8 x 10\textsuperscript{3}</td>
</tr>
<tr>
<td>YopH</td>
<td>$2\text{-}3\text{-}11$</td>
<td>0.003±0.002</td>
<td>0.99±0.13</td>
<td>3.3 x 10\textsuperscript{5}</td>
</tr>
<tr>
<td></td>
<td>$2\text{-}3\text{-}12$</td>
<td>0.007±0.005</td>
<td>0.97±0.18</td>
<td>1.4 x 10\textsuperscript{5}</td>
</tr>
<tr>
<td></td>
<td>$2\text{-}3\text{-}8$</td>
<td>0.088±0.080</td>
<td>1.30±0.3</td>
<td>1.5 x 10\textsuperscript{4}</td>
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<tr>
<td></td>
<td>$2\text{-}3\text{-}3$</td>
<td>0.0445±0.0088</td>
<td>0.243±0.009</td>
<td>5.4 x 10\textsuperscript{3}</td>
</tr>
<tr>
<td>VHR</td>
<td>$2\text{-}3\text{-}11$</td>
<td>0.25±0.09</td>
<td>50.2±12.8</td>
<td>2.0 x 10\textsuperscript{5}</td>
</tr>
<tr>
<td></td>
<td>$2\text{-}3\text{-}12$</td>
<td>0.14±0.02</td>
<td>24.1±1.2</td>
<td>1.7 x 10\textsuperscript{5}</td>
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<td></td>
<td>$2\text{-}3\text{-}8$</td>
<td>0.2±0.05</td>
<td>18.5±1.1</td>
<td>9.2 x 10\textsuperscript{4}</td>
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<tr>
<td></td>
<td>$2\text{-}3\text{-}3$</td>
<td>0.22±0.10</td>
<td>1.3±0.2</td>
<td>5.9 x 10\textsuperscript{3}</td>
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</tbody>
</table>

\textsuperscript{a} Key: $K_i$ – binding constant; $k_i$ – inactivation rate constant; $k_i/K_i$ – measure of catalytic efficiency

In an effort to further understand the contribution of the amino ester portion of the naphthalene seleninates towards the binding of PTPs, seleninato-
naphthoyl D-phenylalanine derivative 2-3-14 was prepared from its respective selenocyanate 2-3-13 (Scheme 2.3.5).

Scheme 2.3.5. Synthesis of seleninato-naphthoyl D-phenylalanine derivative

Biological evaluation of 2-3-14 as an inhibitor of PTPs is currently under investigation.
2.4 References


66. This assay (unpublished) was recently completed in the laboratory of Prof. Zhong-Yin Zhang at the Indiana University School of Medicine.
Electrophilic Aromatic Selenylation

3.1 Aromatic organoselenium compounds

3.1.1 Synthesis of aromatic organoselenium compounds

Selenocarboxylates (Section 2.2.1) are an excellent source for the introduction of a selenium atom into various aliphatic organic structures. These highly nucleophilic reagents, however, are not very useful when setting up a selenium atom in an electron rich aromatic compound. A highly electrophilic selenium reagent would be a better choice for the preparation of aromatic organoselenium compounds.¹

To prepare a new series of aromatic organoselenium compounds by a mild and efficient method the electrophilic propensity of seleninic acids was exploited. Seleninic acids can add to electron rich aromatic and heteroaromatic rings to form the aryl selenoether (Section 2.2.6). Aryl selenoethers can be then oxidized to the corresponding selenoxide or selenone.² Thermal syn elimination of selenoxides gives their respective selenenic acid,³ which in turn can react in situ with other nucleophiles.⁴ Selenones, on the other hand, can be Se-dealkylated leading to the corresponding aromatic seleninates⁵ (Scheme 3.1.1).
3.1.2 Synthesis of ethoxyethaneseleninic acid

Seleninic acids, such as seleninate \( \text{2-2-61} \), are thermally susceptible to eliminate \( \text{H}_2\text{SeO}_2 \) by retro-ene reaction to provide the alkene product (Section 2.2.5). In order to successfully selenylate various aromatic natural substrates, a thermally stable seleninic acid is very desirable. The stability of some seleninates can be attributed to the slow rate of selenoxy retro-ene elimination expected for systems with a \( \text{beta} \)-oxygen substituent. Sharpless, Nicolaou, Reich and others have been able to demonstrate that the elimination reaction is regioselective, occurring away from the carbon atom bearing the oxygen atom.\(^3\,^6\)
Ethoxyethaneseleninic acid 3-1-3 provides a very simple system with a beta-oxygen. The synthesis of 3-1-3 was achieved by the stoichiometric DMDO oxidation of selenoester 3-1-2, itself prepared by displacement reaction of the corresponding bromide 3-1-1 with 2-phenyl-selenocarboxylate anion (Scheme 3.1.2).\(^7\)

![Scheme 3.1.2. Synthesis of ethoxyethaneseleninic acid](image)

The synthesis of ethoxyethaneseleninic acid 3-1-3 was modified for gram scale as follows: treatment of 2-bromoethyl ethyl ether 3-1-1 with an aqueous solution of disodium diselenide in ethanol solution for 30 min at 23 °C and then extractive workup gave the ethoxyethane diselenide 3-1-4.\(^8\) Standard DMDO oxidation of diselenide\(^9\) 3-1-4, purified using a bulb to bulb Kugelrohr distillation, then led to the corresponding seleninic acid 3-1-3 in 96% yield. Alternatively, seleninic acid 3-1-3 was obtained by the direct DMDO oxidation of the crude diselenide 3-1-4; however, the yield was lower (Scheme 3.1.3).
Scheme 3.1.3. Gram scale synthesis of ethoxyethaneseleninic acid

3.1.3 Electrophilic aromatic selenylation of nucleosides and nucleotides

Upon coupling uridine triacetate 3-1-5 with ethoxyethaneseleninic acid 3-1-3 in dichloromethane solution at 37 °C no selenylated product was observed. However, with acid activation of the electrophile and higher reaction temperature, 5'-ethoxyethaneseleno-uridine 3-1-6 was obtained. As this reaction could also be used to prepare other selenylated nucleosides and nucleotides, the selenylation was optimized as follows. Treatment of uridine triacetate 3-1-5 with 2 equiv of ethoxyethaneseleninic acid 3-1-3 and a catalytic amount of trifluoroacetic acid in acetonitrile solution for 16 h at 60 °C and then flash chromatography gave the 5'-ethoxyethaneseleno-uridine 3-1-6 (Scheme 3.1.4).

Scheme 3.1.4. Synthesis of selenylated uridine
By using comparable transformations, a variety of other aryl selenoethers were prepared (Table 3.1.1). The 2-deoxyuridine 3-1-7 and cytidine 3-1-9 systems gave their corresponding selenylated products 3-1-8 and 3-1-10. The cytosine 3-1-11 system gave its respective selenylated product 3-1-12. Guanosine tetraacetate 3-1-13, however, failed to selenylate despite numerous attempts.

Table 3.1.1. Additional electrophilic aromatic selenylations

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Substrate</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="3-1-7" /></td>
<td><img src="image2" alt="3-1-8 (56% from 3-1-7)" /></td>
<td><img src="image3" alt="3-1-11" /></td>
<td><img src="image4" alt="3-1-12 (54% from 3-1-11)" /></td>
</tr>
<tr>
<td><img src="image5" alt="3-1-9" /></td>
<td><img src="image6" alt="3-1-10 (46% from 3-1-9)" /></td>
<td><img src="image7" alt="3-1-13" /></td>
<td><img src="image7" alt="3-1-13" /></td>
</tr>
</tbody>
</table>

Would the electrophilic aromatic selenylation work in water? Treatment of uridine 3-1-14 with 3 equiv of ethoxyethaneseleninic acid 3-1-3 and a catalytic amount of heptafluorobutyric acid in water solution for 16 h at 100 °C and then flash chromatography gave the selenylated uridine 3-1-15 with a 10% higher yield than the acetonitrile reaction. 2-Deoxyuridine 3-1-16, cytidine 3-1-17, and
cytosine \textbf{3-1-12} selenylated systems were prepared by comparable transformations (Scheme 3.1.5).

**Scheme 3.1.5.** Aromatic selenylation in water solution

Selenylated compounds \textbf{3-1-15}, \textbf{3-1-16}, and \textbf{3-1-17} matched the ones obtained from the deacetylation of selenoethers \textbf{3-1-6}, \textbf{3-1-8}, and \textbf{3-1-10} (Scheme 3.1.6).

**Scheme 3.1.6.** Deacetylation of protected selenoethers
3.1.4 Electrophilic aromatic selenylation of amino acids

Comparable to the selenylation of amino acids with gluco-pyranoside seleninate 2-2-4 (Section 2.2.6), tyrosine and tryptophan coupled with 1 equiv of ethoxyethaneseleninic acid 3-1-3 in dichloromethane solution for 16 h at 37 °C to give the selenylated amino acids 3-1-18 and 3-1-19 (Figure 3.1.1). No acid catalyst was necessary. The selenylation of the less activated aromatic ring of phenylalanine was unsuccessful.

Figure 3.1.1. Selenylated tyrosine and tryptophan products

3.1.5 Oxidation and dealkylation of selenylated aromatic substrates

Stoichiometric DMDO oxidation of selenylated urdine 3-1-6 and 2-deoxyuridine 3-1-8 systems led to the corresponding, and stable, selenoxides 3-1-20 and 3-1-21 in quantitative yields. No over oxidation of the selenium was observed, and there were no side products by oxidation of the uracil ring. Deacetylation of selenoxides 3-1-20 and 3-1-21 gave their respective triols 3-1-22 and 3-1-23 respectively (Scheme 3.1.7).
Scheme 3.1.7. Preparation of nucleoside based selenoxides

Oxidation of selenoxides 3-1-20 and 3-1-21 with excess DMDO gave the selenones 3-1-24 and 3-1-25, which were conveniently isolated by chromatography and were stable for storage over long periods of time. Dealkylation of selenones 3-1-24 and 3-1-25 with sodium azide led to the respective seleninic acids 3-1-26 and 3-1-27. Standard deacetylation then led to the deprotected aromatic seleninates 3-1-28 and 3-1-29. Deacetylation of 3-1-24 and 3-1-25 were unsuccessful as the dealkylation reaction occurred competitively (Scheme 3.1.8).
Scheme 3.1.8. Dealkylation of selenones

Tyrosine selenoxide 3-1-30 was similarly prepared by the stoichiometric oxidation of 3-1-18. The product 3-1-30 proved to be unstable to storage, but could be characterized immediately before its decomposition. The selenoxide product 3-1-32 on the other hand, obtained from the oxidation of the ethoxymethyl protected tyrosine 3-1-31, proved to be stable and was conveniently isolated, characterized, and further oxidized to the selenone 3-1-33. Treatment of selenone 3-1-33 with sodium azide then led to the corresponding seleninic acid 3-1-34 (Scheme 3.1.9).
Scheme 3.1.9. Oxidation and dealkylation of selenylated tyrosine

3.1.6. Selenoxide elimination and reaction with other nucleophiles

Most selenoxides are thermally unstable and easily undergo stereospecific syn elimination of selenenic acids to afford the alkenes. Upon exposing uridine selenoxide 3-1-20 to 60 °C for 16 h in acetonitrile solution selenoaldehyde 3-1-35 was obtained in quantitative yield. Reduction of selenoaldehyde 3-1-35 with sodium borohydride, followed by deacetylation, led to its corresponding selenoalcohol 3-1-36 (Scheme 3.1.10).
Scheme 3.1.10. Preparation of selenoalcohol 3-1-36

Thermal decomposition of selenoxide 3-1-20 followed by the reaction of its corresponding products accounts for the formation of the selenoaldehyde 3-1-35 (Scheme 3.1.11). Addition of ethyl vinyl ether 3-1-38 to the electrophilic selenenic acid 3-1-37 would likely give the hemiacetal selenide 3-1-39 which, after ethanol elimination, leads to the product 3-1-35. Apparent support for this mechanism is provided by Reich et al., who reported that 2,4,6-tri-t-butylbenzene methyl selenenate reacts with ethyl vinyl ether over a period of days to give the alkene adduct.\textsuperscript{4b}

Scheme 3.1.11. Mechanism for the formation of selenoaldehyde 3-1-36
The aforementioned mechanism is further supported by the successful trapping of the selenenic acid by \(N,N\)-dimethylaniline (Scheme 3.1.12). Exposure of selenoxide 3-1-20 to thermal decomposition conditions, but in the presence of excess \(N,N\)-dimethylaniline, led to the formation of selenoether 3-1-40. Deacetylation of selenoether adduct 3-1-40 gave triol 3-1-41.

![Scheme 3.1.12. Addition of \(N,N\)-dimethylaniline](image)

3.1.7 Diselenide formation and useful transformations

Selenenic acids, generated \textit{in situ} by \textit{syn} elimination, have been reported to react with simple dialkyl amines to form the selenenamide. \(N,N\)-dimethyl-, \(N,N\)-diethyl-, and \(N,N\)-diisopropyl- benzeneselenenamides have been prepared by Reich \textit{et al.} by reacting the corresponding secondary amine with phenyl selenenic acid generated \textit{in situ}.\textsuperscript{4a,6c} While the less hindered alkylamine-based
selenenamides rather easily hydrolyze, the more hindered derivatives such as the $N,N$-diisopropyl-based were substantially more resistant to hydrolysis.$^{4a,6c,10}$

Upon exposure of selenoxide $3\text{-}1\text{-}20$ to thermal decomposition conditions, but in the presence of excess diisopropylamine, the selenenamide was not isolated. Instead, the uridine-5-diselenide $3\text{-}1\text{-}42$ was collected. While the diselenide was not the anticipated product, it was very useful for the preparation of additional nucleoside-based organoselenium compounds. Treatment of diselenide $3\text{-}1\text{-}42$ with sulfuryl chloride followed by trimethylsilyl imidazole led to the corresponding seleno-imidazole adduct$^{11}$ $3\text{-}1\text{-}44$, which, after deacetylation, gave the triol $3\text{-}1\text{-}45$. Additionally, treatment of $3\text{-}1\text{-}42$ with bromine followed by triethylphosphite led to its respective selenophosphonate$^{12}$ $3\text{-}1\text{-}46$; however, its corresponding deprotected derivative was not successfully isolated (Scheme 3.1.13).

Scheme 3.1.13. Diselenide formation and some useful transformations
3.2 Case study: organoselenium nucleotides and nucleosides as inhibitors of orotate phosphoribosyltransferases (OPRTs)

3.2.1 OPRTs

Orotate phosphoribosyltransferase (OPRT) is an essential enzyme required for the de novo biosynthesis of pyrimidine nucleotides.\textsuperscript{13} It catalyzes the formation of a C–N bond between the ribose moiety of α-D-phosphoribosylpyrophosphate (PRPP) and orotic acid (OA) to give orotidine 5'-monophosphate (OMP), the precursor to all of the pyrimidine nucleotides (Figure 3.2.1).

![Figure 3.2.1. Biosynthesis of OMP catalyzed by OPRT](image)

Pyrimidine de novo biosynthesis has been linked to the pathologies of many disease states, including malaria and cancer. It is the only pathway for nucleotide production in \textit{Plasmodium falciparum},\textsuperscript{13b} one of the most prevalent human parasites causing approximately 70% of known malaria cases.\textsuperscript{13a,14}
Furthermore, it is an apparent feature of rapidly proliferating human cancer cells, which demand constant increasing quantities of nucleic acids.\textsuperscript{13a,15} Interruption of nucleotide synthesis, therefore, may offer a way to understand and combat these disease states.

Human OPRT (\textit{HsOPRT}) and \textit{Plasmodium falciparum} (\textit{PfOPRT}) are an appealing targets for disrupting pyrimidine biosynthesis, leading perhaps to the development of antimalarial,\textsuperscript{16} antineoplastic, and autoimmune disease drugs.\textsuperscript{17} One approach to the inhibition of OPRTs is through analogues that mimic their transition states or their substrates and products. Schramm, McClard, and others have developed and studied a variety of OPRT inhibitors including PRPP-\textsuperscript{-},\textsuperscript{18} nucleobase-\textsuperscript{-},\textsuperscript{19} and transition state-based mimics.\textsuperscript{13a,20} Organoselenium nucleotide and nucleoside mimics could provide an expanded array of options for biochemical and medicinal chemistry studies.

### 3.2.2 Inhibition studies of organoselenium nucleotides and nucleosides

Recent biological analysis, carried out in the laboratory of Prof. Vern L. Schramm at the Albert Einstein College of Medicine, showed the inhibition of several organoselenium nucleotides and nucleosides towards the parasite \textit{Plasmodium falciparum} enzyme (\textit{PfOPRT}) and the human enzyme (\textit{HsOPRT}). Table 3.3.1\textsuperscript{21} summarizes the binding constants obtained for the various organoselenium compounds tested.
Table 3.3.1. Binding constants for organoselenium inhibitors towards human and parasite OPRTs

<table>
<thead>
<tr>
<th>Compound</th>
<th>$K_I, \mu$M (PfOPRT)</th>
<th>$K_I, \mu$M (HsOPRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-1-12</td>
<td>2.15 ± 0.75</td>
<td>1.14 ± 0.48</td>
</tr>
<tr>
<td>3-1-15</td>
<td>1.30 ± 0.33</td>
<td>0.26 ± 0.03</td>
</tr>
<tr>
<td>3-1-17</td>
<td>1.44 ± 0.44</td>
<td>0.44 ± 0.10</td>
</tr>
<tr>
<td>3-1-23</td>
<td>6.10 ± 1.60</td>
<td>2.40 ± 0.39</td>
</tr>
<tr>
<td>3-1-29</td>
<td>10.82 ± 1.98</td>
<td>5.89 ± 1.31</td>
</tr>
<tr>
<td>3-1-36</td>
<td>1.54 ± 0.47</td>
<td>0.72 ± 0.21</td>
</tr>
<tr>
<td>3-1-41</td>
<td>0.75 ± 0.21</td>
<td>0.24 ± 0.10</td>
</tr>
<tr>
<td>3-1-43</td>
<td>0.16 ± 0.02</td>
<td>0.16 ± 0.03</td>
</tr>
<tr>
<td>3-1-45</td>
<td>0.92 ± 0.28</td>
<td>0.91 ± 0.27</td>
</tr>
<tr>
<td>2-2-39</td>
<td>40.45 ± 6.81</td>
<td>2.83 ± 0.78</td>
</tr>
</tbody>
</table>

Even though no exciting pM inhibition was observed, a few conclusions may be drawn from the binding constant values of the various organoselenium compounds. Modifying uridine at the 5 position (pyrimidine base) seems to produce more potent inhibitory effects than its modification at the 5' position (ribose) as apparent by the comparison of compound 2-2-39 to compounds 3-1-15, 3-1-23, 3-1-29, 3-1-36, 3-1-41, 3-1-43, and 3-1-45. Additionally, introducing the selenoalkyl group to the pyrimidine nucleobase only, versus the nucleotide, may generate inhibitors with very similar potency as evident from the comparison of cytosine selenoether 3-1-12 to the cytidine selenoether 3-1-17. Last but not least, human and parasite OPRTs seem to be more selective towards larger groups on the uridine 5 position, as diselenide 3-1-43 and selenoaniline 3-1-41 appear to be more potent than other modified uridines.
While the organoselenium nucleotides and nucleosides have been tested against OPRTs only, they could potentially inhibit other nucleoside processing enzymes. These may include thymidylate synthase,\textsuperscript{22} thymidine phosphorylase,\textsuperscript{23} and orotidine monophosphate decarboxylase.\textsuperscript{14b,24}
3.3 References


21. This assay (unpublished) was recently completed in the laboratory of Prof. Vern L. Schramm at the Albert Einstein College of Medicine.


Mechanistic Studies on Electrophilic Reaction of Seleninic Acids

4.1  Electrophilic reaction of seleninic acids

4.1.1  Proposed mechanism for electrophilic reaction of seleninic acids

The apparent disappearance of an oxygen atom in reactions of a seleninic acid with equimolar nucleophiles has been noted in the literature but has never been satisfactorily explained.\textsuperscript{1} While some oxygen containing products have been identified in the reactions of a seleninic acid with aromatic electrophiles,\textsuperscript{2} none to our knowledge have been isolated in its reaction with equimolar mercaptan.

Studies on isolated uridine-based selenoxide 3-1-21 and on the coupling of ethoxyethaneseleninic acid 3-1-3 with 4-methylbenzenethiol provide additional evidence for the formation of the selenoxide intermediate and the mechanism proposed in Scheme 4.1.1. It further provides the first example to our knowledge of oxygen containing products isolated from the reaction of a stoichiometric mercaptan with a seleninic acid.

![Scheme 4.1.1. Proposed mechanism for the reaction of seleninic acids with nucleophiles](image_url)
4.2 Reaction of seleninic acids with stoichiometric mercaptan

4.2.1 Background

The reduction of seleninic acids to diselenides by a variety of reagents including thiols have been reported as early as 1955.\textsuperscript{1a,3} According to Rheinboldt and Giesbrech\textsuperscript{3a} the stoichiometry of the thiol-seleninic acid reaction was as shown in equation 1.

\[
\text{Eq 1: } 2 \text{ArSeO}_2\text{H} + 6 \text{RSH} \rightarrow \text{ArSeSeAr} + 3 \text{RSSR} + 4 \text{H}_2\text{O}
\]

Later, Kice \textit{et al.} corrected the stoichiometry and established that the reaction proceeds according to equation 2 based on the confirmed isolation of a selenyl sulfide product from the reaction of benzene seleninic acid with 3 equiv of butanethiol.\textsuperscript{1}

\[
\text{Eq 2: } \text{ArSeO}_2\text{H} + 3 \text{RSH} \rightarrow \text{ArSeSAr} + \text{RSSR} + 2 \text{H}_2\text{O}
\]

Furthermore, Kice \textit{et al.} were able to isolate the first, and one of the few known, thioseleninates\textsuperscript{1} upon the reaction of benzene seleninic acid with equimolar amount of \textit{tert}-butylthiol at \(-23 \, ^\circ\text{C}\). The thioseleninate, however, underwent quite rapid decomposition to the non-oxygen-containing mixture of selenosulfide, diselenide, and disulfide (equation 3).\textsuperscript{1b} Upon standing in solution, the mixed selenosulfide did slowly disproportionate\textsuperscript{1a,4} into a mixture of the diselenide and
disulfide (equation 4). No oxygen-containing organic products were isolated and the possibility of \( O_2 \) generation through a proposed mechanism based on the decomposition of the thioseleninate was refuted.\(^{1b}\)

\[
\text{Eq 3:} \quad \text{PhSeO}_2\text{H} + 1 \text{t-BuSH} \rightarrow \text{PhSe(O)SBu-} + \text{PhSeSBu-} + \text{PhSeSePh} + \text{t-BuSSBu-} \\
\text{decomp.}
\]

\[
\text{Eq 4:} \quad 2 \text{PhSeSBu-} \rightarrow \text{PhSeSePh} + \text{t-BuSSBu-}
\]

### 4.2.2 Hydrogen peroxide detection

The numerous unsuccessful attempts to isolate any possible oxygen-containing organic products from the reaction of the glucopyranoside-based seleninic acid 2-2-3 with equimolar amount of \( N\text{-Boc-cysteine methyl ester} \) as well as the previous negation of oxygen evolution,\(^{1b}\) encouraged efforts to detect hydrogen peroxide. Hydrogen peroxide was deemed to be a possible product as its exposure to the mixed selenosulfide 2-2-69 in dichloromethane solution resulted in no reaction (Scheme 4.2.1). Scheme 4.2.2 presents a possible mechanism featuring the production of hydrogen peroxide.

\[
\text{Scheme 4.2.1. Attempted oxidation of 2-2-69 with hydrogen peroxide}
\]
Scheme 4.2.2. Possible mechanism including the formation of hydrogen peroxide

Arylboronic acids are converted to their corresponding phenols in aqueous hydrogen peroxide solution. Treatment of 4-ethoxybenzeneboronic acid 4-2-1 with 1.0 equiv of hydrogen peroxide (30% solution) in water at 23 °C for several hours led to its corresponding 4-ethoxyphenol 4-2-2 (Scheme 4.2.3).
To explore the possibility of hydrogen peroxide generation, the aforementioned arylboronic acid oxidation was utilized. The investigation entailed carrying out the thiol-seleninic acid reaction in dichloromethane solution, then completing a water partition followed by the treatment of the aqueous layer with 4-ethoxybenzeneboronic acid. Scheme 4.2.4 summarizes the results refuting the possibility of hydrogen peroxide production.

**Scheme 4.2.4.** Testing for hydrogen peroxide generation
4.2.3 Isolation of oxygen-containing products

Failure to discover the fate of the oxygen in the reaction of glucopyranoside-based seleninic acid 2-2-3 with a protected cysteine derivative prompted the study of this reaction on a simpler system. Treatment of ethoxyethaneseleninic acid 3-1-3 with 3 equiv of \( p \)-thiocresol gave selenosulfide 4-2-3 and disulfide 4-2-4 in good yields, in addition to a small amount of diselenide 3-1-4 (Scheme 4.2.5). While selenosulfide 4-2-3 was stable to chromatography and characterization, it did eventually disproportionate\(^1\) in solution to give the disulfide 4-2-4 and diselenide 3-1-4.

![Reaction of ethoxyethaneseleninic acid with 3 equiv of \( p \)-thiocresol](image)

**Scheme 4.2.5.** Reaction of ethoxyethaneseleninic acid with 3 equiv of \( p \)-thiocresol

Surprisingly, treatment of ethoxyethaneseleninic acid 3-1-3 with an equimolar amount of \( p \)-thiocresol did not yield the anticipated selenosulfide 4-2-3 as the major product. Instead, the oxygen-containing selenosulfonate 4-2-5 was isolated as the main component. The crude mixture did, however, contain a
smaller percentage of a second oxygen containing product, thiolsulfonate 4-2-6, as well as selenosulfide 4-2-3, disulfide 4-2-4, and diselenide 3-1-4 (Scheme 4.2.6). The oxygen atoms of selenosulfonate 4-2-5 and thiolsulfonate 4-2-6 did approximately account for one half the oxygens of ethoxyethaneseleninic acid 3-1-3, consistent with the possible formation of a selenoxide intermediate.

Scheme 4.2.6. Reaction of ethoxyethaneseleninic acid with 1 equiv of p-thiocresol

Selenosulfonate 4-2-5 was fully characterized using mass spectrometry, and $^1$H, $^{13}$C, and $^{77}$Se NMR spectroscopy. It is very easily distinguished from its corresponding selenosulfide 4-2-3, especially by $^{77}$Se NMR spectroscopy. There is a large difference in their chemical shift values: $\delta$ 857.2 ppm vs 437.4 ppm,
respectively. The identity of selenosulfonate 4-2-5 was further confirmed by exploiting the known reaction of seleninic acids with \( p \)-toluenesulfonyl hydrazides.\(^6\) Treatment of ethoxyethaneseleninic acid 3-1-3 with 1.1 equiv of \( p \)-toluenesulfonyl hydrazide in dichloromethane solution for 30 min at 23 °C did indeed provide quantitatively the selenosulfonate 4-2-5 (Scheme 4.2.7).

Scheme 4.2.7. Preparation of selenosulfonate 4-2-5 from seleninic acid 3-1-3 and \( p \)-toluenesulfonyl hydrazide

To eliminate the possibility of ethoxyethaneseleninic acid 3-1-3 being the actual oxidizing agent generating the oxygen-containing products, rather than the selenoxide, 3-1-3 was treated independently with either selenosulfide 4-2-3 or disulfide 4-2-4. After several hours of stirring in dichloromethane solution at 23 °C, neither reaction indicated the occurrence of any oxidized components. The crude mixture comprised of only the initial starting material (Scheme 4.2.8).
Scheme 4.2.8. Subjecting ethoxyethaneseleninic acid 3-1-3 to selenosulfide 4-2-3 and disulfide 4-2-4

To simulate the probable oxidation of selenosulfide 4-2-3 and disulfide 4-2-4 with the non-isolable selenoxide intermediate, DMDO solution was utilized. Treatment of selenosulfide 4-2-3 and disulfide 4-2-4 with 2 equiv of DMDO in dichloromethane solution for a few minutes at 23 °C did indeed give the corresponding selenosulfonate 4-2-5 and thiolsulfonate 4-2-6 (Scheme 4.2.9).

Scheme 4.2.9. DMDO oxidation of selenosulfide 4-2-3 and disulfide 4-2-4
4.3 Reaction of seleninic acids with aromatic compounds

4.3.1 Selenylation of uridine

While the discussion thus far clearly supports the formation of a selenoxide intermediate in the reaction of seleninic acids with electrophiles, selenoxide 3-1-20 was never isolated or observed in the reaction of uridine triacetate 3-1-5 with ethoxyethaneseleninic acid 3-1-3. Furthermore, even though selenoxide 3-1-20 is stable at room temperature (Section 3.1.5), its exposure to the selenylation reaction temperature conditions of 60 °C led to the formation of selenoaldehyde 3-1-35 (Section 3.1.6), which was not observed in the selenylation of uridine. Therefore, is the selenoxide truly an intermediate in the selenylation reaction (Scheme 4.3.1)?

Scheme 4.3.1. Proposed mechanism for the selenylation of uridine
4.3.2 Simulation of selenylation conditions

Treatment of selenoxide 3-1-20 with 1 equiv of ethoxyethaneseleninic acid 3-1-3 in acetonitrile solution for 16 h at 60 °C gave indeed the selenoether 3-1-6 as the major product. Upon concentration of the acetonitrile solution, however, a white precipitate was observed. Filtration, followed by $^{77}$Se NMR spectroscopy characterization in methanol-d$_4$, suggested that the precipitate is selenium dioxide 4-3-1. Comparison with authentic selenium dioxide purchased from Sigma-Aldrich confirmed that conclusion. The percent yield of the selenium dioxide produced matched that of the selenoether 3-1-6 (Scheme 4.3.2).

![Scheme 4.3.2](image.png)

**Scheme 4.3.2.** Subjecting selenoxide 3-1-20 to uridine triacetate 3-1-5 selenylation conditions

Oxidation of ethoxyethaneseleninic acid 3-1-3 to ethoxyethane selenonic acid 4-3-2 followed by an S$_N$2 cleavage at the C–Se bond with a water molecule accounts for the formation of selenium dioxide 4-3-1 (Scheme 4.3.3).
Scheme 4.3.3. Oxidation of ethoxyethaneseleninic acid 3-1-3 with selenoxide 3-1-20

The aforementioned mechanism is supported by the successful oxidation of ethoxyethaneseleninic acid 3-1-3 with DMDO solution. Exposure of ethoxyethaneseleninic acid 3-1-3 in dichloromethane solution to excess DMDO led to the instantaneous precipitation of selenium dioxide in excellent yield (Scheme 4.3.4).

Scheme 4.3.4. Oxidation of ethoxyethaneseleninic acid 3-1-3 with DMDO
Additional evidence for the selenylation mechanism was obtained upon careful examination and comparison of the minor products isolated from the direct selenylation of uridine triacetate 3-1-5 and the reaction of uridine selenoxide 3-1-20 with ethoxyethaneseleninic acid 3-1-3. In both reactions, ethoxyethane diselenide 3-1-4, uridine diselenide 3-1-42, and the mixed diselenide 4-3-3 have been observed. The formation of uridine diselenide 3-1-42 may be attributed to the redox coupling of selenenic acid 3-1-37 in the reaction mixture, subsequent to retro-ene elimination of selenoxide 3-1-20. Scrambling of diselenides 3-1-42 and 3-1-4 may explain the observation of the mixed diselenide 4-3-3 in the reaction mixtures.

4.3.3 Unsuccessful in situ reduction of selenoxide during selenylation

In an effort to optimize the selenylation reaction, an effective reducing agent of the selenoxide was identified. Treatment of selenoxide 3-1-20 with 1 equiv of dodecyl sulfide 4-3-4 and a catalytic amount of trifluoroacetic acid in dichloromethane solution for 2 h at 23 °C led quantitatively to their corresponding selenoether 3-1-6 and sulfoxide 4-3-5 (Scheme 4.3.5). No reaction occurred without trifluoroacetic acid.
Scheme 4.3.5. Reduction of selenoxide 3-1-20 with dodecyl sulfide 4-3-4

Would subjecting uridine triacetate 3-1-5 to the selenylation conditions, but in the presence of dodecyl sulfide improve the reaction yield? Upon the exposure of uridine triacetate 3-1-5 to 1 equiv of ethoxyethaneseleninic acid 3-1-3, 1 equiv of dodecyl sulfide 4-3-4, and a catalytic amount of trifluoroacetic acid in acetonitrile solution for 16 h at 60 °C no selenylated product was observed. Instead, ethoxyethane diselenide 3-1-4 and dodecyl sulfoxide 4-3-5 were observed. Unfortunately, dodecyl sulfide 4-3-4 reduced the ethoxyethaneseleninic acid 3-1-3 before the latter reacted with uridine triacetate 3-1-5.⁹
4.4 References


Experimental Section

General

All non-aqueous reactions were run under argon and in dry solvents. Silica Gel (E. Merck 230 – 400 mesh) was used for flash chromatography. Silica Gel 60 F\textsubscript{254} precoated plates were used for Thin Layer Chromatography. Melting points were obtained with an Electrothermal\textsuperscript{®} melting point apparatus and are uncorrected. Mass spectra were obtained with a Finnigan LCQ\textsubscript{DUO} LC/MS spectrometer. \textsuperscript{1}H, \textsuperscript{13}C, \textsuperscript{19}F, and \textsuperscript{77}Se Nuclear Magnetic Resonance (NMR) spectra were obtained on a Varian UNITY 400 and 500 MHz.
Experiments

Nuclear Overhauser Effect (NOE) Measurements of GlcNac-Thiazoline 1-1-1

1D NOE’s of GlcNac-thiazoline 1-1-1 were acquired on a solution of 18.9 mg in 0.75 mL of methanol-d$_4$ at 25 °C and 500 MHz.
**Compound 1-3-8.** A solution of 57.9 mg (0.168 mmol) of 1-3-6 in 2 mL of dry acetonitrile was treated sequentially with 32.6 µL (0.403 mmol) of pyridine, 17.8 µL (0.201 mmol) of triflic acid, and 300 µL (16.8 mmol) of deuterium oxide. The reaction mixture was allowed to stir for 8 h, and then was diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, and then concentrated to afford 53.1 mg (91%) of 1-3-8 as a light yellow oil (98% trideuteration by integration of the –CH3 signal in the 1H NMR spectrum): *Rf* 0.53 (2:3 ethyl acetate/dichloromethane); *¹H* NMR (500 MHz, CDCl₃) δ 6.24 (d, *J* = 7.0, 1 H), 5.57 (dd, *J* = 3.5, 2.0, 1 H), 4.96 (dt, *J* = 9.5, 1.5, 1 H), 4.46–4.48 (m, 1 H), 4.12 (d, *J* = 5.0, 2 H), 3.55 (dt, *J* = 9.0, 5.0, 1 H), 2.14, 2.09, 2.09 (s, 3 H each); *¹³C* NMR (125 MHz, CDCl₃) δ 170.84, 169.82, 169.55, 168.38, 89.03, 76.94, 70.98, 69.56, 68.68, 63.53, 21.20, 21.12, 20.98 (–CD₃ signal barely visible above noise); ESI-MS *m/z* 349 MH⁺.
Compound 1-3-9. A solution of 22.4 mg (0.064 mmol) of 1-3-8 in 1 mL of methanol was treated at 0 °C with a catalytic amount of 18.8% methanolic sodium methoxide solution. The reaction was allowed to warm to room temperature over a 1 h period, and then was concentrated and chromatographed with 1:19 methanol/dichloromethane as the eluant to afford 14.3 mg (100%) of 13-9 as a colorless oil with no apparent deuterium loss (1H NMR integration): \( R_f \) 0.37 (1:4 methanol/dichloromethane); \(^1\)H NMR (500 MHz, CD\(_3\)OD) \( \delta \) 6.36 (d, \( J = 6.5 \), 1 H), 4.31–4.33 (m, 1 H), 4.13 (app t, \( J = 4.0 \), 1 H), 3.73 (dd, \( J = 12.0 \), 2.5, 1 H), 3.61 (dd, \( J = 12.0 \), 6.0, 1 H), 3.57 (ddd, \( J = 9.0 \), 3.5, 0.5, 1 H), 3.33 (ddd, \( J = 9.0 \), 6.5, 2.5, 1 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 169.74, 89.54, 79.28, 75.08, 72.95, 70.13, 62.92 (–CD\(_3\) signal barely visible above noise); ESI-MS \( m/z \) 223 MH\(^+\).
Compound 1-3-9. A solution of 48.8 mg (0.223 mmol) of 1-1-1 in 1 mL of methanol-d$_1$ was swirled for 1 min and then concentrated. This procedure was repeated two times. The resultant 1-1-1 with exchanged hydroxyl groups was dissolved in 1 mL of dry acetonitrile, and treated sequentially with 43.3 µL (0.535 mmol) of pyridine, 23.7 µL (0.267 mmol) of triflic acid, and 400 µL (22.3 mmol) of deuterium oxide. The reaction mixture was allowed to stir for 8 h, and then was diluted with 1-butanol, washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, and then azeotropically concentrated with toluene to afford 45.2 mg (93%) of 1-3-9 as a colorless oil (95% of –CD$_3$ by $^1$H NMR integration).
**Compound 1-3-10.** A solution of 36 mg (0.104 mmol) of 1-3-8 in 1 mL of methanol was cooled to 0 °C and then was treated with 1 drop of trifluoroacetic acid and 1 drop of water. The reaction was allowed to warm to room temperature over a 2 h period, and then was concentrated to afford 37.8 mg (100%) of 1-3-10 as a colorless oil (86% –CD₃ by ¹H NMR integration): \( R_f \) 0.36 (1:19 methanol/dichloromethane); ¹H NMR (500 MHz, CDCl₃) δ 5.81 (d, \( J = 8.5, 1 \) H), 5.78 (app t, \( J = 5.5, 1 \) H), 5.14 (app t, \( J = 9.5, 1 \) H), 5.09 (app t, \( J = 9.5, 1 \) H), 4.48 (ddd, \( J = 8.5, 5.5, 2.5, 1 \) H), 4.31 (ddd, \( J = 9.5, 4.0, 2.5, 1 \) H), 4.26 (dd, \( J = 12.5, 4.0, 1 \) H), 4.12 (dd, \( J = 12.5, 2.5, 1 \) H), 2.10, 2.05, 2.05 (s, 3 H each); ¹³C NMR (125 MHz, CDCl₃) δ 171.99, 170.92, 170.21, 169.45, 79.10, 70.90, 69.25, 68.10, 61.98, 52.80, 20.96, 20.95, 20.82 (–CD₃ signal barely visible above noise); ESI-MS m/z 389 MNa⁺.
**Compound 1-3-11.** A solution of 49.9 mg (0.145 mmol) of 1-3-6 in 2 mL of dry acetonitrile was treated sequentially with 28.1 µL (0.347 mmol) of pyridine, 15.4 µL (0.174 mmol) of triflic acid, and 41.9 mg (0.314 mmol) of N-chlorosuccinamide. The reaction mixture was allowed to stir for 15 min and then was diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, concentrated, and then chromatographed with 1:9 ethyl acetate/dichloromethane as the eluant to afford 55.2 mg (45%) of **1-3-11** as a colorless oil: \( R_f \ 0.33 \) (1:9 ethyl acetate/dichloromethane); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 6.46 (s, 1 H), 6.36 (d, 1 H, \( J = 7.5 \) Hz), 5.57 (dd, 1 H, \( J = 3.0, 1.5 \) Hz), 4.96 (d, 1 H, \( J = 9.5 \) Hz), 4.68 (dd, 1 H, \( J = 7.0, 3.0 \) Hz), 4.19 (dd, 1 H, \( J = 12.5, 2.5 \) Hz), 4.12 (dd, 1 H, \( J = 12.5, 6.0 \) Hz), 3.57 (ddd, 1 H, \( J = 9.0, 6.0, 2.5 \) Hz), 2.16 (s, 3 H), 2.09 (s, 6 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 170.7, 170.2, 169.7, 169.5, 83.8, 76.1, 70.2, 69.5, 69.1, 66.7, 63.5, 21.1, 21.0, 20.9; ESI-MS \( m/z \) 436 M\( \text{Na}^+ \).
Compound 1-3-12. A solution of 77.3 mg (0.224 mmol) of 1-3-6 in 2 mL of dry acetonitrile was treated sequentially with 43.5 µL (0.538 mmol) of pyridine, 23.8 µL (0.269 mmol) of triflic acid, and 87.7 mg (0.493 mmol) of N-bromosuccinamide. The reaction mixture was allowed to stir for 15 min and then was diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, concentrated, and then chromatographed with 1:24 ethyl acetate/dichloromethane as the eluant to afford 55.2 mg (49%) of 1-3-12 as a colorless oil: \( R_f \) 0.40 (1:24 ethyl acetate/dichloromethane); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 6.40 (br s, 1 H), 6.37 (d, \( J = 7.0, 1 \) H), 5.56 (dd, \( J = 3.5, 1.5, 1 \) H), 4.95 (dt, 9.0, 1.5, 1 H), 4.72 (ddd, \( J = 7.0, 3.0, 0.5, 1 \) H), 4.21 (dd, \( J = 12.0, 2.5, 1 \) H), 4.11 (dd, \( J = 12.0, 6.0, 1 \) H), 3.60 (ddd, \( J = 9.0, 6.5, 2.5, 1 \) H), 2.17, 2.10, 2.09 (s, 3 H each); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 170.76, 170.65, 169.78, 169.47, 89.22, 76.14, 70.23, 69.58, 69.11, 63.54, 34.36, 21.15, 21.07, 20.95; ESI-MS \( m/z \) 524, 526, 528 (in ratio ~1:2:1) MNa\(^+\).
Compound 1-3-13. A solution of 50.0 mg (0.145 mmol) of 1-3-6 in 2 mL of dry acetonitrile was treated sequentially with 28.1 µL (0.347 mmol) of pyridine, 15.4 µL (0.174 mmol) of triflic acid, and 62.2 mg (0.466 mmol) of N-chlorosuccinamide. The reaction mixture was allowed to stir for 2 h and then was diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, concentrated, and then chromatographed with 1:9 ethyl acetate/dichloromethane as the eluant to afford 55.2 mg (69%) of 1-3-13 as a colorless oil: $R_f$ 0.44 (1:9 ethyl acetate/dichloromethane); $^1$H NMR (500 MHz, CDCl$_3$) δ 6.46 (d, 1 H, $J = 7.0$ Hz), 5.66 (dd, 1 H, $J = 3.0$, 1.5 Hz), 4.97 (dt, 1 H, $J = 8.5$, 1.5 Hz), 4.86 (ddd, 1 H, $J = 7.0$, 3.0, 1.0 Hz), 4.22 (dd, 1 H, $J = 12.0$, 3.0 Hz), 4.15 (dd, 1 H, $J = 12.0$, 6.0 Hz), 3.67 (ddd, 1 H, $J = 9.0$, 6.0, 2.5 Hz), 2.17 (s, 3 H), 2.09 (s, 6 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 170.7, 170.5, 169.7, 169.3, 90.7, 76.1, 69.7, 69.6, 68.9, 63.6, 21.1, 21.0, 20.9; ESI-MS m/z 470 MNa$^+$. 
**Compound 1-3-14.** A solution of 41.0 mg (0.119 mmol) of 1-3-6 in 1 mL of dry acetonitrile was sequentially treated with 23.1 µL (0.285 mmol) of pyridine, 12.6 µL (0.143 mmol) of triflic acid, and 56.1 mg (0.380 mmol) of N-bromosuccinamide. The reaction mixture was allowed to stir for 2 h, and then was diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, concentrated, and then chromatographed with 1:24 ethyl acetate/dichloromethane as the eluant to afford 56.1 mg (81%) of 1-3-14 as a colorless oil: $R_f$ 0.50 (1:24 ethyl acetate/dichloromethane); $^1$H NMR (500 MHz, CDCl$_3$) δ 6.52 (d, $J = 7.0$, 1 H), 5.66 (dd, $J = 3.0$, 1.5, 1 H), 4.96 (dt, 9.0, 1.5, 1 H), 4.93 (ddd, $J = 7.0$, 3.0, 1.5, 1 H), 4.25 (dd, $J = 12.5$, 2.5, 1 H), 4.14 (dd, $J = 12.5$, 6.0, 1 H), 3.73 (ddd, $J = 8.5$, 6.0, 2.5, 1 H), 2.17, 2.10, 2.09 (3 s, 3 H each); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 171.33, 170.74, 169.77, 169.35, 91.56, 76.00, 69.87, 69.62, 68.93, 63.70, 28.43, 21.15, 21.06, 20.95; ESI-MS m/z 602, 604, 606, 608 (in ratio ~1:3:3:1) MNa$^+$. 
**Compound 1-3-15.** A solution of 76.1 mg (0.220 mmol) of 1-3-6 in 2 mL of dry acetonitrile was sequentially treated with 42.8 µL (0.529 mmol) of pyridine, 23.4 µL (0.265 mmol) of triflic acid, and 117 mg (0.331 mmol) of Selectfluor. The reaction mixture was allowed to stir for 3 h, and then was diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, concentrated, and then chromatographed with 1:4 ethyl acetate/dichloromethane as the eluant to afford 56.1 mg (70%) of 1-3-15 as a colorless oil: $R_f$ 0.46 (2:3 ethyl acetate/dichloromethane); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.30 (dd, $J$ = 7.2, 1.2, 1 H), 5.57 (dd, $J$ = 2.8, 1.6, 1 H), 5.25 (ddd, $J$ = 46.8, 13.2, 2.4, 1 H), 5.14 (ddd, $J$ = 46.8, 13.2, 2.4, 1 H), 4.95 (dt, $J$ = 9.6, 1.6, 1 H), 4.52–4.54 (m, 1 H), 4.12 (d, $J$ = 4.8, 2 H), 3.52 (dt, $J$ = 9.2, 4.8, 1 H), 2.13, 2.07, 2.07 (s, 3 H each); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.79, 169.71, 169.49, 169.31 (d, $J$ = 24.5), 87.61, 81.07 (d, $J$ = 172.6), 76.51, 70.59, 69.35, 68.92, 63.40, 21.16, 21.06, 20.944; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ –220.77 (t, $J$ = 46.3); ESI-MS $m/z$ 386 MH$^+$. 
**Compound 1-3-16.** A solution of 18.1 mg (0.050 mmol) of 1-3-15 in 1 mL of methanol was cooled to 0 °C and treated with a catalytic amount of 18.8% methanolic sodium methoxide solution. The reaction was allowed to warm to room temperature over 1 h period and then was concentrated and chromatographed with 1:19 methanol/dichloromethane as the eluant to afford 11.8 mg (100%) of 1-3-16 as a colorless oil: $R_f$ 0.43 (1:4 methanol/dichloromethane); $^1$H NMR (500 MHz, CD$_3$OD) δ 6.44 (d, $J = 7.5$, 1 H), 5.26 (tdd, $J = 46.0$, 13.0, 2.0, 1 H), 5.14 (tdd, $J = 46.5$, 13.0, 2.0, 1 H), 4.40–4.43 (m, 1 H), 4.17 (app t, $J = 4.0$, 1 H), 3.74 (dd, $J = 12.0$, 2.5, 1 H), 3.61 (dd, $J = 12.0$, 6.0, 1 H), 3.58 (ddd, $J = 9.0$, 3.5, 1.0, 1 H), 3.33 (ddd, $J = 9.0$, 6.5, 2.5, 1 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 169.52 (d, $J = 23.6$), 88.57, 81.06 (d, $J = 169.9$), 79.15, 75.24, 72.79, 70.09, 62.31; $^{19}$F NMR (470 MHz, CDCl$_3$) δ –223.21 (dt, $J = 2.4$, 47.0); ESI-MS m/z 238 MH$^+$. 
**Compound 1-3-24.** A solution of 118.3 mg (0.343 mmol) of 1-3-6 in 2 mL of dry dichloromethane was sequentially treated with 55.5 µL (0.686 mmol) of pyridine and 47.7 µL (0.343 mmol) of trifluoroacetic anhydride. The reaction mixture was allowed to stir for 0.5 h, and then was concentrated and chromatographed with 1:19 ethyl acetate/dichloromethane as the eluant to afford 141.6 mg (94%) of 1-3-24 as a white solid: $R_f$ 0.56 (1:19 ethyl acetate/dichloromethane); mp 112–114 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.17 (d, $J = 6.0$, 1 H), 5.69 (br s, 1 H), 5.39 (app t, $J = 9.5$, 1 H), 5.26 (d, $J = 3.0$, 1 H), 5.17 (app t, $J = 10.0$, 1 H), 4.74 (br s, 1 H), 4.34–4.39 (m, 2 H), 4.08–4.11 (m, 1 H), 2.09, 2.04, 2.03 (s, 3 H each); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.74, 170.22, 169.54, 136.36, 115.86 (q, $J = 286.4$), 106.50, 83.75, 70.13, 69.69, 66.68, 61.41, 20.94, 20.73, 20.65; $^{19}$F NMR (470 MHz, CDCl$_3$) $\delta$ –68.69 (s); ESI-MS $m/z$ 442 MH$. 
Compound 1-1-1. A solution of 23.4 mg (0.0531 mmol) of 1-3-24 in 1 mL of methanol was cooled to 0 °C and treated with a catalytic amount of 18.8% methanolic sodium methoxide solution. The reaction was allowed to warm to room temperature over a 1 h period, and then was concentrated and chromatographed with 1:19 methanol/dichloromethane as the eluant to afford 11.6 mg (100%) of 1-1-1 as a colorless oil: \(^1\)H NMR (500 MHz, CD\(_3\)OD) \(\delta\) 6.36 (d, \(J = 7.0, 1\) H), 4.30–4.33 (m, 1 H), 4.13 (app t, \(J = 4.0, 1\) H), 3.73 (dd, \(J = 12.0, 2.5, 1\) H), 3.61 (dd, \(J = 12.0, 6.0, 1\) H), 3.57 (ddd, \(J = 9.0, 3.5, 0.5, 1\) H), 3.33 (ddd, \(J = 9.0, 6.5, 2.5, 1\) H), 2.26 (d, \(J = 2.0, 3\) H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 169.71, 89.59, 79.33, 75.12, 72.99, 70.15, 62.33, 19.46; ESI-MS \(m/z\) 220 MH\(^+\).
Compound 1-3-25. A solution of 90.7 mg (0.263 mmol) of 1-3-6 in 2 mL of dry dichloromethane was sequentially treated with 55.3 µL (0.684 mmol) of pyridine and 76.7 µL (0.552 mmol) of trifluoroacetic anhydride. The reaction mixture was allowed to stir for 3 h and then was concentrated and chromatographed with 1:19 ethyl acetate/dichloromethane as the eluant to afford 95.1 mg (82%) of 1-3-25 as a colorless oil: $R_f$ 0.32 (1:19 ethyl acetate/dichloromethane); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.22 (d, $J$ = 7.0, 1 H), 5.67 (s, 1 H), 5.28 (app t, $J$ = 4.0, 1 H), 5.02 (dd, $J$ = 9.0, 3.5, 1 H), 4.39 (dd, $J$ = 6.5, 4.5, 1 H), 4.24 (dd, $J$ = 12.5, 5.5, 1 H), 4.20 (dd, $J$ = 12.5, 3.0, 1 H), 3.94 (ddd, $J$ = 9.0, 5.5, 3.0, 1 H), 2.15, 2.09, 2.08 (s, 3 H each); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 176.02 (q, $J$ = 33.9), 171.65, 170.64, 169.70, 169.52, 117.46 (q, $J$ = 287.0), 85.43, 82.76, 70.14, 70.00, 67.74, 62.95, 61.63, 20.92, 20.91, 20.89; $^{19}$F NMR (470 MHz, CDCl$_3$) $\delta$ –77.14 (s); ESI-MS m/z 442 MH$^+$. 
**Compound 1-3-26.** A solution of 8.3 mg (0.0189 mmol) of **1-3-25** in 1 mL of methanol was cooled to 0 °C and treated with a catalytic amount of 18.8% methanolic sodium methoxide solution. The reaction was allowed to warm to room temperature over a 1 h period, and then was concentrated and chromatographed with 4:23 methanol/dichloromethane as the eluant to afford 5.9 mg (100%) of **1-3-26** as a colorless oil: $R_f$ 0.45 (1:4 methanol/dichloromethane); $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 6.39 (br s, 1 H), 5.70 (br s, 1 H), 4.00 (br s, 1 H), 3.83 (dd, $J$ = 12.0, 2.5, 1 H), 3.79 (app t, $J$ = 6.5, 1 H), 3.72 (dd, $J$ = 12.5, 5.5, 1 H), 3.67 (ddd, $J$ = 8.5, 6.0, 2.0, 1 H), 3.48 (dd, $J$ = 9.0, 7.0, 1 H); $^{19}$F NMR (470 MHz, CDCl$_3$) $\delta$ –78.58 (s); ESI-MS $m/z$ 316 MH$^+$. 
**Compound 1-3-27.** A solution of 12.3 mg (0.0390 mmol) of 1-3-26 in ½ mL of pyridine was treated with 10 drops of acetic anhydride. The reaction mixture was allowed to stir for 2 h, and then was concentrated and chromatographed with 1:9 ethyl acetate/dichloromethane as the eluant to afford 15.3 mg (81%) of 1-3-27 as a colorless oil: $R_f$ 0.36 (1:9 ethyl acetate/dichloromethane); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.01 (s, 1 H), 6.13 (d, $J = 6.5$, 1 H), 5.32 (app t, $J = 9.0$, 1 H), 5.12 (app t, $J = 10.0$, 1 H), 4.86 (dd, $J = 9.0$, 6.5, 1 H), 4.38 (dd, $J = 12.5$, 4.5, 1 H), 4.33 (ddd, $J = 9.5$, 4.5, 1.5, 1 H), 4.13 (dd, $J = 12.5$, 1.5, 1 H), 2.38, 2.10, 2.05, 2.04 (s, 3 H each); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 179.04 (q, $J = 35.0$), 170.66, 170.42, 169.58, 168.12, 161.99, 116.61 (q, $J = 333.6$), 102.60, 82.25, 71.96, 70.83, 66.15, 61.83, 61.40, 24.63, 20.89, 20.86, 20.71; $^{19}$F NMR (470 MHz, CDCl$_3$) $\delta$ –77.97 (s); ESI-MS $m/z$ 506 MNa$. 
Compound 1-3-28. A solution of 27.9 mg (0.0633 mmol) of 1-3-24 and a catalytic amount of benzoyl peroxide in 1 mL of dry acetonitrile was stirred at 23 °C. An ultraviolet lamp (254 nm) was directed at the solution for 10 min, and then the reaction mixture was allowed to stir for an additional 10 min. Concentration and chromatography with 1:9 ethyl acetate/dichloromethane as the eluant afforded 21.8 mg (84%) of 1-3-28 as a colorless oil: $R_f$ 0.30 (1:9 ethyl acetate/dichloromethane); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.33 (d, $J = 7.0$, 1 H), 5.62 (d, $J = 2.0$, 1 H), 4.95 (d, $J = 9.0$, 1 H), 4.56–4.58 (m, 1 H), 4.17 (dd, $J = 12.5$, 3.0, 1 H), 4.10 (dd, $J = 12.5$, 6.5, 1 H), 3.49 (ddd, $J = 9.0$, 6.0, 2.5, 1 H), 3.35–3.44 (m, 2 H), 2.15, 2.08, 2.08 (s, 3 H each); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.75, 169.79, 169.46, 161.52 (q, $J = 3.1$), 124.10 (q, $J = 276.3$), 89.19, 76.44, 70.18, 69.19, 69.06, 63.57, 39.56 (q, $J = 31.0$), 21.16, 20.96, 20.91; $^{19}$F NMR (470 MHz, CDCl$_3$) $\delta$ −63.87 (t, $J = 10.3$); ESI-MS m/z 436 M$^{+}$Na.
Compound 1-3-29. A solution of 8.0 mg (0.0194 mmol) of 1-3-28 in 1 mL of methanol was cooled to 0 °C and treated with a catalytic amount of 18.8% methanolic sodium methoxide solution. The reaction was allowed to warm to room temperature over a 1 h period, and then was concentrated and chromatographed with 4:23 methanol/dichloromethane as the eluant to afford 5.5 mg (100%) of 1-3-29 as a colorless oil: \( R_f \) 0.41 (1:4 methanol/dichloromethane); \(^1\)H NMR (500 MHz, CD\(_3\)OD) \( \delta \) 6.45 (d, \( J = 7.0 \), 1 H), 4.36–4.39 (m, 1 H), 4.16 (app t, \( J = 4.5 \), 1 H), 3.74 (dd, \( J = 12.0 \), 2.5, 1 H), 3.62 (dd, \( J = 12.0 \), 6.0, 1 H), 3.54–3.61 (m, 3 H), 3.33 (ddd, \( J = 9.0 \), 6.0, 2.5, 1 H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 162.22 (q, \( J = 3.6 \)), 124.67 (q, \( J = 275.3 \)), 90.00, 79.23, 75.34, 72.86, 70.02, 62.23, 38.91 (q, \( J = 30.5 \)); \(^1^9\)F NMR (470 MHz, CDCl\(_3\)) \( \delta \) –65.46 (t, \( J = 10.8 \)); ESI-MS \( m/z \) 288 MH\(^+\).
**Compound 1-3-30.** A solution of 6.0 mg (0.021 mmol) of 1-3-29 in 2 mL of methanol was treated with 10 µL of 18.8% methanolic sodium methoxide solution. The reaction was allowed to stir at reflux over a 2 h period and then was concentrated and chromatographed with 1:9 methanol/dichloromethane as the eluant to afford 6.4 mg (95%) of 1-3-30 as a colorless oil: \( R_f \) 0.53 (1:4 methanol/dichloromethane); \(^1\)H NMR (500 MHz, CD\(_3\)OD) \( \delta \) 6.29 (d, 1 H, \( J = 7.0 \) Hz), 4.30 (dt, 1 H, \( J = 6.0, 1.0 \) Hz), 4.18 (t, 1 H, \( J = 4.0 \) Hz), 3.73 (dd, 1 H, \( J = 12.0, 2.5 \) Hz), 3.61 (dd, 1 H, \( J = 12.0, 6.5 \) Hz), 3.55 (ddd, 1 H, \( J = 9.0, 3.5, 0.5 \) Hz), 3.38 (ddd, 1 H, \( J = 9.0, 6.0, 2.5 \) Hz), 3.31 (s, 9 H), 3.08 – 3.11 (m, 2 H); \(^{13}\)C NMR (125 MHz, CD\(_3\)OD) \( \delta \) 169.8, 114.0, 88.5, 78.2, 74.9, 72.8, 70.3, 62.4, 49.3, 37.0; ESI-MS \( m/z \) 346 MNa\(^+\).
**Compound 1-3-31.** A solution of 44.2 mg (0.0860 mmol) of 1-3-24 in 1 mL of dry acetonitrile was cooled to –30 °C and treated sequentially with excess methyl mercaptan and a catalytic amount of benzoyl peroxide. An ultra violet lamp (254 nm) was directed at the solution for 20 min, and the reaction mixture was allowed to stir for an additional 100 min. Concentration and chromatography with 1:19 ethyl acetate/dichloromethane as the eluant afforded 36.8 mg (75%) of 1-3-31 as colorless oil: \( R_f \) 0.49 (1:19 ethyl acetate/dichloromethane); \(^1\)H NMR (500 MHz, CDCl\(_3\)) data for isomer \( a \) (90% of mixture by integration) \( \delta \) 5.94 (d, \( J = 5.5, 1 \) H), 5.67 (dd, \( J = 11.0, 3.0, 1 \) H), 5.59 (app t, \( J = 10.0, 1 \) H), 5.10 (app t, \( J = 10.0, 1 \) H), 4.54 (dd, \( J = 9.0, 5.5, 1 \) H), 4.48 (d, \( J = 9.5, 1 \) H), 4.36 (dd, \( J = 12.5, 4.0, 1 \) H), 4.09 (dd, \( J = 12.5, 2.0, 1 \) H), 3.29 (dd, \( J = 13.5, 3.0, 1 \) H), 3.01 (app t, \( J = 13.0, 1 \) H); data for isomer \( b \) (10% of mixture by integration) \( \delta \) 6.21 (d, \( J = 5.0, 1 \) H), 5.62 (app t, \( J = 10.0, 1 \) H), 5.52 (dd, \( J = 7.0, 2.0, 1 \) H), 5.09 (app t, \( J = 10.0, 1 \) H), 4.67 (dd, \( J = 9.0, 5.0, 1 \) H), 4.39 (br s, 1 H), 4.31–4.35 (overlapping dd, 12.5, 4.5, 1 H), 4.07–4.10 (obscured signal, 1 H), 3.24 (br d, \( J = 15.0, 1 \) H), 3.15 (dd, \( J = 14.0, 7.0, 1 \) H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) data for isomer \( a \) \( \delta \) 170.74, 170.20, 169.50, 156.25 (q, \( J = 37.9 \)), 115.77 (q, \( J = 286.5 \)), 83.29, 71.02, 70.30, 67.44, 65.13, 61.45, 61.16, 40.09, 20.92, 20.73, 20.55, 15.48; data for isomer \( b \) \( \delta \)
170.42, 156.49 (q, $J = 37.8$), 115.90 (q, $J = 287.4$), 81.67, 70.56, 70.46, 67.29, 65.74, 63.03, 61.57, 43.55, 16.97; $^{19}$F NMR (470 MHz, CDCl$_3$) $\delta$ –69.32 (s); ESI-MS $m/z$ 512 MNa$^+$. 
Compound 1-3-32. A solution of 23.3 mg (0.0477 mmol) of 1-3-31 in 1 mL of methanol was cooled to 0 °C and treated with a catalytic amount of 18.8% methanolic sodium methoxide solution. The reaction was allowed to warm to room temperature over an 8 h period, and then was concentrated and chromatographed with 1:9 methanol/dichloromethane as the eluant to afford 12.2 mg (100%) of 1-3-32 as a colorless oil: \( R_f 0.23 \) (1:9 methanol/dichloromethane); \(^1\)H NMR (500 MHz, CD\(_3\)OD) data for isomer a (80% by integration) \( \delta 5.98 \) (d, \( J = 5.5, 1 \text{ H} \)), 5.00 (app t, \( J = 6.0, 1 \text{ H} \)), 3.85 (ddd, \( J = 9.0, 6.0, 3.0, 1 \text{ H} \)), 3.79 (dd, \( J = 12.0, 2.5, 1 \text{ H} \)), 3.75 (dd, \( J = 12.0, 5.5, 1 \text{ H} \)), 3.65 (app t, \( J = 9.0, 1 \text{ H} \)), 3.38 (app t, \( J = 9.0, 1 \text{ H} \)), 3.37 (dd, 9.0, 3.0, 1 H), 2.94 (dd, \( J = 14.0, 6.0, 1 \text{ H} \)), 2.74 (dd, 13.5, 6.5), 2.19 (s, 3 H); data for isomer b (20% by integration) \( \delta 5.77 \) (d, \( J = 3.5, 1 \text{ H} \)), 4.63 (app t, \( J = 6.0, 1 \text{ H} \)), 3.99 (app t, \( J = 4.5, 1 \text{ H} \)), 3.92 (dd, \( J = 12.0, 7.5, 1 \text{ H} \)), 3.85–3.88 (overlapping m, 1 H), 3.68 (dd, \( J = 12.0, 3.0, 1 \text{ H} \)), 3.62 (app t, \( J = 5.0, 1 \text{ H} \)), 3.13 (app t, \( J = 3.5, 1 \text{ H} \)), 3.07 (dd, \( J = 13.5, 5.5, 1 \text{ H} \)), 2.90 (dd, \( J = 14.0, 6.5, 1 \text{ H} \)), 2.20 (s, 3 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) data for isomer a \( \delta 89.47, 73.46, 70.83, 69.55, 67.60, 61.16, 40.11, 15.30 \); data for isomer b \( \delta 84.17, 78.10, 70.13, 69.43, 69.32, 68.43, 60.90, 39.54, 15.39 \); ESI-MS m/z 290 MNa\(^+\).
Compound 1-4-2. A solution of 63 mg (0.17 mmol) of 1-4-1 in 1.3 mL of dichloromethane was added dropwise via cannula to a solution of 49 mg (0.21 mmol) of p-methylbenzenesulfonyl bromide and 36 µL (0.21 mmol) of diisopropylethylamine in 1.5 mL of dichloromethane at 0 °C. After stirring for 1.5 h at room temperature, the mixture was concentrated and chromatographed on silica with 17:3 hexane/ethyl acetate as the eluant to give 86 mg (96%) of 1-4-2 as a white solid: mp 138–140 °C; Rf 0.46 (13:7 hexane/ethyl acetate); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.81 (d, 2 H, $J$ = 8.1 Hz), 7.35 (d, 2 H, $J$ = 8.4 Hz), 6.05 (d, 1 H, $J$ = 5.1 Hz), 5.64 (d, 1 H, $J$ = 8.4 Hz), 5.15 (app t, 1 H, $J$ = 9.9, 9.6 Hz), 4.81 (dd, 1 H, $J$ = 12.6, 9.3 Hz), 4.56 (ddd, 1 H, $J$ = 11.4, 8.1, 5.1 Hz), 4.06 (dd, 1 H, $J$ = 12.6, 3.3 Hz), 3.83 (dt, 1 H, $J$ = 10.2, 2.7 Hz), 3.65 (dd, 1 H, $J$ = 12.6, 2.4 Hz), 2.45 (s, 3 H), 2.06 (s, 3 H), 2.02 (s, 3 H), 2.00 (s, 3 H), 1.89 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.7, 170.5, 170.0, 169.0, 145.7, 142.5, 130.1, 127.4, 89.6, 71.4, 71.0, 67.3, 61.0, 52.8, 23.3, 22.0, 21.0, 20.9, 20.8; ESI-MS m/z 540 MNa$^+$. 
**Compound 1-4-3.** A solution of 25.2 mg (0.049 mmol) of 1-4-2 in 0.5 mL of methanol was treated with a catalytic amount of methanolic sodium methoxide (1 µL of an 18.8% solution) and stirred for 3 min at 23 °C (further reaction time led to decomposition of the base-sensitive product). The reaction was immediately chromatographed on silica with 1:19 methanol/dichloromethane as the eluant to afford 18.7 mg (98%) of 1-4-3 as a white solid: mp 150–152 °C with decomposition; $R_f$ 0.52 (1:4 methanol/dichloromethane); $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 7.80 (d, 2 H, $J = 8.5$ Hz), 7.42 (d, 2 H, $J = 8.0$ Hz), 6.08 (d, 1 H, $J = 5.5$ Hz), 4.06 (dd, 1 H, $J = 11.0$, 5.0 Hz), 3.57 (dd, 1 H, $J = 12.0$, 3.5 Hz), 3.46 (dd, 1 H, $J = 10.0$, 9.0 Hz), 3.38 (dt, 1 H, $J = 9.0$, 3.0 Hz), 3.29–3.35 (m, 1 H), 3.26 (dd, 1 H, $J = 12.0$, 2.5 Hz), 2.46 (s, 3 H), 1.88 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 173.9, 146.7, 144.7, 131.2, 128.4, 92.1, 77.1, 73.1, 71.3, 61.4, 55.9, 22.6, 21.8; ESI-MS $m/z$ 414 MNa$^+$. 

![Diagram of compounds 1-4-2 and 1-4-3]
Compound 1-4-4. A stirred solution of 13.1 mg (0.0335 mmol) of thiolsulfonate 1-4-3 in 0.5 mL of methanol was cooled by using a –78 °C bath. Diisopropylethylamine (6.4 µL, 0.037 mmol) was added, followed by a solution of 7.6 µL (0.037 mmol) of N-(tert-butoxycarbonyl)-L-cysteine methyl ester in 250 µL of dichloromethane. After 5 min of stirring, the cold reaction mixture was directly and immediately placed on the head of a silica column. Elution with 9:1 dichloromethane / methanol gave 9.3 mg (59%) of the cysteine conjugate 1-4-4 as a colorless oil: Rf 0.55 (1:4 methanol/dichloromethane); $^1$H NMR (500 MHz, CD$_3$OD) δ 5.56 (d, 1 H, $J = 5.0$ Hz), 4.47 (dd, 1 H, $J = 9.5$, 4.5 Hz), 4.01, (dd, 1 H, $J = 11.5$, 5.5 Hz), 3.88 (br ddd, 1 H, $J = 9.0$, 4.5, 2.5 Hz), 3.84 (dd, 1 H, $J = 12$, 2.5 Hz), 3.78 (dd, 1 H, $J = 12$, 4.5 Hz), 3.73 (s, 3 H), 3.55 (dd, 1 H, $J = 11$, 8.5 Hz), 3.44 (t, 1 H, $J = 9.0$), 3.33 (partially obscured dd, 1 H, $J = 14$, 4.5 Hz), 2.86 (dd, 1 H, $J = 14$, 9.5 Hz), 2.00 (s, 3 H), 1.45 (s, 9 H); $^{13}$C NMR (125 MHz, CD$_3$OD) δ 172.5, 172.1, 156.8, 94.1, 79.6, 74.3, 71.2, 71.1, 61.1, 55.1, 53.1, 51.7, 40.0, 27.5, 21.3; ESI-MS m/z 493 MNa$^+$. 
**Compound 2-2-2.** A solution of (2-phenyl)-selenoacetic acid [prepared by heating a 2 mL toluene solution of 142 mg (1.05 mmol) of phenylacetic acid and 185 mg (0.349 mmol) of Woollins’s reagent at reflux for 1 h] was added by cannula to a stirred solution of 225 mg (0.523 mmol) of methyl 2,3,4-tri-O-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside 2-2-1 in 2 mL of DMF, followed by 183 µL (1.05 mmol) of diisopropylethylamine. After 2 h of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 3:1 hexane / ethyl acetate as the eluant to give 235 mg (90%) of the selenoester 2-2-2 as a colorless oil: R<sub>f</sub> 0.26 (3:1 hexane/ethyl acetate); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.26–7.36 (m, 5 H), 5.15 (t, 1 H, J = 9.5 Hz), 4.92 (t, 1 H, J = 9.5 Hz), 4.83 (partially obscured dd, 1 H, J = 12.5, 4.0 Hz), 4.82 (obscured d, 1 H, J = 4.0 Hz), 3.90 (ddd, 1 H, J = 10.0, 7.0, 2.5 Hz), 3.85 (s, 2 H), 3.31 (s, 3 H), 3.15 (dd, 1 H, J = 13.0, 3.0 Hz), 2.98 (ddd, 1 H, J = 13.0, 7.5 Hz), 2.06 (s, 3 H), 2.05 (s, 3 H), 1.99 (s, 3 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 199.5, 170.4, 170.3, 170.2, 132.9, 130.2, 129.0, 128.0, 96.8, 72.1, 71.2, 70.2, 68.8, 55.5, 54.1, 26.9, 21.0, 21.0, 20.9; <sup>77</sup>Se NMR (76 MHz, CDCl<sub>3</sub>) δ 520.8 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS m/z 525 MNa<sup>+</sup>.
**Compound 2-2-3.** A solution of dimethyldioxirane was added to a stirred solution of 700 mg (1.40 mmol) of selenoester 2-2-2 in 4 mL of acetone until all of 2-2-2 was consumed according to TLC analysis (total ~ 32.6 mL of a 0.090 M titrated solution of DMDO in moist acetone, ~ 2.1 equiv). Once 2-2-2 was consumed, seleninic acid 2-2-3 precipitated out of solution to give, after filtration and drying, 545 mg (94%) of a white solid: mp 146–148 °C; R$_f$ 0.20 (9:9:2 hexane/dichloromethane/methanol); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.98 (br s, 1 H), 5.48 (t, 1 H, J = 9.5 Hz), 4.95 (t, 1 H, J = 9.5 Hz), 4.92 (d, 1 H, J = 3.5 Hz), 4.86 (dd, 1 H, J = 10.5, 3.5 Hz), 4.37 (dt, 1 H, J = 10.0, 3.5 Hz), 3.44 (s, 3 H), 3.35 (dd, 1 H, J = 12.5, 3.5 Hz), 3.18 (app t, 1 H, J = 12.5 Hz), 2.07 (s, 3 H), 2.07 (s, 3 H), 2.01 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.4, 170.1, 170.1, 97.3, 72.2, 71.0, 69.5, 64.6, 57.6, 56.5, 20.9, 20.9, 20.9; $^{77}$Se NMR (76 MHz, CDCl$_3$) $\delta$ 1205.2 [vs PhSeSePh at 460.0 ppm as an external standard]; NI ESI-MS m/z 415 M$^-$. The crystal for X-ray analysis was grown by dissolving 2-2-3 in a minimum amount of chloroform and then diffusing in ether.
**Compound 2-2-4.** A solution of 10.0 mg (0.0240 mmol) of seleninic acid 2-2-3 in 1 mL of methanol was treated with 7 µL of 18.8% methanolic sodium methoxide solution. After 30 min of stirring at room temperature, the reaction was concentrated to give 7.5 mg (100%) of seleninate 2-2-4 as a colorless oil: $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 4.64 (d, 1 H, $J$ = 4.0 Hz), 3.99 (dt, 1 H, $J$ = 9.5, 4.0 Hz), 3.60 (t, 1 H, $J$ = 9.5 Hz), 3.42 (partially obscured dd, 1 H, $J$ = 9.0, 4.0 Hz), 3.43 (s, 3 H), 3.17 (t, 1 H, $J$ = 9.5 Hz), 2.90 (dd, 1 H, $J$ = 12.0, 4.0 Hz), 2.79 (dd, 1 H, $J$ = 12.0, 9.0 Hz); $^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$ 100.2, 74.7, 73.6, 72.5, 67.5, 61.8, 54.9; $^{77}$Se NMR (76 MHz, CD$_3$OD) $\delta$ 1170.8 [vs PhSeSePh at 460.0 ppm as an external standard]; NI ESI-MS $m/z$ 289 M$^-$. 
Compound 2-2-5. A solution of dimethyldioxirane in acetone was added to a stirred solution of 30.0 mg (0.0720 mmol) of seleninic acid 2-2-3 in 1 mL of dichloromethane. After all of 2-2-3 was consumed according to TLC analysis, the reaction mixture was concentrated and then chromatographed on silica with 22:22:5:1 hexane / dichloromethane / methanol / triethylamine as the eluant to give 36.8 mg (96%) of the selenonate 2-2-5 as a colorless oil: $R_f$ 0.21 (22:22:5:1 hexane/dichloromethane/methanol/triethylamine); $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 5.42 (dd, 1 H, $J = 10.0, 9.0$ Hz), 5.00 (t, 1 H, $J = 10.0$ Hz), 4.96 (d, 1 H, $J = 3.5$ Hz), 4.91 (dd, 1 H, $J = 10.0, 3.5$ Hz), 4.51 (dt, 1 H, $J = 9.5, 2.5$ Hz), 3.55 (s, 3 H), 3.49 (dd, 1 H, $J = 13.0, 9.0$ Hz), 3.44 (dd, 1 H, $J = 13.0, 2.5$ Hz), 3.21 (q, 6 H, $J = 7.5$ Hz), 2.05 (s, 3 H), 2.03 (s, 3 H), 1.98 (s, 3 H), 1.32 (t, 9 H, $J = 7.5$ Hz); $^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$ 170.4, 170.4, 170.3, 96.9, 71.5, 70.7, 70.1, 64.7, 58.6, 55.6, 46.8, 19.5, 19.4, 19.3, 8.1; $^{77}$Se NMR (76 MHz, CD$_3$OD) $\delta$ 1037.8 [vs PhSeSePh at 460.0 ppm as an external standard]; NI ESI-MS $m/z$ 431 M$^-$. 
Compound 2-2-5. A solution of dimethyldioxirane in acetone was added to a stirred solution of 55.3 mg (0.110 mmol) of selenoester 2-2-2 in 1 mL of dichloromethane. After all of 2-2-2, as well as the corresponding intermediate seleninate 2-2-3, was consumed according to TLC analysis, the reaction mixture was concentrated and then chromatographed on silica with 22:22:5:1 hexane / dichloromethane / methanol / triethylamine as the eluant to give 47.5 mg (81%) of the triethylammonium selenonate 2-2-5 as a colorless oil.
**Compound 2-2-6.** A solution of 9.9 mg (0.019 mmol) of selenonate 2-2-5 in 1 mL of methanol was treated with 6 µL of 18.8% methanolic sodium methoxide solution. After 30 min of stirring at room temperature, the reaction was concentrated to give 6.1 mg (100%) of selenonate 2-2-6 as a colorless oil: $^1$H NMR (500 MHz, CD$_3$OD) δ 4.68 (d, 1 H, $J = 4.0$ Hz), 4.22 (dt, 1 H, $J = 10.0$, 2.0 Hz), 3.74 (dd, 1 H, $J = 13.0$, 2.0 Hz), 3.63 (t, 1 H, $J = 9.0$ Hz), 3.52 (s, 3 H), 3.42 (dd, 1 H, $J = 10.0$, 4.0 Hz), 3.41 (dd, 1 H, $J = 13.0$, 9.5 Hz), 3.17 (t, 1 H, $J = 9.0$ Hz); $^{13}$C NMR (125 MHz, CD$_3$OD) δ 100.0, 73.7, 73.6, 72.2, 67.1, 59.9, 55.3; $^{77}$Se NMR (76 MHz, CD$_3$OD) δ 1053.0 [vs PhSeSePh at 460.0 ppm as an external standard]; NI ESI-MS $m/z$ 305 M$^-$. 
Compound 2-2-8. A solution of (2-phenyl)-selenoacetic acid [prepared by heating a 2 mL toluene solution of 93.1 mg (0.684 mmol) of phenylacetic acid and 121 mg (0.228 mmol) of Woollins’s reagent at reflux for 1 h] was added by cannula to a stirred solution of 147 mg (0.342 mmol) of methyl 2,3,4-tri-O-acetyl-6-deoxy-6-iodo-α-D-mannopyranoside 2-2-7 in 2 mL of DMF, followed by 119 µL (0.684 mmol) of diisopropylethylamine. After 2 h of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 3:1 dichloromethane / ethyl acetate as the eluant to give 137 mg (80%) of the selenoester 2-2-8 as a colorless oil: $R_f$ 0.58 (3:1 dichloromethane/ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.27–7.36 (m, 5 H), 5.27 (dd, 1 H, $J$ = 10.0, 3.5 Hz), 5.19 (dd, 1 H, $J$ = 3.0, 1.5 Hz), 5.16 (t, 1 H, $J$ = 10.0 Hz), 4.58 (d, 1 H, $J$ = 1.5 Hz), 3.86 (s, 2 H), 3.83 (partially obscured dt, 1 H, $J$ = 9.5, 2.5 Hz), 3.30 (s, 3 H), 3.19 (dd, 1 H, $J$ = 13.0, 2.5 Hz), 2.97 (dd, 1 H, $J$ = 13.0, 9.0 Hz), 2.13 (s, 3 H), 2.08 (s, 3 H), 1.98 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 200.0, 170.4, 170.3, 170.1, 133.0, 130.2, 129.0, 128.0, 98.6, 70.4, 69.9, 69.8, 69.2, 55.4, 54.2, 27.2, 21.1, 21.1, 20.9; ESI-MS $m/z$ 525 MNa$^+$. 
**Compound 2-2-9.** A solution of dimethyldioxirane was added to a stirred solution of 23.9 mg (0.0477 mmol) of selenoester 2-2-8 in 1 mL of acetone until all of 2-2-8 was consumed according to TLC analysis (total ~ 1.2 mL of a 0.090 M titrated solution of DMDO in moist acetone, ~ 2.2 equiv). The reaction mixture was concentrated and then chromatographed on silica with 9:9:2 hexane / dichloromethane / methanol as the eluant to give 17.6 mg (89%) of the seleninic acid 2-2-9 as a colorless oil: \( R_f \) 0.12 (9:9:2 hexane/dichloromethane/methanol); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.08 (br s, 1 H), 5.32 (dd, 1 H, \( J = 10.0, 3.5 \) Hz), 5.25 (dd, 1 H, \( J = 3.0, 1.5 \) Hz), 5.19 (t, 1 H, \( J = 10.0 \) Hz), 4.65 (s, 1 H), 4.33 (dt, 1 H, \( J = 10.0, 3.0 \) Hz), 3.42 (s, 3 H), 3.36 (dd, 1 H, \( J = 12.0, 3.0 \) Hz), 3.26 (t, 1 H, \( J = 12.0 \) Hz), 2.15 (s, 3 H), 2.07 (s, 3 H), 1.98 (s, 3 H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 170.3, 170.1, 169.9, 99.1, 69.7, 69.4, 68.6, 65.8, 57.8, 56.3, 21.1, 21.0, 20.9; NI ESI-MS \( m/z \) 415 M\(^-\).
Compound 2-2-10. A solution of 6.9 mg (0.017 mmol) of seleninic acid 2-2-9 in 1 mL of methanol was treated with 5 µL of 18.8% methanolic sodium methoxide solution. After 30 min of stirring at room temperature, the reaction was concentrated to give 5.2 mg (100%) of seleninate 2-2-10 as a colorless oil: $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 4.59 (d, 1 H, $J$ = 1.5 Hz), 3.94 (dt, 1 H, $J$ = 9.5, 4.0 Hz), 3.79 (dd, 1 H, $J$ = 3.0, 1.5 Hz), 3.65 (dd, 1 H, $J$ = 9.5, 3.5 Hz), 3.53 (t, 1 H, $J$ = 9.5 Hz), 3.49 (s, 3 H), 2.92 (dd, 1 H, $J$ = 12.0, 4.0 Hz), 2.86 (dd, 1 H, $J$ = 12.0, 9.5 Hz); $^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$ 101.8, 71.2, 71.1, 71.0, 68.4, 61.7, 54.6; NI ESI-MS $m/z$ 289 M$^-$. 
Compound 2-2-11. A solution of excess dimethyldioxirane in acetone was added to a stirred solution of 19.9 mg (0.0397 mmol) of selenoester 2-2-8 in 1 mL of dichloromethane. After all of 2-2-8, as well as the corresponding seleninate intermediate 2-2-9, was consumed according to TLC analysis, the reaction mixture was concentrated and then chromatographed on silica with 93:5:2 dichloromethane / methanol / triethylamine as the eluant to give 17.8 mg (84%) of the selenonate 2-2-11 as a colorless oil: \( R_f \) 0.27 (93:5:2 dichloromethane/methanol/triethylamine); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 5.35 (dd, 1 H, \( J = 10.0, \ 3.5 \) Hz), 5.22 (dd, 1 H, \( J = 3.0, \ 1.5 \) Hz), 5.14 (t, 1 H, \( J = 10.0 \) Hz), 4.77 (d, 1 H, \( J = 1.5 \) Hz), 4.60 (dt, 1 H, \( J = 10.0, \ 2.0 \) Hz), 3.56 (s, 3 H), 3.49 (t, 1 H, \( J = 11.0 \) Hz), 3.36 (d, 1 H, \( J = 11.5 \) Hz), 3.14 (q, 6 H, \( J = 7.5 \) Hz), 2.12 (s, 3 H), 2.05 (s, 3 H), 1.98 (s, 3 H), 1.36 (t, 9 H, \( J = 7.5 \) Hz); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 170.4, 170.3, 169.9, 98.5, 69.9, 69.1, 69.0, 65.8, 59.1, 56.2, 46.0, 21.1, 21.0, 20.9, 8.9; NI ESI-MS \text{m/z} \) 431 M\(^-\).
Compound 2-2-12. A solution of 9.0 mg (0.017 mmol) of selenonate 2-2-11 in 1 mL of methanol was treated with 5 µL of 18.8% methanolic sodium methoxide solution. After 30 min of stirring at room temperature, the reaction was concentrated to give 5.5 mg (100%) of selenonate 2-2-12 as a colorless oil: $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 4.65 (d, 1 H, $J = 1.5$ Hz), 4.17 (dt, 1 H, $J = 10.0, 2.0$ Hz), 3.79 (dd, 1 H, $J = 3.5, 1.5$ Hz), 3.77 (dd, 1 H, $J = 13.0, 2.0$ Hz), 3.69 (dd, 1 H, $J = 10.0, 3.5$ Hz), 3.53 (t, 1 H, $J = 9.5$ Hz), 3.49 (partially obscured dd, 1 H, $J = 13.0, 10.0$ Hz), 3.49 (s, 3 H); $^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$ 101.5, 71.1, 70.9, 70.1, 68.0, 60.0, 55.0; NI ESI-MS $m/z$ 305 M$^-$. 
Compound 2-2-14. A solution of (2-phenyl)-selenoacetic acid [prepared by heating a 2 mL toluene solution of 18.6 mg (0.137 mmol) of phenylacetic acid and 24.2 mg (0.0455 mmol) of Woollins’s reagent at reflux for 1 h] was added by cannula to a stirred solution of 31.3 mg (0.0683 mmol) of 1,2,3,4-tetra-O-acetyl-6-deoxy-6-iodo-D-glucopyranose 2-2-13 in 1 mL of DMF, followed by 24 µL (0.14 mmol) of diisopropylethylamine. After 2 h of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 8:2 hexane / ethyl acetate as the eluant to give 32.3 mg (87%) of the selenoester 2-2-14 as a colorless oil: $R_f$ 0.30 (8:2 hexane/ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.27–7.37 (m, 10 H), 6.22 (d, 1 H, $J$ = 4.0 Hz), 5.66 (d, 1 H, $J$ = 8.5 Hz), 5.42 (t, 1 H, $J$ = 10.0 Hz), 5.20 (t, 1 H, $J$ = 10.0 Hz), 5.08 (dd, 1 H, $J$ = 9.5, 8.5 Hz), 5.03 (dd, 1 H, $J$ = 10.5, 3.5 Hz), 5.02 (t, 1 H, $J$ = 9.5 Hz), 5.01 (t, 1 H, $J$ = 9.5), 4.13 (ddd, 1 H, $J$ = 10.0, 6.0, 3.5 Hz), 3.84 (s, 4 H), 3.83 (partially obscured ddd, 1 H, $J$ = 9.5, 6.0, 2.5 Hz), 3.17 (dd, 1 H, $J$ = 13.5, 3.5 Hz), 3.14 (dd, 1 H, $J$ = 14.0, 3.5 Hz), 3.08 (dd, 1 H, $J$ = 13.5, 6.0 Hz), 3.07 (dd, 1 H, $J$ = 13.5, 6.0 Hz), 2.13 (s, 3 H), 2.08 (s, 3 H), 2.07 (s, 3 H), 2.06 (s, 3 H), 2.02 (s, 3 H), 2.01 (s, 3 H), 2.00 (s, 3 H), 2.00 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 199.6, 199.6, 170.5, 170.4, 169.9, 169.9, 169.9, 169.5, 169.2, 169.1, 132.8, 132.8, 130.4, 130.3,
129.0, 129.0, 128.0, 128.0, 91.8, 89.1, 74.2, 73.0, 71.2, 71.1, 70.8, 70.6, 70.1, 69.5, 54.0, 54.0, 26.6, 26.4, 21.1, 21.0, 20.9, 20.9, 20.8, 20.8, 20.7; ESI-MS m/z 553 MNa⁺.
Compound 2-2-15. A solution of dimethyldioxirane was added to a stirred solution of 15.2 mg (0.0287 mmol) of selenoester 2-2-14 in 1 mL of acetone until all of 2-2-14 was consumed according to TLC analysis (total ~ 0.70 mL of a 0.090 M titrated solution of DMDO in moist acetone, ~ 2.2 equiv). The reaction mixture was concentrated and then chromatographed on silica with 9:9:2 hexane / dichloromethane / methanol as the eluant to give 11.7 mg (92%) of the seleninic acid 2-2-15 as a colorless oil: \( R_f \) 0.13 (9:9:2 hexane/dichloromethane/methanol);

\( ^1H \) NMR (500 MHz, CD\(_3\)OD) \( \delta \) 6.24 (d, 1 H, \( J = 3.5 \) Hz), 5.81 (d, 1 H, \( J = 8.5 \) Hz), 5.45 (t, 1 H, \( J = 9.0 \) Hz), 5.37 (t, 1 H, \( J = 9.0 \) Hz), 5.12 (dd, 1 H, \( J = 9.5, 8.5 \) Hz), 5.12 (dd, 1 H, \( J = 9.5, 4.0 \) Hz), 5.09 (t, 1 H, \( J = 9.5 \) Hz), 5.04 (t, 1 H, \( J = 9.5 \) Hz), 4.51 (dt, 1 H, \( J = 10.5, 3.5 \) Hz), 4. (dt, 1 H, \( J = 10.0, 3.5 \) Hz), 3.39 (app t 1 H, \( J = 12.0 \) Hz), 3.20 (app t, 1 H, \( J = 12.0 \) Hz), 3.13 (dd, 1 H, \( J = 12.0, 3.5 \) Hz), 3.00 (dd, 1 H, \( J = 12.0, 3.5 \) Hz), 2.21 (s, 3 H), 2.08 (s, 3 H), 2.06 (s, 3 H), 2.05 (s, 3 H), 2.02 (s, 3 H), 2.01 (s, 3 H), 2.01 (s, 3 H), 1.98 (s, 3 H), 1.30 (t, 9 H, \( J = 7.5 \) Hz);

\( ^{13}C \) NMR (125 MHz, CD\(_3\)OD) \( \delta \) 174.3, 174.2, 174.1, 174.0, 173.7, 173.3, 95.9, 92.8, 76.5, 75.6, 75.4, 75.1, 74.3, 73.7, 73.6, 73.3, 70.6, 61.9, 61.4, 23.3, 23.3, 23.2, 23.2, 23.0; ESI-MS (in methanol solution) \( m/z \) 481 as seleninate methyl ester · Na\(^+\).
**Compound 2-2-16.** A solution of 8.0 mg (0.018 mmol) of seleninic acid 2-2-15 in 1 mL of methanol was treated with 5 µL of 18.8% methanolic sodium methoxide solution. After 30 min of stirring at room temperature, the reaction was concentrated to give 5.4 mg (100%) of seleninate 2-2-16 as a colorless oil: $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 5.08 (d, 1 H, $J = 4.0$ Hz), 4.50 (d, 1 H, $J = 7.5$ Hz), 4.24 (dt, 1 H, $J = 9.5$, 4.0 Hz), 3.73 (dt, 1 H, $J = 9.0$, 4.5 Hz), 3.66 (t, 1 H, $J = 9.0$ Hz), 3.37 (dd, 1 H, $J = 9.0$, 3.5 Hz), 3.34 (t, 1 H, $J = 9.0$ Hz), 3.19 (t, 1 H, $J = 9.0$ Hz), 3.16 (t, 1 H, $J = 9.0$ Hz), 3.14 (dd, 1 H, $J = 9.0$, 7.5 Hz), 2.88 (dd, 1 H, $J = 12.0$, 4.0 Hz), 2.86 (dd, 1 H, $J = 12.5$, 4.0 Hz), 2.81 (dd, 1 H, $J = 12.0$, 8.5 Hz), 2.79 (dd, 1 H, $J = 12.0$, 9.0 Hz); $^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$ 97.0, 93.0, 76.6, 75.2, 75.0, 74.4, 73.4, 72.9, 71.7, 67.0, 61.6, 61.1; NI ESI-MS $m/z$ 275 M⁻.
Compound 2-2-17. A solution of excess dimethyldioxirane in acetone was added to a stirred solution of 16.9 mg (0.0319 mmol) of selenoester 2-2-14 in 1 mL of dichloromethane. After all of 2-2-14, as well as the corresponding seleninate intermediate 2-2-15, was consumed according to TLC analysis, the reaction mixture was concentrated and then chromatographed on silica with 22:22:5:1 hexane / dichloromethane / methanol / triethylamine as the eluant to give 14.5 mg (81%) of the selenonate 2-2-17 as a colorless oil: \( R_f \) 0.13 (22:22:5:1 hexane/dichloromethane/methanol/triethylamine); \(^1\)H NMR (500 MHz, CD\(_3\)OD) \( \delta \) 6.33 (d, 1 H, \( J = 3.5 \) Hz), 5.92 (d, 1 H, \( J = 8.5 \) Hz), 5.43 (t, 1 H, \( J = 10.0 \) Hz), 5.35 (t, 1 H, \( J = 9.5 \) Hz), 5.11 (t, 1 H, \( J = 10.0 \) Hz), 5.10 (dd, 1 H, \( J = 10.0, 3.5 \) Hz), 5.08 (t, 1 H, \( J = 10.0 \) Hz), 5.08 (dd, 1 H, \( J = 10.0, 8.5 \) Hz), 4.66 (dt, 1 H, \( J = 12.5, 6.0 \) Hz), 4.42 (dt, 1 H, \( J = 12.5, 6.0 \) Hz), 3.43–3.47 (m, 4 H), 3.20 (q, 6 H, \( J = 7.5 \) Hz), 2.18 (s, 3 H), 2.05 (s, 3 H), 2.05 (s, 3 H), 2.04 (s, 3 H), 1.99 (s, 3 H), 1.99 (s, 3 H), 1.97 (s, 3 H), 1.96 (s, 3 H), 1.30 (t, 9 H, \( J = 7.5 \) Hz); \(^{13}\)C NMR (100 MHz, CD\(_3\)OD) \( \delta \) 170.4, 170.3, 170.2, 170.2, 170.1, 169.8, 169.2, 168.7, 91.5, 88.5, 72.7, 70.9, 70.7, 70.7, 69.9, 69.9, 69.5, 67.3, 58.4, 58.4, 46.7, 19.5, 19.4, 19.4, 19.4, 19.3, 19.3, 19.2, 19.1, 8.0; NI ESI-MS \( m/z \) 459 M\(^-\).
Compound 2-2-18. A solution of 13.7 mg (0.0245 mmol) of selenonate 2-2-17 in 1 mL of methanol was treated with 7 µL of 18.8% methanolic sodium methoxide solution. After 30 min of stirring at room temperature, the reaction was concentrated to give 7.7 mg (100%) of selenonate 2-2-18 as a colorless oil: $^1$H NMR (500 MHz, CD$_3$OD) δ 5.13 (d, 1 H, J = 3.5 Hz), 4.57 (d, 1 H, J = 8.0 Hz), 4.44 (dt, 1 H, J = 10.0, 2.0 Hz), 3.91 (dt, 1 H, J = 10.0, 2.0 Hz), 3.74 (dd, 1 H, J = 13.0, 2.0 Hz), 3.73 (dd, 1 H, J = 13.0, 2.0 Hz), 3.69 (t, 1 H, J = 9.5 Hz), 3.44, (dd, 1 H, J = 12.5, 10.0 Hz), 3.43 (dd, 1 H, J = 13.0, 10.5 Hz), 3.39 (dd, 1 H, J = 9.5, 3.5 Hz), 3.38 (t, 1 H, J = 10.0 Hz), 3.20 (t, 1 H, J = 9.5 Hz), 3.18 (t, 1 H, J = 9.0 Hz), 3.16 (dd, 1 H, J = 9.5, 8.0 Hz); $^{13}$C NMR (125 MHz, CD$_3$OD) δ 97.5, 93.0, 76.6, 75.1, 73.8, 73.5, 73.4, 72.5, 71.2, 66.7, 60.5, 59.9; NI ESI-MS m/z 291 M$^-$.
Compound 2-2-20. A solution of (2-phenyl)-selenoacetic acid [prepared by refluxing a 2 mL toluene solution of 87.0 mg (0.639 mmol) of phenylacetic acid and 102 mg (0.192 mmol) of Woollins’s reagent for 1 h] was added by cannula to a stirred solution of 65.4 mg (0.160 mmol) of chloride 2-2-19 in 2 mL of DMF, followed by 111 µL (0.639 mmol) of diisopropylethylamine. After 2 h of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 7:3 dichloromethane / ethyl acetate as the eluant to give 64.9 mg (71%) of the selenoester 2-2-20 as a colorless oil: Rf 0.44 (3:2 dichloromethane/ethyl acetate); ¹H NMR (500 MHz, CDCl₃) δ 7.28 – 7.38 (m, 5 H), 5.73 (d, 1 H, J = 9.5 Hz), 5.16 (t, 1 H, J = 10.0 Hz), 5.10 (t, 1 H, J = 10.0 Hz), 4.82 (d, 1 H, J = 3.5 Hz), 4.32 (ddd, 1 H, J = 10.5, 9.5, 3.5 Hz), 4.21 (dd, 1 H, J = 12.5, 4.5 Hz), 4.06 (dd, 1 H, J = 12.5, 2.5 Hz), 3.95 (ddd, 1 H, J = 10.0, 4.5, 2.0 Hz), 3.88 (s, 2 H), 3.85 (ddd, 1 H, J = 10.5, 7.0, 6.0 Hz), 3.64 (ddd, 1 H, J = 12.0, 10.0, 6.0 Hz), 3.13 (ddd, 1 H, J = 13.0, 7.0, 6.0 Hz), 3.03 (dt, 1 H, J = 12.0, 6.0 Hz), 2.07 (s, 3 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 1.92 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 200.2, 171.5, 170.9, 170.3, 169.5, 132.8, 130.3, 129.0, 128.2, 97.5, 71.5, 68.3, 67.8, 62.1, 54.3, 51.9, 25.1, 23.4, 21.0, 20.9, 20.9; ESI-MS m/z 596 MNa⁺.
Compound 2-2-21. Dimethyldioxirane was added to a stirred solution of 21.4 mg (0.0374 mmol) of selenoester 2-2-20 in 1 mL of dichloromethane until all of 2-2-20 was consumed according to TLC analysis (total ~ 873 µL of a 0.090 M titrated solution of DMDO in moist acetone, ~ 2.1 equiv). The reaction mixture was concentrated and then chromatographed on silica with 9:9:1 hexanes / dichloromethane / methanol as the eluant to give 16.4 mg (90%) of the seleninic acid 2-2-21 as a colorless oil: $R_f$ 0.10 (9:9:1 hexanes/dichloromethane/methanol); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.61 (d, 1 H, $J$ = 9.5 Hz), 5.79 (br s, 1 H), 5.18 (t, 1 H, $J$ = 10.0 Hz), 5.12 (t, 1 H, $J$ = 10.0 Hz), 4.92 (d, 1 H, $J$ = 3.5 Hz), 4.36 (ddd, 1 H, $J$ = 10.5, 9.5, 3.5 Hz), 4.31 (dt, 1 H, $J$ = 11.0, 5.5 Hz), 4.23 (dd, 1 H, $J$ = 12.5, 4.5 Hz), 4.12 (dd, 1 H, $J$ = 12.5, 2.5 Hz), 4.04 (ddd, 1 H, $J$ = 11.0, 6.5, 4.5 Hz), 3.99 (ddd, 1 H, $J$ = 10.0, 4.5, 2.5 Hz), 3.32 – 3.42 (m, 2 H), 2.10 (s, 3 H), 2.03 (s, 3 H), 2.01 (s, 3 H), 1.97 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 171.6, 170.9, 170.9, 169.5, 98.1, 71.2, 68.6, 68.3, 62.2, 62.1, 55.4, 51.9, 23.3, 21.0, 21.0, 20.8; NI ESI-MS $m/z$ 486 M$^+$. 
**Compound 2-2-22.** A solution of 15.4 mg (0.0317 mmol) of seleninic acid 2-2-21 in 1 mL of methanol was treated with 10 µL of 18.8% methanolic sodium methoxide solution. After 30 min of stirring at room temperature, the reaction was concentrated to give 12.1 mg (100%) of seleninate 2-2-22 as a colorless oil: $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 4.79 (d, 1 H, $J = 3.6$ Hz), 4.15 (ddd, 1 H, $J = 10.8$, 6.8, 5.2 Hz), 3.89 (dd, 1 H, $J = 10.8$, 3.6 Hz), 3.80 – 3.86 (m, 2 H), 3.63 – 3.70 (m, 2 H), 3.62 (ddd, 1 H, $J = 10.0$, 5.6, 2.4 Hz), 3.33 (d, 1 H, $J = 10.0$, 9.2 Hz), 2.76 – 2.86 (m, 2 H), 1.99 (s, 3 H); $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 172.6, 97.8, 72.8, 71.7, 71.2, 62.4, 61.4, 58.2, 54.1, 21.5; NI ESI-MS m/z 360 M$^+$. 
**Compound 2-2-23.** Excess dimethyldioxirane was added to a stirred solution of 11.3 mg (0.0198 mmol) of selenoester 2-2-20 in 1 mL of dichloromethane. After all of 2-2-20, as well as the corresponding intermediate 2-2-21, were consumed according to TLC analysis, the reaction mixture was concentrated and then immediately chromatographed on silica with 44:2:1 dichloromethane / methanol / triethylamine as the eluant to give 9.9 mg (83%) of the selenonate 2-2-23 as a colorless oil: $R_f$ 0.18 (44:2:1 dichloromethane/methanol/triethylamine); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.90 (d, 1 H, $J$ = 9.5 Hz), 5.24 (dd, 1 H, $J$ = 10.5, 9.5 Hz), 5.11 (t, 1 H, $J$ = 10.0 Hz), 4.90 (d, 1 H, $J$ = 3.5 Hz), 4.40 (ddd, 1 H, $J$ = 10.5, 9.5, 3.5 Hz), 4.33 (ddd, 1 H, $J$ = 11.5, 5.0, 3.5 Hz), 4.23 (dd, 1 H, $J$ = 12.5, 4.5 Hz), 4.11 (ddd, 1 H, $J$ = 13.0, 9.5, 2.5 Hz), 4.10 (dd, 1 H, $J$ = 12.5, 2.5 Hz), 4.04 (ddd, 1 H, $J$ = 10.5, 4.5, 2.5 Hz), 3.50 (ddd, 1 H, $J$ = 13.0, 9.5, 3.5 Hz), 3.40 (ddd, $J$ = 13.0, 5.0, 2.5 Hz), 3.14 (q, 6 H, $J$ = 7.5 Hz), 2.09 (s, 3 H), 2.00 (s, 3 H), 1.99 (s, 3 H), 1.98 (s, 3 H), 1.37 (t, 9 H, $J$ = 7.5 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 171.5, 171.0, 171.0, 169.5, 99.1, 72.2, 68.7, 68.5, 63.5, 62.2, 57.3, 51.3, 46.1, 23.2, 21.0, 21.0, 20.9, 9.0; NI ESI-MS $m/z$ 502 M$. 
**Compound 2-2-24.** A solution of 9.9 mg (0.0164 mmol) of selenonate 2-2-23 in 1 mL of methanol was treated with 5 µL of 18.8% methanolic sodium methoxide solution. After 30 min of stirring at room temperature, the reaction was concentrated to give 6.5 mg (100%) of selenonate 2-2-24 as a colorless oil: $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 4.81 (d, 1 H, $J$ = 3.6 Hz), 4.25 – 4.31 (m, 1 H), 3.95 (m, 1 H), 3.93 (dd, 1 H, $J$ = 10.4, 3.6 Hz), 3.79 – 3.85 (m, 1 H), 3.64 – 3.72 (m, 2 H), 3.52 – 3.57 (m, 2 H), 3.33 (t, 1 H, $J$ = 9.2 Hz), 2.02 (s, 3 H); $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 173.0, 98.5, 73.1, 72.5, 70.9, 62.0, 61.4, 57.9, 53.9, 21.7; NI ESI-MS $m/z$ 376 M$^-$.
Compound 2-2-26. A solution of 150.0 mg (0.312 mmol) of benzyloxyethyl-β-D-glucopyranoside 2-2-25 in 3 mL of ethanol was treated with a small scoop of 10% palladium on activated carbon. The reaction mixture was flushed with hydrogen for 10 minutes and then allowed to stir under hydrogen for 3 h at room temperature before it was filtered through celite, concentrated, and chromatographed on silica with 1:19 methanol / dichloromethane as the eluant to give 97.5 mg (80%) of the hydroxyethyl-β-D-glucopyranoside 2-2-26 as a colorless oil: $R_f$ 0.15 (1:19 methanol/dichloromethane); $^1$H NMR (500 MHz, CDCl$_3$) δ 6.08 (d, 1 H, $J$ = 9.0 Hz), 5.24 (t, 1 H, $J$ = 10.0 Hz), 5.04 (t, 1 H, $J$ = 10.0 Hz), 4.70 (d, 1 H, $J$ = 8.5 Hz), 4.21 (dd, 1 H, $J$ = 12.0, 5.5 Hz), 4.15 (dd, 1 H, $J$ = 12.0, 2.0 Hz), 3.92 (dt, 1 H, $J$ = 10.5, 8.5 Hz), 3.85 – 3.88 (m, 1 H), 3.70 – 3.79 (m, 4 H), 3.01 (br s, 1 H), 2.08 (s, 3 H), 2.03 (s, 3 H), 2.02 (s, 3 H), 1.95 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 171.2, 171.1, 170.9, 169.6, 101.8, 72.6, 72.6, 72.1, 68.8, 62.4, 62.1, 54.9, 23.6, 20.9, 20.9, 20.8; ESI-MS m/z 414 MNa$^+$.
Compound 2-2-27. A mixture of Hydroxyethyl-β-D-glucopyranoside 2-2-26 (69.5 mg, 0.178 mmol), triphenylphosphine (69.9 mg, 0.267 mmol), imidazole (36.3 mg, 0.533 mmol), and iodine (63.2 mg, 0.249 mmol) in 3 mL of tetrahydrofuran was vigorously stirred for 3 h at room temperature and then concentrated and chromatographed on silica with 3:2 dichloromethane / ethyl acetate as the eluant to give 71.0 mg (80%) of the iodide 2-2-27 as a colorless oil: \( R_f 0.35 \) (1:1 dichloromethane/ethyl acetate); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 5.29 (dd, 1 H, \( J = 10.4, 9.2 \) Hz), 4.97 (t, 1 H, \( J = 9.2 \) Hz), 4.76 (d, 1 H, \( J = 8.4 \) Hz), 4.18 (dd, 1 H, \( J = 12.4, 4.8 \) Hz), 4.04 (dd, 1 H, \( J = 12.4, 2.4 \) Hz), 3.94 (ddd, 1 H, \( J = 11.2, 7.6, 6.0 \) Hz), 3.81 (dt, 1 H, \( J = 10.4, 8.4 \) Hz), 3.72 (dt, 1 H, \( J = 11.2, 7.2 \) Hz), 3.59 (ddd, 1 H, \( J = 10.4, 5.2, 2.8 \) Hz), 3.13 – 3.22 (m, 2 H), 2.01 (s, 3 H), 1.94 (s, 3 H), 1.94 (s, 3 H), 1.86 (s, 3 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 171.0, 170.8, 170.7, 169.6, 100.8, 72.7, 71.9, 70.5, 69.1, 62.4, 54.5, 23.6, 21.0, 20.9, 20.9, 2.9; ESI-MS \( m/z \) 524 MNa\(^{+}\).
**Compound 2-2-28.** A solution of (2-phenyl)-selenoacetic acid [prepared by refluxing a 2 mL toluene solution of 38.0 mg (0.280 mmol) of phenylacetic acid and 45.0 mg (0.0847 mmol) of Woollins’s reagent for 1 h] was added by cannula to a stirred solution of 70.0 mg (0.140 mmol) of iodide 2-2-27 in 2 mL of DMF, followed by 49 µL (0.28 mmol) of diisopropylethylamine. After 2 h of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 3:2 dichloromethane / ethyl acetate as the eluant to give 66.9 mg (84%) of the selenoester 2-2-28 as a colorless oil: $R_f$ 0.39 (3:2 dichloromethane/ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.22 – 7.35 (m, 5 H), 5.91 (d, 1 H, $J$ = 9.0 Hz), 5.24 (dd, 1 H, $J$ = 10.5, 9.0 Hz), 5.02 (t, 1 H, $J$ = 9.5 Hz), 4.63 (d, 1 H, $J$ = 8.0 Hz), 4.22 (dd, 1 H, $J$ = 12.0, 5.0 Hz), 4.09 (dd, 1 H, $J$ = 12.0, 2.5 Hz), 4.01 (ddd, 1 H, $J$ = 10.5, 7.0, 6.0 Hz), 3.82 (s, 2 H), 3.81 (partially obscured dt, 1 H, $J$ = 10.5, 8.5 Hz), 3.59 – 3.65 (m, 2 H), 2.95 – 3.09 (m, 2 H), 2.05 (s, 3 H), 2.00 (s, 3 H), 2.00 (s, 3 H), 1.87 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 200.1, 171.1, 170.9, 170.4, 169.6, 133.0, 130.2, 129.0, 128.1, 101.0, 72.5, 72.1, 69.3, 68.8, 62.3, 54.9, 54.3, 25.3, 23.6, 20.9, 20.9, 20.8; ESI-MS $m/z$ 596 MNa$^+$. 
**Compound 2-2-29.** Dimethyldioxirane was added to a stirred solution of 13.2 mg (0.0231 mmol) of selenoester 2-2-28 in 1 mL of dichloromethane until all of 2-2-28 was consumed according to TLC analysis (total ~ 538 µL of a 0.090 M titrated solution of DMDO in moist acetone, ~ 2.1 equiv). The reaction mixture was concentrated and then chromatographed on silica with 9:1 dichloromethane/methanol as the eluant to give 9.7 mg (87%) of the seleninic acid 2-2-29 as a colorless oil: $R_f$ 0.14 (9:1 dichloromethane/methanol); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.90 (d, 1 H, $J =$ 9.2 Hz), 5.18 (dd, 1 H, $J =$ 10.4, 9.6 Hz), 5.05 (t, 1 H, $J =$ 9.6 Hz), 4.76 (br s, 1 H), 4.67 (d, 1 H, $J =$ 8.4 Hz), 4.39 (dt, 1 H, $J =$ 10.4, 4.4 Hz), 4.25 (dd, 1 H, $J =$ 12.4, 4.4 Hz), 4.14 (dd, 1 H, $J =$ 12.4, 2.4 Hz), 4.00 – 4.11 (m, 2 H), 3.74 (ddd, 1 H, $J =$ 10.0, 4.4, 2.4 Hz), 3.41 (ddd, 1 H, $J =$ 12.8, 10.4, 4.8 Hz), 3.18 (dt, 1 H, $J =$ 12.8, 4.0 Hz), 2.08 (s, 3 H), 2.01 (s, 3 H), 2.01 (s, 3 H), 1.97 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.4, 171.2, 171.0, 169.6, 101.4, 72.7, 72.2, 68.7, 63.8, 62.1, 56.3, 54.0, 23.5, 21.0, 20.9, 20.8; NI ESI-MS m/z 486 M$^+$. 
**Compound 2-2-30.** A solution of 9.7 mg (0.020 mmol) of seleninic acid 2-2-29 in 1 mL of methanol was treated with 6 µL of 18.8% methanolic sodium methoxide solution. After 30 min of stirring at room temperature, the reaction was concentrated to give 7.6 mg (100%) of seleninate 2-2-30 as a colorless oil: \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta\) 4.41 (d, 1 H, \(J = 8.8\) Hz), 4.25 (ddd, 1 H, \(J = 11.2, 6.0, 4.8\) Hz), 3.94 (ddd, 1 H, \(J = 11.2, 8.8, 4.4\) Hz), 3.85 (dd, 1 H, \(J = 12.0, 2.0\) Hz), 3.67 (dd, 1 H, \(J = 12.0, 5.2\) Hz), 3.65 (dd, 1 H, \(J = 10.0, 8.4\) Hz), 3.39 (dd, 1 H, \(J = 10.0, 8.8\) Hz), 3.26 – 3.33 (partially obscured m, 2 H), 2.81 (ddd, 1 H, \(J = 12.4, 8.4, 4.8\) Hz), 2.65 (ddd, 1 H, \(J = 12.4, 6.0, 4.4\) Hz), 1.97 (s, 3 H); \(^{13}\)C NMR (125 MHz, CD\(_3\)OD) \(\delta\) 172.7, 101.5, 77.0, 75.3, 71.0, 64.1, 61.6, 58.7, 56.0, 21.9; N\(_I\) ESI-MS \(m/z\) 360 M\(^+\).
Compound 2-2-31. Excess dimethyldioxirane was added to a stirred solution of 19.5 mg (0.0341 mmol) of selenoester 2-2-28 in 1 mL of dichloromethane. After all of 2-2-28, as well as the corresponding intermediate 2-2-29, were consumed according to TLC analysis, the reaction mixture was concentrated and then immediately chromatographed on silica with 44:2:1 dichloromethane / methanol / triethylamine as the eluant to give 16.9 mg (82%) of the selenonate 2-2-31 as a colorless oil: \( R_f \) 0.17 (44:2:1 dichloromethane/methanol/triethylamine); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.51 (d, 1 H, \( J = 8.0 \) Hz), 5.08 (m, 2 H), 4.93 (d, 1 H, \( J = 8.8 \) Hz), 4.26 – 4.37 (m, 2 H), 4.23 (dd, 1 H, \( J = 12.4, 4.4 \) Hz), 4.07 (dd, 1 H, \( J = 12.4, 2.4 \) Hz), 4.00 – 4.05 (m, 1 H), 3.71 (ddd, 1 H, \( J = 9.6, 4.8, 2.4 \) Hz), 3.52 (ddd, 1 H, \( J = 13.2, 9.6, 4.8 \) Hz), 3.37 (dt, \( J = 13.2, 3.6 \) Hz), 3.12 (q, 6 H, \( J = 7.2 \) Hz), 2.06 (s, 3 H), 1.97 (s, 3 H), 1.97 (s, 3 H), 1.95 (s, 3 H), 1.35 (t, 9 H, \( J = 7.2 \) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 171.6, 171.0, 170.9, 169.6, 101.5, 74.2, 72.2, 68.7, 64.2, 62.3, 58.9, 53.9, 46.2, 23.4, 21.0, 21.0, 20.9, 9.0; NI ESI-MS \( m/z \) 502 M\(^+\).
**Compound 2-2-35.** A solution of (2-phenyl)-selenoacetic acid [prepared by heating a 2 mL toluene solution of 108 mg (0.790 mmol) of phenylacetic acid and 140 mg (0.263 mmol) of Woollins’s reagent at reflux for 1 h] was added by cannula to a stirred solution of 173 mg (0.395 mmol) of 2,3-di-O-acetyl-5-deoxy-5-iodo-uridine 2-2-23 in 2 mL of DMF, followed by 138 µL (0.790 mmol) of diisopropylethylamine. After 2 h of stirring at room temperature, the reaction mixture was concentrated and then chromatographed on silica with 3:2 dichloromethane / ethyl acetate as the eluant to give 164 mg (82%) of the selenoester 2-2-35 as a colorless oil: $R_f$ 0.36 (3:2 dicloromethane/ethyl acetate); $^{1}H$ NMR (500 MHz, CDCl$_3$) $\delta$ 9.2 (br s, 1 H), 7.27–7.38 (m, 5 H), 7.23 (d, 1 H, $J$ = 8.0 Hz), 5.95 (d, 1 H, $J$ = 5.0 Hz), 5.71 (dd, 1 H, $J$ = 8.0, 2.0 Hz), 5.28 (t, 1 H, $J$ = 6.0 Hz), 5.07 (t, 1 H, $J$ = 6.0 Hz), 4.29 (q, 1 H, $J$ = 5.0 Hz), 3.87 and 3.91 (AB q, 2 H $J$ = 15.5 Hz), 3.25 (d, 2 H, $J$ = 5.0 Hz), 2.10 (s, 3 H), 2.08 (s, 3 H); $^{13}C$ NMR (125 MHz, CDCl$_3$) $\delta$ 199.2, 169.8, 169.8, 163.0, 150.4, 140.0, 132.6, 130.3, 129.1, 128.3, 103.6, 87.6, 80.5, 73.0, 72.3, 54.1, 27.2, 20.7, 20.6; ESI-MS $m/z$ 533 MNa$^+$. 
**Compound 2-2-36.** A solution of (2-phenyl)-selenoacetic acid [prepared by heating a 2 mL toluene solution of 86.0 mg (0.632 mmol) of phenylacetic acid and 112 mg (0.211 mmol) of Woollins’s reagent at reflux for 1 h] was added by cannula to a stirred solution of 120 mg (0.316 mmol) of 3-O-acetyl-2,5-dideoxy-5-iodo-uridine 2-2-34 in 2 mL of DMF, followed by 110 µL (0.632 mmol) of diisopropylethylamine. After 2 h of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 3:2 dichloromethane / ethyl acetate as the eluant to give 120 mg (84%) of the selenoester 2-2-36 as a colorless oil: \( R_f \) 0.40 (3:2 dichloromethane/ethyl acetate); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.8 (br s, 1 H), 7.28–7.39 (m, 5 H), 6.21 (dd, 1 H, \( J = 8.5, 6.0 \) Hz), 5.69 (dd, 1 H, \( J = 8.5, 2.0 \) Hz), 4.98 (dt, 1 H, \( J = 6.0, 2.5 \) Hz), 4.23 (dt, 1 H, \( J = 5.5, 2.5 \) Hz), 3.89 (s, 2 H), 3.23 (d, 2 H, \( J = 5.5 \) Hz), 2.41 (ddd, 1 H, \( J = 14.5, 6.0, 2.5 \) Hz), 2.14 (partially obscured ddd, 1 H, \( J = 14.5, 8.0, 6.5 \) Hz), 2.10 (s, 3 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 199.3, 170.5, 162.9, 150.3, 139.4, 132.6, 130.2, 129.1, 128.3, 103.2, 84.8, 83.1, 75.9, 54.2, 37.7, 27.8, 21.1; ESI-MS \( m/z \) 475 MNa\(^+\).
Compound 2-2-37. A solution of dimethyldioxirane was added to a stirred solution of 90.4 mg (0.178 mmol) of selenoester 2-2-35 in 2 mL of dichloromethane until all of 2-2-35 was consumed according to TLC analysis (total ~ 4.4 mL of a 0.090 M titrated solution of DMDO in moist acetone, ~ 2.2 equiv). The seleninic ester 2-2-37 precipitated out of solution as it was formed to give, after filtration and drying, 66.1 mg (92%) of a white solid: R<sub>f</sub> 0.32 (7:3 dichloromethane/methanol); <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.66 (d, 1 H, J = 8.0 Hz), 7.64 (d, 1 H, J = 8.0 Hz), 5.80 (d, 1 H, J = 4.5 Hz), 5.75 (d, 1 H, J = 4.0 Hz), 5.71 (d, 1 H, J = 8.5 Hz), 5.71 (d, 1 H, J = 7.5 Hz), 5.65 (t, 1 H, J = 6.5 Hz), 5.64 (t, 1 H, J = 6.5 Hz), 5.49 (t, 1 H, J = 6.0 Hz), 5.45 (t, 1 H, J = 6.0 Hz), 4.59 (q, 1 H, J = 5.0 Hz), 4.57 (q, 1 H, J = 5.0 Hz), 3.59 (dd, 1 H, J = 12.0, 8.5 Hz), 3.42 (dd, 1 H, J = 12.0, 5.0 Hz), 3.41 (dd, 1 H, J = 12.5, 8.0 Hz), 3.26 (dd, 1 H, J = 12.5, 4.5 Hz), 2.11 (s, 3 H), 2.11 (s, 3 H), 2.09 (s, 3 H), 2.09 (s, 3 H); <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>OD) δ 170.2, 170.2, 164.7, 164.7, 150.7, 150.7, 143.4, 143.1, 102.1, 101.0, 92.1, 91.5, 76.7, 76.6, 73.1, 72.9, 72.6, 72.5, 58.0, 57.7, 19.2, 19.1, 19.1, 19.1; ESI-MS (in methanol solution) m/z 461 as seleninate methyl ester · Na<sup>+</sup>.
**Compound 2-2-38.** A solution of dimethylidioxirane was added to a stirred solution of 26.8 mg (0.0594 mmol) of selenoester 2-2-36 in 1 mL of dichloromethane until all of 2-2-36 was consumed according to TLC analysis (total ~ 1.5 mL of a 0.090 M titrated solution of DMDO in moist acetone, ~ 2.2 equiv). The seleninic ester 2-3-38 precipitated out of solution as it was formed to give, after filtration and drying, 19.3 mg (94%) of a white solid: \( R_f 0.18 \) (8:2 dichloromethane/methanol); \(^1^H\) NMR (500 MHz, CD\(_3\)OD) \( \delta \) 7.73 (d, 1 H, \( J = 8.5 \) Hz), 7.70 (d, 1 H, \( J = 8.5 \) Hz), 6.14 (app q, 2 H, \( J = 8.0 \) Hz), 5.73 (d, 2 H, \( J = 8.0 \) Hz), 5.28 (dt, 1 H, \( J = 6.5, 3.0 \) Hz), 5.25 (dt, 1 H, \( J = 6.5, 2.5 \) Hz), 4.47–4.52 (m, 2 H), 3.60 (dd, 1 H, \( J = 12.5, 9.5 \) Hz), 3.46 (dd, 1 H, \( J = 12.5, 5.0 \) Hz), 3.40 (dd, 1 H, \( J = 12.5, 9.0 \) Hz), 3.27 (dd, 1 H, \( J = 12.5, 5.0 \) Hz), 2.59–2.67 (m, 2 H), 2.42–2.47 (m, 2 H), 2.10 (s, 3 H); \(^{13}\)C NMR (125 MHz, CD\(_3\)OD) \( \delta \) 171.1, 171.0, 164.8, 164.8, 150.8, 150.8, 142.1, 142.0, 102.0, 102.0, 87.5, 87.3, 79.4, 79.3, 77.1, 76.9, 59.0, 58.8, 35.3, 35.2, 19.5; ESI-MS (in methanol solution) \( m/z \) 403 as seleninate methyl ester · Na\(^+\).
Compound 20. A solution of 19.2 mg (0.0474 mmol) of seleninic ester 2-2-37 in 1 mL of methanol was treated with 14 µL of 18.8% methanolic sodium methoxide solution. After 3 h of stirring at room temperature, the reaction was concentrated to give 17.1 mg (100%) of seleninate 2-2-39 as a colorless oil: $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 7.49 (d, 1 H, $J = 7.5$ Hz), 5.85 (d, 1 H, $J = 3.5$ Hz), 5.69 (d, 1 H, $J = 8.0$ Hz), 4.38 (dt, 1 H, $J = 7.5$, 6.5 Hz), 4.17 (dd, 1 H, $J = 5.5$, 3.5 Hz), 4.03 (dd, 1 H, $J = 6.5$, 5.5 Hz), 3.05 (dd, 1 H, $J = 12.0$, 7.5 Hz), 2.83 (dd, 1 H, $J = 12.0$, 5.5 Hz); $^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$ 175.4, 158.4, 139.8, 102.3, 91.9, 78.3, 74.5, 73.9, 60.5; NI ESI-MS $m/z$ 339 M$^-$. 
**Compound 2-2-40.** A solution of 9.7 mg (0.028 mmol) of seleninic ester 2-2-38 in 1 mL of methanol was treated with 8 µL of 18.8% methanolic sodium methoxide solution. After 3 h of stirring at room temperature, the reaction was concentrated to give 9.6 mg (100%) of seleninate 2-2-40 as a colorless oil: $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 7.53 (d, 1 H, $J = 7.5$ Hz), 6.30 (t, 1 H, $J = 6.5$ Hz), 5.70 (d, 1 H, $J = 7.5$ Hz), 4.22–4.29 (m, 2 H), 3.00 (dd, 1 H, $J = 12.0$, 8.0 Hz), 2.81 (dd, 1 H, $J = 12.0$, 5.5 Hz), 2.30 (ddd, 1 H, $J = 13.5$, 6.5, 5.0 Hz), 2.22 (dt, 1 H, $J = 13.5$, 7.0 Hz); $^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$ 176.6, 159.3, 139.1, 102.6, 85.5, 81.2, 74.2, 61.1, 39.3; NI ESI-MS $m/z$ 323 M$^-$. 
**Compound 2-2-41.** A solution of 5.6 mg (0.016 mmol) of seleninate 2-2-39 in 1 mL of methanol was treated at 0 °C with 0.076 mL of a 0.21 M titrated solution of DMDO in chloroform. The reaction was allowed to warm up to room temperature over a period of 30 min, and then was concentrated to give 5.9 mg (100 %) of selenonate 2-2-41 as a hygroscopic white solid: $^1$H NMR (500 MHz, CD$_3$OD) δ 7.73 (d, 1 H, $J = 8.0$ Hz), 5.86 (d, 1 H, $J = 4.0$ Hz), 5.70 (d, 1 H, $J = 7.5$ Hz), 4.48 (dt, 1 H, $J = 6.5$, 5.0 Hz), 4.30 (app pent, 2 H, $J = 5.5$ Hz), 3.71 (dd, 1 H, $J = 13.0$, 5.5 Hz), 3.68 (dd, 1 H, $J = 13.0$, 6.5 Hz); $^{13}$C NMR (100 MHz, CD$_3$OD) δ 170.8, 155.3, 141.3, 102.1, 91.3, 78.6, 73.5, 72.8, 59.6; NI ESI-MS m/z 355 M$^-$.
Compound 2-2-42. A solution of 9.0 mg (0.026 mmol) of seleninate 2-2-40 in 1 mL of methanol was treated at 0 °C with 0.13 mL of 0.21 M titrated solution of DMDO in chloroform. The reaction was allowed to warm up to room temperature over a period of 30 min, and then was concentrated to give 9.4 mg (100%) of selenonate 2-2-42 as a hygroscopic white solid: $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 7.77 (d, 1 H, $J$ = 7.5 Hz), 6.29 (t, 1 H, $J$ = 6.5 Hz), 5.70 (d, 1 H, $J$ = 7.5 Hz), 4.52 (dt, 1 H, $J$ = 6.5, 3.5 Hz), 4.40 (dt, 1 H, $J$ = 6.5, 3.5 Hz), 3.66 (dd, 1 H, $J$ = 13.0, 6.0 Hz), 3.63 (dd, 1 H, $J$ = 13.0, 7.0 Hz), 2.33 (ddd, 1 H, $J$ = 13.0, 6.0, 4.0 Hz), 2.28 (dt, 1 H, $J$ = 13.5, 6.5 Hz); $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 175.2, 158.2, 139.9, 102.3, 86.3, 81.1, 73.7, 59.8, 38.9; NI ESI-MS m/z 339 M$^-$.
**Compound 2-2-44.** A solution of 90.1 mg (0.354 mmol) of 4-iodobutane-1,2-diol 1,2-acetonide 2-2-43 in 3 mL of dichloromethane was treated at 0 °C with 1 mL of 1:1 butyryl chloride / butyric acid and a catalytic amount of sulfuric acid. The reaction was allowed to warm up to room temperature, and then stir for an additional 24 h before it was washed with sodium bicarbonate, dried over sodium sulfite, concentrated and chromatographed on silica with 9:1 hexane / ethyl acetate to give 76.7 mg (61%) of 4-iodobutane-1,2-diol O,O-dibutanoate 2-2-44 as a colorless oil: $R_f$ 0.31 (9:1 hexane/ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.14 (dq, 1 H, $J$ = 9.0, 4.0 Hz), 4.70 (dd, 1 H, $J$ = 12.0, 3.5 Hz), 4.06 (dd, 1 H, $J$ = 12.0, 6.0 Hz), 3.09–3.20 (m, 2 H), 2.30 (t, 2 H, $J$ = 7.5 Hz), 2.30 (t, 2 H, $J$ = 7.5 Hz), 2.09 – 2.24 (m, 2 H), 1.65 (app sept, 4 H, $J$ = 7.5 Hz), 0.96 (t, 3 H, $J$ = 7.5 Hz), 0.95 (t, 3 H, $J$ = 7.5 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 173.5, 173.2, 71.6, 64.2, 36.4, 36.2, 35.2, 18.7, 18.6, 13.9, 13.9, 0.51; ESI-MS $m/z$ 379 MNa$^+$. 

![Chemical structure of 2-2-43 and 2-2-44]
Compound 2-2-45. A solution of (2-phenyl)-selenoacetic acid [prepared by heating a 2 mL toluene solution of 18.8 mg (0.138 mmol) of phenylacetic acid and 24.5 mg (0.0461 mmol) of Woollins’s reagent at reflux for 1 h] was added by cannula to a stirred solution of 16.4 mg (0.0461 mmol) of 4-iodobutane-1,2-diol O,O-dibutanoate 2-2-44 in 1 mL of DMF, followed by 24 µL (0.046 mmol) of diisopropylethylamine. After 2 h of stirring at room temperature, the reaction mixture was concentrated and then chromatographed on silica with 4:1 hexane / ethyl acetate as the eluant to give 18.8 mg (95%) of the selenoester 2-2-45 as a colorless oil: $R_f$ 0.41 (4:1 hexane/ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.27–7.37 (m, 5 H), 5.10 (m, 1 H), 4.30 (dd, 1 H, $J = 11.5, 3.5$ Hz), 4.04 (dd, 1 H, $J = 12.0, 6.0$ Hz), 3.84 (s, 2 H), 2.79–2.92 (m, 2 H), 2.29 (app q, 4 H, $J = 7.5$ Hz), 1.96–2.03 (m, 1 H), 1.85–1.92 (m, 1 H), 1.64 (app sept, 4 H, $J = 7.5$ Hz), 0.95 (t, 3 H, $J = 7.5$ Hz), 0.94 (t, 3 H, $J = 7.5$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 200.2, 173.5, 173.3, 133.0, 130.2, 129.0, 128.0, 71.0, 64.7, 54.4, 36.5, 36.2, 31.9, 21.2, 18.7, 18.6, 13.9, 13.9; ESI-MS $m/z$ 451 MNa$^+$. 
Compound 2-2-46. A solution of dimethyldioxirane was added to a stirred solution of 10.5 mg (0.0246 mmol) of selenoester 2-2-45 in 1 mL of dichloromethane until all of 2-2-45 was consumed according to TLC analysis (total ~ 0.60 mL of a 0.090 M titrated solution of DMDO in moist acetone, ~ 2.2 equiv). The reaction mixture was concentrated and then chromatographed on silica with 9:9:2 hexane / dichloromethane / methanol as the eluant to give 7.7 mg (92%) of the seleninic acid 2-2-46 as a colorless oil: $R_f$ 0.17 (9:9:2 hexane/dichloromethane/methanol); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.92 (br s, 1 H), 5.19 (dq, 1 H, $J$ = 8.5, 4.5 Hz), 4.30 (dd, 1 H, $J$ = 12.0, 4.0 Hz), 4.09 (dd, 1 H, $J$ = 12.0, 6.0 Hz), 3.08–3.18 (m, 2 H), 2.31 (app q, 4 H, $J$ = 7.5 Hz), 2.17–2.30 (m, 2 H), 1.66 (app sept, 4 H, $J$ = 7.0 Hz), 0.96 (t, 3 H, $J$ = 7.5 Hz), 0.95 (t, 3 H, $J$ = 7.5 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 173.4, 173.2, 70.5, 64.3, 52.3, 36.4, 36.1, 23.8, 18.6, 18.5, 13.9, 13.8; ESI-MS (in methanol solution) $m/z$ 379 as seleninate methyl ester · Na$^+$. 
Compound 2-2-47. A solution of excess dimethyldioxirane in chloroform was added to a stirred solution of 10.1 mg (0.0236 mmol) of selenoester 2-2-45 in 1 mL of dichloromethane. After all of 2-2-45, as well as the corresponding seleninate intermediate 2-2-46, was consumed according to TLC analysis, the reaction mixture was concentrated and then chromatographed on silica with 22:22:5:1 hexane / dichloromethane / methanol / triethylamine as the eluant to give 8.6 mg (80%) of the selenonate 2-2-47 as a colorless oil: $R_f$ 0.13 (22:22:5:1 hexane/dichloromethane/methanol/triethylamine); $^1$H NMR (500 MHz, CDCl$_3$) δ 5.25 (dq, 1 H, $J = 9.5$, 4.5 Hz), 4.31 (dd, 1 H, $J = 12.0$, 4.0 Hz), 4.07 (dd, 1 H, $J = 12.0$, 5.5 Hz), 3.31–3.40 (m, 2 H), 3.15 (q, 6 H, $J = 7.0$ Hz), 2.31–2.39 (m, 2 H), 2.30 (t, 2 H, $J = 7.5$ Hz), 2.29 (t, 2 H, $J = 7.5$ Hz), 1.64 (app sext, 2 H, $J = 7.5$ Hz), 1.64 (app sext, 2 H, $J = 7.5$ Hz), 1.37 (t, 9 H, $J = 7.0$ Hz), 0.95 (t, 3 H, $J = 7.5$ Hz), 0.94 (t, 3 H, $J = 7.5$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 173.4, 173.2, 69.9, 64.5, 54.3, 46.2, 36.3, 36.2, 25.4, 18.6, 18.6, 13.9, 13.9, 8.9; NI ESI-MS m/z 357 M$^-$. 
Compound 2-2-49. A solution of selenobutyric acid [prepared by heating a 2 mL toluene solution of 64 µL (0.70 mmol) of butyric acid and 124 mg (0.230 mmol) of Woollins's reagent at reflux for 1 h] was added by cannula to a stirred solution of 49 µL (0.35 mmol) of commercial glycidyl butyrate 2-2-48 in 1 mL of DMF at −30 °C, followed by 122 µL (0.700 mmol) of diisopropylethylamine. The reaction mixture was allowed to warm to room temperature over a period of 1 h, and then concentrated and chromatographed on silica with 4:1 hexane / ethyl acetate as the eluant to give 76.7 mg (75%) of the selenoester 2-2-49 as a colorless oil: \( R_f \) 0.26 (4:1 hexane/ethyl acetate); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 4.15 (dd, 1 H, \( J = 11.5, 4.0 \text{ Hz} \)), 4.10 (dd, 1 H, \( J = 11.5, 6.0 \text{ Hz} \)), 4.02 (m, 1 H), 3.12 (dd, 1 H, \( J = 13.5, 5.0 \text{ Hz} \)), 3.02 (dd, 1 H, \( J = 13.5, 6.5 \text{ Hz} \)), 2.64 (t, 2 H, \( J = 7.5 \text{ Hz} \)), 2.34 (t, 2 H, \( J = 7.5 \text{ Hz} \)), 1.70 (app sext, 2 H, \( J = 7.5 \text{ Hz} \)), 1.68 (app sext, 2 H, \( J = 7.5 \text{ Hz} \)), 0.96 (app q, 6 H, \( J = 7.0 \text{ Hz} \)); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 202.1, 173.9, 69.7, 67.5, 50.1, 36.2, 28.9, 19.2, 18.6, 13.9, 13.6; ESI-MS \( m/z \) 319 MNa\(^+\).
**Compound 2-2-50.** A stirred solution of 28.0 mg (0.0949 mmol) of selenoester 2-2-49 in 1 mL of pyridine was treated at 0 °C with 20 µL (0.19 mmol) of butyryl chloride. The reaction mixture was allowed to warm to room temperature over a period of 2 h, and then was concentrated and chromatographed on silica with 9:1 hexane / ethyl acetate as the eluant to give 30.3 mg (88%) of the selenoester 2-2-50 as a colorless oil: $R_f$ 0.35 (9:1 hexane/ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.20 (dq, 1 H, $J = 6.0, 4.0$ Hz), 4.27 (dd, 1 H, $J = 12.0, 4.0$ Hz), 4.14 (dd, 1 H, $J = 11.5, 6.0$ Hz), 3.19 (dd, 1 H, $J = 13.0, 6.0$ Hz), 3.08 (dd, 1 H, $J = 13.0, 7.0$ Hz), 2.61 (t, 2 H, $J = 7.5$ Hz), 2.30 (t, 2 H, $J = 7.5$ Hz), 2.28 (t, 2 H, $J = 7.5$ Hz), 1.70 (app sext, 2 H, $J = 7.5$ Hz), 1.65 (app sext, 4 H, $J = 7.5$ Hz), 0.96 (app q, 6 H, $J = 7.0$ Hz), 0.95 (t, 3 H, $J = 7.0$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 200.4, 173.4, 172.9, 70.6, 64.4, 50.0, 36.4, 36.2, 25.3, 19.2, 18.6, 18.6, 13.9, 13.8, 13.6; ESI-MS $m/z$ 389 MNa$^+$. 
Compound 2-2-51. A solution of dimethyldioxirane was added to a stirred solution of 16.5 mg (0.0559 mmol) of selenoester 2-2-49 in 1 mL of dichloromethane until all of 2-2-49 was consumed according to TLC analysis (total ~ 1.4 mL of a 0.090 M titrated solution of DMDO in moist acetone, ~ 2.2 equiv). The reaction mixture was concentrated and then chromatographed on silica with 9:9:2 hexane / dichloromethane / methanol as the eluant to give 11.6 mg (81%) of the seleninic acid 2-2-51 as a colorless oil: \( R_f \) 0.10 (9:9:2 hexane/dichloromethane/methanol); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 5.53 (br s, 2 H), 4.60 (br s, 1 H), 4.22 (dd, 1 H, \( J = 11.0, 6.0 \) Hz), 4.15 (dd, 1 H, \( J = 11.0, 4.0 \) Hz), 3.30 (app t, 1 H, \( J = 11.0 \) Hz), 3.20 (d, 1 H, \( J = 11.0 \) Hz), 2.35 (t, 2 H, \( J = 7.0 \) Hz), 1.66 (app sext, 2 H, \( J = 7.0 \) Hz), 0.96 (t, 3 H, \( J = 7.5 \) Hz); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 173.9, 67.4, 36.2, 18.6, 13.9; ESI-MS (in methanol solution) \( m/z \) 295 as seleninate methyl ester · Na\(^+\).
**Compound 2-2-52.** Dimethyldioxirane was added to a stirred solution of 10.6 mg (0.0290 mmol) of selenoester **2-2-50** in 1 mL of dichloromethane until all of **2-2-50** was consumed according to TLC analysis (total ~ 0.71 mL of a 0.090 M titrated solution of DMDO in moist acetone, ~ 2.2 equiv). The reaction mixture was concentrated and then chromatographed on silica with 9:9:2 hexane / dichloromethane / methanol as the eluant to give 7.6 mg (80%) of the seleninic acid **2-2-52** as a colorless oil: $R_f$ 0.37 (9:9:2 hexane/dichloromethane/methanol);

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.38 (dq, $J = 8.5$, 4.0 Hz), 4.74 (br s, 1 H), 4.39 (dd, 1 H, $J = 12.0$, 4.0 Hz), 4.24 (dd, 1 H, $J = 12.0$, 5.0 Hz), 3.44 (dd, 1 H, $J = 13.0$, 4.0 Hz), 3.33 (dd, 1 H, $J = 13.5$, 8.0 Hz), 2.33 (app q, 4 H, $J = 7.5$ Hz), 1.66 (app sept, 4 H, $J = 7.5$ Hz), 0.96 (t, 3 H, $J = 7.5$ Hz), 0.95 (t, 3 H, $J = 7.5$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 173.6, 173.1, 67.4, 64.6, 58.4, 36.1, 36.1, 18.5, 18.4, 13.9, 13.8; ESI-MS (in methanol solution) $m/z$ 365 as seleninate methyl ester · Na$^+$. 
Compound 2-2-53. A solution of excess dimethyldioxirane in chloroform was added to a stirred solution of 16.9 mg (0.0573 mmol) of selenoester 2-2-49 in 1 mL of dichloromethane. After all of 2-2-49, as well as the corresponding intermediate 2-2-51, was consumed according to TLC analysis, the reaction mixture was concentrated and then chromatographed on silica with 22:22:5:1 hexane / dichloromethane / methanol / triethylamine as the eluant to give 18.1 mg (85%) of the selenonate 2-2-53 as a colorless oil: $R_f$ 0.10 (22:22:5:1 hexane/dichloromethane/methanol/triethylamine); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.68 (br s, 1 H), 4.55 (ddt, 1 H, $J$ = 10.0, 5.0, 2.0 Hz), 4.21 (dd, 1 H, $J$ = 11.0, 5.0 Hz), 4.15 (dd, 1 H, $J$ = 11.5, 5.5 Hz), 3.42 (q, 6 H, $J$ = 7.5 Hz), 3.39 (partially obscured dd, 1 H, $J$ = 12.5, 2.5 Hz), 3.32 (dd, 1 H, $J$ = 12.5, 10.0 Hz), 2.32 (t, 2 H, $J$ = 7.5 Hz), 1.65 (app sext, 2 H, $J$ = 7.5 Hz), 1.35 (t, 9 H, $J$ = 7.5 Hz), 0.94 (t, 3 H, $J$ = 7.5 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 173.6, 66.8, 65.5, 59.9, 59.2, 36.2, 18.6, 13.9, 8.6; NI ESI-MS $m/z$ 273 M$^+$. 
**Compound 2-2-54.** A solution of excess dimethyldioxirane in chloroform was added to a stirred solution of 13.8 mg (0.0378 mmol) of selenoester 2-2-50 in 1 mL of dichloromethane. After all of 2-2-50, as well as the corresponding seleninate intermediate 2-2-52, was consumed according to TLC analysis, the reaction mixture was concentrated and then chromatographed on silica with 22:22:5:1 hexane / dichloromethane / methanol / triethylamine as the eluant to give 13.4 mg (80%) of the selenonate 2-2-54 as a colorless oil: $R_f$ 0.14 (22:22:5:1 hexane/dichloromethane/methanol/triethylamine); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.67 (dq, $J = 10.0, 6.0$ Hz), 4.51 (dd, 1 H, $J = 12.0, 3.5$ Hz), 4.29 (dd, 1 H, $J = 12.0, 5.5$ Hz), 3.52 (d, 2 H, $J = 6.5$ Hz), 3.14 (q, 6 H, $J = 7.5$ Hz), 2.28–2.38 (m, 4 H), 1.65 (app sext, 2 H, $J = 7.5$ Hz), 1.64 (app sext, 2 H, $J = 7.5$ Hz), 1.37 (t, 9 H, $J = 7.5$ Hz), 0.94 (t, 3 H, $J = 7.5$ Hz), 0.94 (t, 3 H, $J = 7.5$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 173.3, 172.7, 66.5, 64.1, 57.3, 46.2, 36.3, 36.2, 18.6, 18.5, 13.9, 13.8, 8.9; ESI-MS $m/z$ 343 M$^-$. 
**Compound 2-2-56.** A solution selenopivalic acid [prepared by heating a 2 mL toluene solution of 123 mg (1.20 mmol) of trimethylacetic acid and 213 mg (0.400 mmol) of Woollins’s reagent at reflux for 1 h] was added by cannula to a stirred solution of 252 mg (0.601 mmol) of \((S)-2-N\text{-}t\text{ert-}\text{butoxycarbonylamino-}4\text{-}\text{i}

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\text{odo-}

\text{butanoic acid benzyl ester 2-2-55 in 2 mL of DMF, followed by 210 µL (1.20 mmol) of diisopropylethylamine. After 2 h of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 19:1 hexane / ethyl acetate as the eluant to give 239 mg (87%) of the selenoester 2-2-56 as a colorless oil: \(R_f\) 0.45 (17:3 hexane/ethyl acetate); \(^1\text{H NMR (500 MHz, CDCl}_3\text{)} \delta 7.32–7.36 (m, 5 H), 5.17 and 5.20 (AB q, 2 H, \(J = 12.0 \text{ Hz})), 5.14 (d, 1 H, \(J = 8.0 \text{ Hz})), 4.36–4.42 (m, 1 H), 2.78–2.88 (m, 2 H), 2.11–2.21 (m, 1 H), 1.94–2.01 (m, 1 H), 1.45 (s, 9 H), 1.21 (s, 9 H); \(^{13}\text{C NMR (125 MHz, CDCl}_3\text{)} \delta 209.6, 172.3, 155.6, 135.6, 128.8, 128.6, 128.5, 80.2, 67.4, 54.1, 49.6, 33.9, 28.5, 27.2, 20.2; ESI-MS \text{m/z 480 MNa}^+\).
Compound 2-2-57. A solution of dimethyldioxirane was added to a stirred solution of 35.3 mg (0.0774 mmol) of selenoester 2-2-56 in 1 mL of dichloromethane until all of 2-2-56 was consumed according to TLC analysis (total ~ 0.81 mL of a 0.21 M titrated solution of DMDO in chloroform, ~ 2.2 equiv). The reaction mixture was concentrated and then chromatographed on silica with 9:9:2 hexane / dichloromethane / methanol as the eluant to give 26.7 mg (89%) of the seleninamide 2-2-57 as a colorless oil: $R_f$ 0.25 (9:9:2 hexane/dichloromethane/methanol); $^1$H NMR (500 MHz, CDCl$_3$, 7:3 mixture of diasteriomers) $\delta$ 7.32–7.35 (m, 5 H), 5.12 and 5.25 (AB q, 1.4 H, $J = 12.5$ Hz), 5.12 and 5.22 (AB q, 0.6 H, $J = 12.5$ Hz), 4.84 (d, 0.7 H, $J = 5.5$ Hz), 4.70 (d, 0.3 H, $J = 6.5$ Hz), 2.65–3.29 (m, 4 H), 1.51 (s, 6.3 H), 1.34 (s, 2.7 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 171.2, 154.0, 153.8, 135.3, 135.2, 129.1, 129.0, 128.9, 128.8, 128.4, 84.0, 83.8, 67.8, 67.6, 62.6, 62.4, 51.7, 49.9, 32.5, 30.9, 28.3, 28.1; ESI-MS (in methanol solution) $m/z$ 442 as seleninate methyl ester · Na$^+$. 
Compound 2-2-58. A solution of excess dimethyldioxirane in chloroform was added to a stirred solution of 16.9 mg (0.0438 mmol) of seleninamide 2-2-57 in 1 mL of dichloromethane. After all of 2-2-57 was consumed according to TLC analysis, the reaction mixture was concentrated and then chromatographed on silica with 22:22:5:1 hexane / dichloromethane / methanol / triethylamine as the eluant to give 15.9 mg (70%) of the selenonate 2-2-58 as a colorless oil: \( R_f \) 0.13 (22:22:5:1 hexane/dichloromethane/methanol/triethylamine); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.29–7.36 (m, 5 H), 5.70 (d, 1 H, \( J = 8.0 \) Hz), 5.15 (s, 2 H), 4.42–4.45 (m, 1 H), 3.23–3.33 (m, 2 H), 3.10 (q, 6 H, \( J = 7.0 \) Hz), 2.55–2.62 (m, 1 H), 2.32–2.40 (m, 1 H), 1.41 (s, 9 H), 1.33 (s, 9 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 171.7, 155.7, 135.4, 128.8, 128.7, 128.5, 80.2, 67.6, 53.9, 53.0, 46.0, 28.5, 26.5, 8.9; NI ESI-MS \( m/z \) 420 M\(^-\).
Compound 2-2-60. A solution of 152 mg (0.578 mmol) of triphenylphosphine in 1 mL of tetrahydrofuran was stirred at –20 °C. DIAD (114 \( \mu \)L, 0.578 mmol) was added dropwise and the reaction mixture was maintained at –20 °C until the white phosphonium intermediate formed. The reaction mixture was then cooled to –50 °C, and a solution of 95.0 mg (0.289 mmol) of commercial \( N \)-(carbobenzyloxy)-L-serine benzyl ester 2-2-59 in 1 mL of tetrahydrofuran was added dropwise by syringe. After 5 min of stirring, 2 mL of a toluene solution of (2-phenyl)-selenoacetic acid [prepared by heating a 2 mL toluene solution of 118 mg (0.866 mmol) of phenylacetic acid and 153 mg (0.289 mmol) of Woollins’s reagent at reflux for 1 h] was added by cannula and the reaction mixture was allowed to warm to 23 °C, and then was stirred for 2 h. The solution was concentrated and then chromatographed on silica with 9:1 hexane / ethyl acetate as the eluant to give 127 mg (86%) of the selenoester 2-2-60 as a colorless oil: \( R_f \) 0.25 (9:1 hexane/ethyl acetate); \( ^1H \) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.23–7.35 (m, 15 H), 5.47 (d, 1 H, \( J = 7.5 \) Hz), 5.09 and 5.14 (AB q, 2 H, \( J = 12.0 \) Hz), 5.10 (s, 2 H), 4.70 (dd, 1 H, \( J = 12.5, 6.0 \) Hz), 3.80 (s, 2 H), 3.38 (dd, 1 H, \( J = 13.0, 6.0 \) Hz), 3.29 (dd, 1 H, \( J = 13.0, 6.0 \) Hz); \( ^{13}C \) NMR (125 MHz, CDCl\(_3\)) \( \delta \) 200.0, 170.5, 155.9, 136.4, 135.3, 132.7, 130.2, 129.0, 128.9, 128.8, 128.7, 128.4, 128.4, 128.1, 67.9, 67.3, 54.1, 54.0, 27.8; ESI-MS \( m/z \) 534 MNa\(^+\).
**Compound 2-2-63.** A solution of dimethylidioxirane was added to a stirred solution of 31.6 mg (0.0619 mmol) of selenoester 2-2-60 in 1 mL of dichloromethane until all of 2-2-60 was consumed according to TLC analysis (total ~ 0.65 mL of a 0.21 M titrated solution of DMDO in chloroform, ~ 2.2 equiv). Immediately, 12.7 mg (0.0681 mmol) of p-toluenesulfonylhydrazide was added and the reaction mixture was allowed to stir for 5 min before it was concentrated. Chromatography on silica with 3:2 hexane / ethyl acetate as the eluant gave 25.2 mg (75%) of the selenolsulfonate 2-2-63 as a colorless oil: $R_f$ 0.46 (3:2 hexane/ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.72 (d, 2 H, $J = 8.0$ Hz), 7.27–7.39 (m, 10 H), 7.26 (d, 2 H, $J = 8.0$ Hz), 5.66 (d, 1 H, $J = 7.0$ Hz), 5.18 (s, 2 H), 5.11 (s, 2 H), 4.81 (dd, 1 H, $J = 12.5$, 6.0 Hz), 3.70 (dd, 1 H, $J = 13.0$, 4.5 Hz), 3.62 (dd, 1 H, $J = 13.0$, 6.5 Hz), 2.41 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.9, 155.9, 145.2, 144.0, 136.2, 135.0, 130.1, 129.0, 128.9, 128.8, 128.5, 128.4, 126.9, 68.3, 67.5, 54.0, 34.9, 21.9; ESI-MS m/z 570 MNa$^+$. 
**Compound 2-2-62.** A solution of excess dimethyldioxirane in chloroform was added to a stirred solution of 23.8 mg (0.0467 mmol) of selenoester 2-2-60 in 1 mL of dichloromethane. After all of 2-2-60 was consumed according to TLC analysis, the reaction mixture was concentrated and then chromatographed on silica with 3:2 hexane / ethyl acetate as the eluant to give 11.9 mg (82%) of dehydroalanine 2-2-62 as a colorless oil: \( R_f \) 0.67 (4:1 hexane/ethyl acetate); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.26–7.39 (m, 10 H), 6.27 (s, 1 H), 5.85 (s, 1 H), 5.26 (s, 2 H), 5.17 (s, 2 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 163.8, 153.4, 136.1, 135.3, 131.3, 128.9, 128.9, 128.8, 128.6, 128.5, 128.5, 106.6, 68.0, 67.3; ESI-MS \( m/z \) 334 MNa\(^+\).
Compound 2-2-66. A solution of 125 mg (0.478 mmol) of triphenylphosphine in 1 mL of tetrahydrofuran was stirred at −20 °C. DIAD (94 µL, 0.48 mmol) was added dropwise and the reaction mixture was maintained at −20 °C until the white phosphonium intermediate formed. The reaction mixture was then cooled to −50 °C, and a solution of 50.0 mg (0.239 mmol) of N-(carbobenzyloxy)-L-alaninol benzyl ester 2-2-64 in 1 mL of tetrahydrofuran was added dropwise by syringe. After 5 min of stirring, 2 mL of a toluene solution of (2-phenyl)-selenoacetic acid [prepared by heating a 2 mL toluene solution of 97.6 mg (0.717 mmol) of phenylacetic acid and 127 mg (0.239 mmol) of Woollins’s reagent at reflux for 1 h] was added by cannula, and the reaction mixture was allowed to warm to 23 °C, and then was stirred for 2 h. The solution was concentrated and chromatographed on silica with 4:1 hexane/ethyl acetate as the eluant to give 70.6 mg (76%) of the selenoester 2-2-66 as a colorless oil: \( R_f \) 0.25 (4:1 hexane/ethyl acetate); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.26–7.38 (m, 5 H), 5.06 and 5.09 (AB q, 2 H, \( J = 12.0 \) Hz), 4.75 (br s, 1 H), 3.96 (br s, 1 H), 3.85 (s, 2 H), 3.09 (dd, 1 H, \( J = 13.0, 5.0 \) Hz), 3.01 (dd, 1 H, \( J = 13.0, 6.0 \) Hz), 1.17 (d, 3 H, \( J = 7.0 \) Hz); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 200.3, 155.8, 136.8, 133.0, 130.2, 129.0, 128.7, 128.3, 128.0, 66.8, 54.3, 47.4, 32.5, 21.1; ESI-MS m/z 414 MNa\(^+\).
**Compound 2-2-66.** A solution of (2-phenyl)-selenoacetic acid [prepared by heating a 2 mL toluene solution of 42.8 mg (0.314 mmol) of phenylacetic acid and 55.7 mg (0.105 mmol) of Woollins’s reagent at reflux for 1 h] was added by cannula to a stirred solution of 50.0 mg (0.157 mmol) of (S)-2-benzyloxy carbonylamino-1-iodopropane 2-2-65 in 1 mL of DMF, followed by 55 µL (0.314 mmol) of diisopropylethylamine. After 2 h of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 4:1 hexane / ethyl acetate as the eluant to give 58.3 mg (95%) of the selenoester 2-2-66 as a colorless oil.
Compound 2-2-67. A solution of dimethyldioxirane was added to a stirred solution of 9.2 mg (0.0236 mmol) of selenoester 2-2-66 in 1 mL of dichloromethane until all of 2-2-66 was consumed according to TLC analysis (total ~ 0.25 mL of a 0.21 M titrated solution of DMDO in chloroform, ~ 2.2 equiv). The reaction mixture was concentrated and then chromatographed on silica with 9:9:2 hexane / dichloromethane / methanol as the eluant to give 6.0 mg (83%) of the seleninic acid 2-2-67 as a colorless oil: $R_f$ 0.15 (9:9:2 hexane/dichloromethane/methanol); $^1$H NMR (500 MHz, CDCl₃) $\delta$ 7.26–7.37 (m, 5 H), 5.40 (br s, 1 H), 5.18 (br s, 1 H), 5.08 and 5.12 (AB q, 2 H, $J$ = 12.0 Hz), 4.24 (m, 1 H), 3.29 (dd, 1 H, $J$ = 12.0, 2.5 Hz), 3.24 (dd, 1 H, $J$ = 12.5, 9.5 Hz), 1.35 (d, 3 H, $J$ = 7.0 Hz); $^{13}$C NMR (125 MHz, CDCl₃) $\delta$ 156.5, 136.2, 128.8, 128.6, 128.5, 67.5, 64.1, 43.5, 21.7; NI ESI-MS $m/z$ 304 M⁻.
**Compound 2-2-68.** A solution of excess dimethyldioxirane in chloroform was added to a stirred solution of 20.0 mg (0.0658 mmol) of selenoester 2-2-66 in 1 mL of dichloromethane. After all of 2-2-66, as well as the corresponding seleninate intermediate 2-2-67, was consumed according to TLC analysis, the reaction mixture was concentrated and then chromatographed on silica with 22:22:5:1 hexane / dichloromethane / methanol / triethylamine as the eluant to give 20.3 mg (73%) of the selenonate 2-2-68 as a colorless oil: $R_f$ 0.15 (22:22:5:1 hexane/dichloromethane/methanol/triethylamine); $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 7.27–7.35 (m, 5 H), 5.07 (s, 2 H), 4.32 (m, 1 H), 3.55 (dd, 1 H, $J = 12.0$, 4.5 Hz), 3.36 (dd, 1 H, $J = 12.0$, 7.0 Hz), 3.21 (q, 6 H, $J = 7.5$ Hz), 1.43 (d, 3 H, $J = 7.0$ Hz), 1.31 (t, 9 H, $J = 7.5$ Hz); $^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$ 156.4, 137.1, 128.3, 127.8, 127.7, 66.3, 62.5, 46.7, 43.6, 19.4, 8.0; NI ESI-MS $m/z$ 320 M$^-$.
**Compound 2-2-69.** Neat commercial *N-(tert-butoxycarbonyl)-L-cysteine methyl ester* (97%, d = 1.143 g/mL, 5.1 µL, 0.024 mmol) was added by micropipette over a 10 sec period to a stirred solution of 10.0 mg (0.024 mmol) of seleninic acid 2-2-3 in 1 mL of moist dichloromethane. After 1 min of stirring at room temperature, TLC analysis indicated that 2-2-3 was consumed. The reaction mixture was concentrated and then chromatographed on silica with 3:2 hexane / ethyl acetate as the eluant to give 10.1 mg (81%) of the selenylsulfide 2-2-69 as a colorless oil: *R*, 0.30 (3:2 hexane/ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) δ 5.47 (t, 1 H, J = 10.0 Hz), 5.32 (d, 1 H, J = 7.5 Hz), 4.92 (t, 1 H, J = 10.0 Hz), 4.91 (d, 1 H, J = 3.5 Hz), 4.87 (dd, 1 H, J = 10.0, 3.5 Hz), 4.57 (m, 1 H), 4.04 (ddd, 1 H, J = 10.0, 6.5, 5.0 Hz), 3.78 (s, 3 H), 3.43 (s, 3 H), 3.33 (dd, 1 H, J = 14.0, 4.5 Hz), 3.22 (dd, 1 H, J = 14.0, 5.5 Hz), 3.09 (d, 1 H, J = 8.0 Hz), 3.05 (dd, 1 H, J = 13.0, 2.5 Hz), 2.07 (s, 3 H), 2.07 (s, 3 H), 2.01 (s, 3 H), 1.45 (s, 9 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 171.4, 170.4, 170.3, 170.1, 155.2, 96.9, 80.5, 72.5, 71.2, 70.1, 68.4, 55.8, 53.9, 52.8, 40.8, 34.9, 28.5, 21.0, 20.9, 20.9; ESI-MS *m/z* 640 MNa$^+$. Similar results were obtained upon running the reaction in water, methanol, acetonitrile, isopropanol, or tetrahydrofuran solutions.
Compound 2-2-70. *N*-benzoyl-L-tyrosine ethyl ester (15.7 mg, 0.0501 mmol) was added to a solution of 20.8 mg (0.0501 mmol) of seleninic acid 2-2-3 in 1 mL of moist dichloromethane. After 24 h of stirring at 37 °C, the reaction mixture was concentrated and then chromatographed on silica with 7:7:6 hexane/dichloromethane/ethyl acetate as the eluant to give 10.3 mg (30%) of the selenylated product 2-2-70 as a colorless oil: $R_f$ 0.21 (7:7:6 hexane/dichloromethane/ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.75 (d, 2 H, $J = 7.5$ Hz), 7.52 (t, 1 H, $J = 7.5$ Hz), 7.44 (t, 2 H, $J = 7.0$ Hz), 7.38 (d, 1 H, $J = 2.0$ Hz), 7.06 (dd, 1 H, $J = 8.0, 2.0$ Hz), 6.92 (d, 1 H, $J = 8.0$ Hz), 6.70 (s, 1 H), 6.61 (d, 1 H, $J = 7.0$ Hz), 5.45 (t, 1 H, $J = 10.0$ Hz), 5.01 (dd, 1 H, $J = 12.5, 5.5$ Hz), 4.97 (d, 1 H, $J = 4.0$ Hz), 4.93 (t, 1 H, $J = 10.0$ Hz), 4.88 (dd, 1 H, $J = 10.0, 4.0$ Hz), 4.23 (q, 2 H, $J = 7.0$ Hz), 3.96 (ddd, 1 H, $J = 10.0, 8.0, 2.5$ Hz), 3.47 (s, 3 H), 3.21 (dd, 1 H, $J = 14.0, 6.0$ Hz), 3.14 (dd, 1 H, $J = 14.0, 5.5$ Hz), 2.88 (dd, 1 H, $J = 12.5, 3.0$ Hz), 2.74 (dd, 1 H, $J = 12.5, 8.5$ Hz), 2.08 (s, 3 H), 2.00 (s, 6 H), 1.31 (t, 3 H, $J = 7.0$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 171.7, 170.3, 170.2, 170.1, 167.0, 156.2, 138.6, 134.2, 133.0, 132.0, 128.9, 128.5, 127.2, 115.7, 115.2, 97.1, 72.2, 71.1, 70.0, 68.4, 62.0, 56.0, 53.8, 37.1, 31.1, 20.9, 20.9, 20.9, 14.5; ESI-MS m/z 718 MNa$^+$. 
**Compound 2-2-71.** N-acetyl-L-tryptophan ethyl ester (13.6 mg, 0.0496 mmol) was added to a solution of 20.6 mg (0.0496 mmol) of seleninic acid 2-2-3 in 1 mL of moist dichloromethane. After 24 h of stirring at 37 °C, the reaction mixture was concentrated and chromatographed on silica with 7:3 hexane / ethyl acetate as the eluant to give 19.4 mg (60%) of the selenylated product 2-2-71 as a colorless oil: 

$R_f$ 0.31 (7:3 hexane/ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.75 (s, 1 H), 7.51 (d, 1 H, $J = 8.0$ Hz), 7.32 (d, 1 H, $J = 8.0$ Hz), 7.18 (t, 1 H, $J = 7.5$ Hz), 7.09 (t, 1 H, $J = 7.0$ Hz), 6.00 (d, 1 H, $J = 8.0$ Hz), 5.53 (t, 1 H, $J = 10.0$ Hz), 5.21 (t, 1 H, $J = 9.5$ Hz), 5.06 (d, 1 H, $J = 3.5$ Hz), 4.94 (dd, 1 H, $J = 10.0$, 4.0 Hz), 4.90 (dd, 1 H, $J = 13.5$, 6.0 Hz), 4.02–4.18 (m, 3 H), 3.50 (s, 3 H), 3.37 (dd, 1 H, $J = 14.5$, 6.0 Hz), 3.33 (dd, 1 H, $J = 14.5$, 6.0 Hz), 3.13 (dd, 1 H, $J = 13.0$, 3.0 Hz), 2.76 (1 H, $J = 13.0$, 6.5 Hz), 2.11 (s, 3 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 1.96 (s, 3 H), 1.19 (t, 3 H, $J = 7.0$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.2, 170.6, 170.5, 170.2, 169.8, 137.7, 128.1, 123.0, 121.7, 120.1, 118.8, 115.8, 111.0, 97.2, 72.1, 71.2, 69.9, 68.9, 61.8, 56.0, 53.1, 30.9, 28.7, 23.6, 21.0, 21.0, 20.9, 14.2; ESI-MS $m/z$ 679 MNa$^+$. 
**Compound 2-2-72.** *N-(tert-Butoxycarbonyl)-L-histidine ethyl ester* (32.2 mg, 0.0933 mmol) was added to a solution of 38.7 mg (0.0933 mmol) of seleninic acid 2-2-3 in 1 mL of moist dichloromethane. After 24 h of stirring at 37 °C, the reaction mixture was concentrated and then chromatographed on silica with 1:1 dichloromethane / ethyl acetate as the eluant to give 37.9 mg (56%) of the selenylated product 2-2-72 as a colorless oil: $R_f$ 0.13 (3:2 dichloromethane/ethyl acetate); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.68 (br s, 1 H), 7.55 (s, 1 H), 7.26–7.35 (m, 5 H), 6.03 (br s, 1 H), 5.47 (t, 1 H, $J = 9.6$ Hz), 5.12 (s, 2 H), 4.94 (d, 1 H, $J = 3.2$ Hz), 4.86 (dt, 2 H, $J = 10.0, 3.6$ Hz), 4.60 (m, 1 H), 3.98 (m, 1 H), 3.41 (m, 1 H), 3.11 (s, 3 H), 2.97 – 3.26 (m, 3 H), 2.55 (br s, 1 H), 2.07 (s, 3 H), 2.00 (s, 3 H), 1.99 (s, 3 H), 1.40 (s, 9 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.1, 170.5, 170.4, 170.2, 155.8, 137.1, 135.8, 128.7, 128.4, 97.0, 80.0, 72.0, 71.1, 69.9, 68.5, 67.1, 55.9, 53.6, 31.2, 29.5, 28.5, 21.0, 20.9, 20.9; ESI-MS $m/z$ 750 MNa$^+$. 
**Compound 2-2-1.** Iodoethane (16 µL, 0.20 mmol) was added to a stirred solution of 10.7 mg (0.0201 mmol) of selenonate 2-2-5 in 1 mL of dimethylformamide. After 24 h of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 3:2 hexane/ethyl acetate as the eluant to give 4.1 mg (48%) of the known iodide 2-2-1 as a colorless oil: $R_f$ 0.42 (3:2 hexane/ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.47 (t, 1 H, $J = 10.0$ Hz), 4.97 (1 H, $J = 4.0$ Hz), 4.89 (dd, 1 H, $J = 10.0$, 4.0 Hz), 4.88 (t, 1 H, $J = 10.0$ Hz), 3.80 (ddd, 1 H, $J = 10.5$, 8.5, 2.5 Hz), 3.49 (s, 3 H), 3.31 (dd, 1 H, $J = 11.0$, 2.5 Hz), 3.14 (dd, 1 H, $J = 11.0$, 8.5 Hz), 2.08 (s, 3 H), 2.06 (s, 3 H), 2.01 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.3, 170.2, 169.9, 96.9, 72.7, 71.1, 69.9, 68.9, 56.0, 20.9, 20.9, 20.9, 3.8; ESI-MS $m/z$ 453 MNa$^+$. 
Compounds 2-2-75 and 2-2-76. Ethyl triflate (19 µL, 0.15 mmol) was added to a stirred solution of 8.0 mg (0.015 mmol) of selenonate 2-2-5 in 1 mL of dimethylformamide. After 14 h of stirring at room temperature, the reaction mixture was concentrated and then chromatographed on silica with 3:2 hexane / ethyl acetate as the eluant to give 1.3 mg (27%) of 2-2-75 and 2.4 mg (46%) of 2-2-76 as a colorless oils. Both products were identified by comparison of their $^1$H NMR spectra with the literature values. Alcohol 2-2-75: $R_f$ 0.27 (3:2 hexane/ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.09 (s, 1 H), 5.49 (t, 1 H, $J = 10.0$ Hz), 5.07 (dd, 1 H, $J = 9.5, 9.0$ Hz), 4.96 (d, 1 H, $J = 4.0$ Hz), 4.89 (dd, 1 H, $J = 10.5, 3.5$ Hz), 4.29 (dd, 1 H, $J = 12.0, 4.0$ Hz), 4.26 (dd, 1 H, $J = 12.0, 2.5$ Hz), 4.03 (ddd, 1 H, $J = 10.0, 4.5, 2.5$ Hz), 3.42 (s, 3 H), 2.08 (s, 3 H), 2.05 (s, 3 H), 2.02 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 170.3, 170.3, 169.8, 160.6, 100.0, 71.0, 70.2, 68.9, 67.2, 61.7, 55.8, 20.9, 20.9, 20.8; ESI-MS m/z 371 MNa$^+$. Formate 2-2-76: $R_f$ 0.42 (3:2 hexane/ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) δ 5.55 (t, 1 H, $J = 10.0$ Hz), 5.03 (t, 1 H, $J = 10.0$ Hz), 4.98 (d, 1 H, $J = 4.0$ Hz), 4.80 (dd, 1 H, $J = 10.0, 4.0$ Hz), 3.79 (ddd, 1 H, $J = 10.0, 4.0, 2.0$ Hz), 3.73 (dd, 1 H, $J = 12.5, 2.0$ Hz), 3.60 (dd, 1 H, $J = 12.5, 4.0$ Hz), 3.41 (s, 3 H), 2.09 (s, 3 H), 2.07 (s, 3 H), 2.03 (s, 3 H); ESI-MS m/z 343 MNa$^+$. 
Compounds 2-2-75 and 2-2-78. Selenonate 2-2-5 (8.0 mg, 0.015 mmol) was dissolved in 1 mL of 4:1 trifluoroacetic acid/dichloromethane. After 1 h of stirring at room temperature, the reaction mixture was concentrated and then chromatographed on silica with 2:2:1 ethyl acetate / dichloromethane / hexanes as the eluant to give 0.9 mg (19%) of 2-2-75 and 3.5 mg (73%) of 2-2-78 as a colorless oils. Both products were identified by comparison of their $^1$H NMR spectra with the literature values. Alcohol 2-2-78: $R_f$ 0.29 (2:2:1 ethyl acetate/dichloromethane/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.29 (t, 1 H, $J$ = 9.6 Hz), 4.90 (d, 1 H, $J$ = 3.6 Hz), 4.86 (dd, 1 H, $J$ = 10.0, 3.6 Hz), 4.48 (dd, 1 H, $J$ = 12.0, 4.0 Hz), 4.29 (dd, 1 H, $J$ = 12.0, 2.0 Hz), 3.81 (ddd, 1 H, $J$ = 10.0, 4.0, 2.0 Hz), 3.54 (dt, 1 H, $J$ = 9.6, 4.8 Hz), 2.92 (d, 1 H, $J$ = 4.8 Hz), 2.12 (s, 3 H), 2.09 (s, 3 H), 2.08 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 171.9, 171.7, 170.5, 97.1, 73.2, 70.8, 70.0, 69.6, 63.0, 55.5, 29.9, 21.1, 21.1, 21.0; ESI-MS $m/z$ 371 MNa$^+$
**Compound 2-3-2.** A stirred solution of 76.6 mg (0.292 mmol) of triphenylphosphine in 1 mL of tetrahydrofuran was stirred at −20 °C. Diisopropyl azodicarboxylate (57.8 µL, 0.292 mmol) was added dropwise and the reaction mixture was maintained at −20 °C until the white phosphonium intermediate formed. The reaction mixture was then cooled to −50 °C, and a solution of 45.0 mg (0.146 mmol) of alcohol 2-3-1 in 1 mL of tetrahydrofuran was added dropwise by syringe. After 5 min of stirring, 2 mL of a toluene solution of (2-phenyl)-selenoacetic acid [prepared by heating at reflux a 2 mL toluene solution of 59.6 mg (0.438 mmol) of phenylacetic acid and 69.9 mg (0.131 mmol) of Woollins’s reagent for 1 h] was added by cannula and the reaction mixture was allowed to warm to 23 °C, and then was stirred for 2 h. The solution was concentrated and chromatographed on silica with 17:3 hexane / ethyl acetate as the eluant to give 56.0 mg (78%) of the selenoester 2-3-2 as a colorless oil: $R_f$ 0.46 (13:7 hexane/ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.27 – 7.36 (m, 5 H), 7.17 (d, 2 H, $J = 7.5$ Hz), 7.00 (d, 2 H, $J = 8.0$ Hz), 4.94 (d, 1 H, $J = 8.0$ Hz), 4.56 (br app q, 1 H, $J = 7.5$ Hz), 4.08 (s, 2 H), 3.86 (s, 2 H), 3.70 (s, 3 H), 3.07 (dd, 1 H, $J = 14.0$, 6.0 Hz), 2.99 (dd, 1 H, $J = 14.0$, 6.0 Hz), 1.42 (s, 9 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 200.4, 172.5, 155.3, 137.8, 134.9, 133.0, 130.3, 129.8, 129.3, 128.9, 128.0, 80.2, 54.6, 54.1, 52.4, 38.2, 29.2, 28.5; $^{77}$Se NMR (76 MHz, CDCl$_3$) $\delta$ 630.6 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS $m/z$ 514 MNa$^+$. 
**Compound 2-3-3.** Dimethyldioxirane was added to a stirred solution of 11.6 mg (0.0237 mmol) of selenoester 2-3-2 in 1 mL of acetone until all of 2-3-2 was consumed according to TLC analysis (total ~575 µL of 0.09 M solution of DMDO in moist acetone). The reaction mixture was concentrated and then chromatographed on silica with 9:9:2 hexane / dichloromethane / methanol as the eluant to give 8.4 mg (88%) of the seleninic acid 2-3-3 as a colorless oil: \( R_f \) 0.11 (9:9:2 hexane/dichloromethane/methanol); \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 8.01 (br s, 1H), 7.24 (d, 2 H, \( J = 7.5 \) Hz), 7.08 (d, 2 H, \( J = 7.5 \) Hz), 4.97 (d, 1 H, \( J = 8.0 \) Hz), 4.52 (br app q, 1 H, \( J = 7.0 \) Hz), 4.28 (s, 2 H), 3.66 (s, 3 H), 3.05 (dd, 1 H, \( J = 14.0, 5.5 \) Hz), 2.97 (dd, 1 H, \( J = 14.0, 6.0 \) Hz), 1.36 (s, 9 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 172.4, 155.3, 137.0, 130.7, 130.3, 127.9, 80.3, 62.1, 54.6, 52.5, 38.3, 28.5; \(^{77}\)Se NMR (76 MHz, CDCl\(_3\)) δ 1298.4 [vs PhSeSePh at 460.0 ppm as an external standard]; NI-ESI-MS \( m/z \) 404 M\(^-\).
**Compound 2-3-4.** *N*(tert-Butoxycarbonyl)-L-cysteine methyl ester (neat, 97%, 4.5 µL, d = 1.143 g/mL, 0.021 mmol) was added to a stirred solution of 8.3 mg (0.021 mmol) of seleninic acid 2-3-3 in 1 mL of moist dichloromethane. After 2 min of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 7:3 hexane / ethyl acetate as the eluant to give 10.1 mg (82%) of the selenylsulfide 2-3-4 as a colorless oil: $R_f$ 0.39 (3:2 hexane/ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.24 (d, 2 H, $J = 8.5$ Hz), 7.06 (d, 2 H, $J = 8.0$ Hz), 5.31 (d, 1 H, $J = 8.0$ Hz), 5.07 (d, 1 H, $J = 8.0$ Hz), 4.58 (br app q, 1 H, $J = 7.0$ Hz), 4.50 (br app q, 1 H, $J = 6.5$ Hz), 4.08 (s, 2 H), 3.74 (s, 3 H), 3.72 (s, 3 H), 3.11 (dd, 1 H, $J = 14.0$, 5.5 Hz), 3.04 (dd, 1 H, $J = 14.0$, 6.0 Hz), 2.90 (br d, 1 H, $J = 11.0$ Hz), 2.83 (dd, 1 H, $J = 14.0$, 5.0 Hz), 1.45 (s, 9 H), 1.45 (s, 9 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 172.4, 171.5, 155.3, 155.2, 136.7, 135.5, 129.8, 129.6, 80.4, 80.2, 54.6, 53.8, 52.7, 52.5, 39.9, 38.2, 35.1, 28.6; $^{77}$Se NMR (76 MHz, CDCl$_3$) δ 474.3 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS $m/z$ 629 MNa$^+$. 
Compound 2-3-6. A suspension of 200 mg (1.07 mmol) of 6-amino-2-naphthoic acid in 3 mL of 6 M HCl was stirred for 5 min and then cooled down to 0 °C. A solution of 147 mg (2.14 mmol) of sodium nitrite in 2 mL of water was then added slowly and the suspension was allowed to stir and warm up to room temperature over a period of 30 min. Sodium acetate was added to give a pH ~ 6 on pH paper after which 462 mg (3.20 mmol) of potassium selenocyanate was added. After 4 h of stirring at room temperature, citric acid was added to give a pH ~ 3 on pH paper, and the product was extracted into dichloromethane, dried over sodium sulfate, concentrated and chromatographed on silica with 9:9:1 hexanes / dichloromethane / methanol as the eluant to give 177 mg (60%) of selenocyanate 2-3-6 as a light orange solid: mp 228 – 230 °C; $R_f$ 0.27 (9:9:1 hexanes/dichloromethane/methanol); $^1$H NMR (500 MHz, CD$_3$OD) δ 8.65 (s, 1 H), 8.31 (d, 1 H, $J = 1.0$ Hz), 8.13 (dd, 1 H, $J = 8.5, 1.5$ Hz), 8.08 (d, 1 H, $J = 8.5$ Hz), 7.97 (d, 1 H, $J = 8.5$ Hz), 7.81 (dd, 1 H, $J = 8.5, 1.5$ Hz); $^{13}$C NMR (125 MHz, CD$_3$OD) δ 168.1, 136.1, 132.4, 131.9, 131.1, 130.8, 129.6, 129.6, 127.9, 126.7, 123.5, 102.5; $^{77}$Se NMR (76 MHz, CD$_3$OD) δ 336.9 [vs PhSeSePh at 460.0 ppm as an external standard]; NI ESI-MS m/z 276 M$^+$. 
**Compound 2-3-7.** A solution of 15.4 mg (0.0558 mmol) of selenocyanato naphthoic acid 2-3-6 in 1 mL of dimethylformamide was treated sequentially with 17.3 µL (0.278 mmol) of methyl iodide and 29.5 mg (0.278 mmol) of sodium carbonate. After 12 h of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 1:4 hexanes/ethyl acetate as the eluant to give 15.2 mg (94%) of 2-3-7 as a colorless oil: $R_f$ 0.41 (7:3 hexanes/ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.62 (s, 1 H), 8.16 (d, 1 H, J = 1.5 Hz), 8.15 (dd, 1 H, J = 8.5, 1.5 Hz), 7.98 (d, 1 H, J = 8.5 Hz), 7.87 (d, 1 H, J = 8.5 Hz), 7.70 (dd, 1 H, J = 8.5, 1.5 Hz), 4.00 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 166.8, 136.1, 132.5, 131.8, 131.7, 131.1, 129.3, 129.3, 128.1, 127.1, 122.4, 101.1, 52.7; $^{77}$Se NMR (76 MHz, CDCl$_3$) δ 332.2 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS $m/z$ 314 MNa\(^+\).
**Compound 2-3-8.** Dimethyldioxirane was added to a stirred solution of 11.3 mg (0.0390 mmol) of selenocyanate 2-3-7 in 1 mL of dichloromethane until all of X was consumed according to TLC analysis (total ~ 487 µL of a 0.080 M titrated solution of DMDO in moist acetone, ~ 1.0 equiv). Once 2-3-7 was consumed, seleninic acid 2-3-8 precipitated out of solution to give, after filtration and drying, 11.1 mg (96%) of a white solid: mp 213–215 °C; Rf 0.15 (9:1 dichloromethane/methanol); $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 8.72 (s, 1 H), 8.49 (s, 1 H), 8.26 (d, 1 H, $J = 8.5$ Hz), 8.17 (dd, 1 H, $J = 8.5, 1.5$ Hz), 8.15 (d, 1 H, $J = 8.5$ Hz), 7.97 (dd, 1 H, $J = 8.5, 1.5$ Hz), 3.99 (s, 3 H); $^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$ 166.9, 144.9, 135.0, 134.6, 130.7, 130.7, 129.8, 129.3, 127.1, 126.4, 122.7, 51.8; $^{77}$Se NMR (76 MHz, CD$_3$OD) $\delta$ 1226.2 [vs PhSeSePh at 460.0 ppm as an external standard]; NI ESI-MS $m/z$ 297 M$^+$. 
Compound 2-3-9. A mixture of selenocytanto naphthoic acid 2-3-6 (20.0 mg, 0.0725 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (20.8 mg, 0.109 mmol), and L-phenylalanine ethyl ester hydrochloride (25.0 mg, 0.109 mmol) in 1 mL of dichloromethane was treated dropwise with 39.8 µL (0.362 mmol) of N-methyl morpholine. After 12 h of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 1:1 hexanes/ethyl acetate as the eluant to give 24.8 mg (76%) of 2-3-9 as a colorless oil: Rf 0.29 (3:2 hexanes/ethyl acetate); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.24 (s, 1 H), 8.14 (d, 1 H, $J = 1.6$ Hz), 7.92 (d, 1 H, $J = 8.4$ Hz), 7.86 (s, 2 H), 7.69 (dd, 1 H, $J = 8.4$, 2.0 Hz), 7.24 – 7.32 (m, 3 H), 7.17 (d, 2 H, $J = 8.0$ Hz), 6.78 (d, 1 H, $J = 7.2$ Hz), 5.12 (dt, 1 H, $J = 7.6$, 6.0 Hz), 4.25 (q, 2 H, $J = 7.2$ Hz), 3.34 (dd, 1 H, $J = 14.0$, 6.0 Hz), 3.27 (dd, 1 H, $J = 14.0$, 5.6 Hz), 1.30 (t, 3 H, $J = 7.2$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.9, 166.4, 136.1, 135.4, 133.0, 132.6, 131.9, 131.4, 129.7, 129.5, 128.8, 128.5, 127.8, 127.5, 125.4, 121.7, 101.2, 62.0, 54.0, 38.2, 14.4; $^{77}$Se NMR (76 MHz, CDCl$_3$) $\delta$ 331.4 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS m/z 453 MH⁺.
**Compound 2-3-10.** A mixture of selenocyanato naphthoic acid 2-3-6 (17.1 mg, 0.0620 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (17.8 mg, 0.0929 mmol), and L-alanine ethyl ester hydrochloride (14.3 mg, 0.0929 mmol) in 1 mL of dichloromethane was treated dropwise with 34.1 µL (0.310 mmol) of N-methyl morpholine. After 12 h of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 1:1 hexanes/ethyl acetate as the eluant to give 16.5 mg (71%) of 2-3-10 as a colorless oil: $R_f$ 0.45 (1:1 hexanes/ethyl acetate); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.32 (s, 1 H), 8.14 (d, 1 H, $J$ = 1.2 Hz), 7.94 (d, 2 H, $J$ = 8.8 Hz), 7.86 (d, 1 H, $J$ = 8.4 Hz), 7.69 (dd, 1 H, $J$ = 8.4, 1.6 Hz), 6.98 (d, 1 H, $J$ = 6.8 Hz), 4.84 (quint, 1 H, $J$ = 6.8 Hz), 4.28 (q, 2 H, $J$ = 7.2 Hz), 1.57 (d, 3 H, $J$ = 6.8 Hz), 1.33 (t, 3 H, $J$ = 7.2 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.5, 166.4, 135.4, 133.1, 132.6, 132.0, 131.4, 129.5, 128.4, 127.8, 125.5, 121.7, 101.2, 62.0, 49.0, 18.9, 14.4; $^{77}$Se NMR (95 MHz, CDCl$_3$) $\delta$ 331.4 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS $m/z$ 377 MH$^+$. 
**Compound 2-3-11.** Dimethyldioxirane was added to a stirred solution of 8.2 mg (0.0182 mmol) of selenocyanate 2-3-9 in 1 mL of dichloromethane until all of 2-3-9 was consumed according to TLC analysis (total ~ 260 µL of a 0.070 M titrated solution of DMDO in moist acetone, ~ 1.0 equiv). The reaction mixture was concentrated and then chromatographed on silica with 9:1 dichloromethane / methanol as the eluant to give 7.9 mg (95%) of the seleninic acid 2-3-11 as a colorless oil: $R_f$ 0.32 (9:1 dichloromethane/methanol); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.16 (br s, 2 H), 7.88 (br s, 1 H), 7.81 (br s, 1 H), 7.75 (br s, 2 H), 7.25 – 7.33 (m, 3 H), 7.22 (d, 2 H, $J$ = 7.0 Hz), 7.10 (br s, 1 H), 5.13 (app q, 1 H, $J$ = 6.5 Hz), 4.61 (br s, 1 H), 4.26 (q, 2 H, $J$ = 7.0 Hz), 3.37 (dd, 1 H, $J$ = 14.0, 6.0 Hz), 3.31 (dd, 1 H, $J$ = 14.0, 6.0 Hz), 1.31 (t, 3 H, $J$ = 7.0 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 172.0, 166.8, 136.3, 13.4, 134.1, 133.9, 130.9, 129.6, 129.6, 128.9, 127.9, 127.5, 126.9, 125.4, 122.7, 62.0, 54.2, 38.1, 14.4; NI ESI-MS $m/z$ 458 M$^-$. 
Compound 2-3-12. Dimethyldioxirane was added to a stirred solution of 8.0 mg (0.0213 mmol) of selenocyanate 2-3-10 in 1 mL of dichloromethane until all of 2-3-10 was consumed according to TLC analysis (total ~ 305 µL of a 0.070 M titrated solution of DMDO in moist acetone, ~ 1.0 equiv). The reaction mixture was concentrated and then chromatographed on silica with 9:1 dichloromethane / methanol as the eluant to give 7.6 mg (94%) of the seleninic acid 2-3-12 as a colorless oil: $R_f$ 0.21 (9:1 dichloromethane/methanol); $^1$H NMR (500 MHz, CD$_3$OD) δ 8.53 (s, 1 H), 8.49 (s, 1 H), 8.24 (d, 1 H, $J = 8.5$ Hz), 8.16 (d, 1 H, $J = 8.5$ Hz), 8.05 (dd, 1 H, $J = 8.5, 1.5$ Hz), 7.97 (dd, 1 H, $J = 8.5, 1.5$ Hz), 4.66 (q, 1 H, $J = 7.5$ Hz), 4.23 (q, 2 H, $J = 7.0$ Hz), 1.55 (d, 3 H, $J = 7.5$ Hz), 1.30 (t, 3 H, $J = 7.0$ Hz); $^{13}$C NMR (125 MHz, CD$_3$OD) δ 173.2, 168.4, 144.2, 134.7, 134.3, 133.8, 130.4, 129.3, 128.0, 127.1, 126.7, 122.7, 61.3, 49.3, 16.1, 13.3; NI ESI-MS m/z 382 M$. 
**Compound 2-3-13.** A mixture of selenocyanato naphthoic acid 2-3-6 (17.0 mg, 0.0616 mmol), \(N\)-(3-dimethylaminopropyl)-\(N'\)-ethylcarbodiimide hydrochloride (17.7 mg, 0.0924 mmol), and \(D\)–phenylalanine methyl ester hydrochloride (19.9 mg, 0.0924 mmol) in 1 mL of dichloromethane was treated dropwise with 33.9 µL (0.308 mmol) of \(N\)-methyl morpholine. After 12 h of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 1:1 hexanes / ethyl acetate as the eluant to give 19.6 mg (73%) of 2-3-13 as a colorless oil: \(R_f\) 0.27 (3:2 hexanes/ethyl acetate); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.22 (s, 1 H), 8.13 (d, 1 H, \(J = 1.5\) Hz), 7.90 (d, 1 H, \(J = 8.5\) Hz), 7.84 (s, 2 H), 7.68 (dd, 1 H, \(J = 8.5, 2.0\) Hz), 7.26 – 7.33 (m, 3 H), 7.17 (d, 2 H, \(J = 8.0\) Hz), 6.79 (d, 1 H, \(J = 8.0\) Hz), 5.15 (dt, 1 H, \(J = 7.5, 6.0\) Hz), 3.81 (s, 3 H), 3.35 (dd, 1 H, \(J = 14.0, 6.0\) Hz), 3.27 (dd, 1 H, \(J = 14.0, 6.0\) Hz); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 172.3, 166.5, 136.0, 135.4, 133.0, 132.5, 131.9, 131.4, 129.6, 129.5, 128.9, 128.5, 127.8, 127.5, 125.4, 121.8, 101.2, 54.0, 52.8, 38.1; \(^{77}\)Se NMR (95 MHz, CDCl\(_3\)) \(\delta\) 331.6 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS \(m/z\) 439 MH\(^+\).
**Compound 2-3-14.** Dimethyldioxirane was added to a stirred solution of 16.2 mg (0.0370 mmol) of selenocyanate 2-3-13 in 1 mL of dichloromethane until all of 2-3-13 was consumed according to TLC analysis (total ~ 530 µL of a 0.070 M titrated solution of DMDO in moist acetone, ~ 1.0 equiv). The reaction mixture was concentrated and then chromatographed on silica with 9:1 dichloromethane / methanol as the eluant to give 15.1 mg (92%) of the seleninic acid 2-3-14 as a colorless oil: $R_f$ 0.24 (9:1 dichloromethane/methanol); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.43 (s, 1 H), 8.35 (s, 1 H), 8.16 (d, 1 H, $J$ = 9.0 Hz), 8.07 (d, 1 H, $J$ = 8.5 Hz), 7.93 (dt, 1 H, $J$ = 8.5, 1.5 Hz), 7.90 (dd, 1 H, $J$ = 8.5, 1.5 Hz), 7.27 – 7.30 (m, 4 H), 7.19 – 7.23 (m, 1 H), 4.93 (dd, 1 H, $J$ = 9.5, 5.5 Hz), 3.34 (dd, 1 H, $J$ = 14.0, 5.5 Hz), 3.17 (dd, 1 H, $J$ = 14.0, 9.5 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.4, 168.4, 144.2, 137.3, 134.6, 134.2, 133.7, 130.4, 129.2, 129.1, 128.4, 127.9, 127.1, 126.8, 125.4, 122.6, 54.9, 51.7, 37.0; $^{77}$Se NMR (95 MHz, CD$_3$OD) $\delta$ 1227.5 [vs PhSeSePh at 460.0 ppm as an external standard]; NI ESI-MS m/z 444 M$.^{-1}$.
**Compound 3-1-2.** A solution of (2-phenyl)-selenoacetic acid [prepared by heating a 2 mL toluene solution of 71.1 mg (0.522 mmol) of phenylacetic acid and 84.3 mg (0.158 mmol) of Woollins’s reagent at reflux for 1 h] was added by cannula to a stirred solution of 40 mg (0.261 mmol) of 2-bromoethyl ethyl ether 3-1-1 in 1 mL of dimethylformamide, followed by 90.9 µL (0.522 mmol) of diisopropylethylamine. After 2 h of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 9:1 hexane / ethyl acetate as the eluant to give 66.5 mg (94%) of selenoester 3-1-2 as a colorless oil: Rf 0.39 (9:1 hexane/ethyl acetate); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.25 – 7.36 (m, 5 H), 3.84 (s, 2 H), 3.59 (t, 2 H, J = 6.8 Hz), 3.48 (q, 2 H, J = 7.2 Hz), 3.05 (t, 2 H, J = 6.8 Hz), 1.17 (t, 3 H, J = 6.8 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 200.2, 133.2, 130.2, 128.9, 127.9, 69.9, 66.4, 54.3, 25.6, 15.4; ESI-MS m/z 295 MNa$^+$. 
**Compound 3-1-4.** To a stirring suspension of 300 mg (3.79 mmol) of selenium metal in 5 mL of water was added 300 mg (7.93 mmol) of sodium borohydride. After the initial reaction has subsided, an additional equivalent of selenium (300 mg, 3.79 mmol) was added. The reaction mixture was stirred for 15 min and then warmed briefly over a steam bath to complete the dissolution of the selenium. The resulting brownish red aqueous solution was ready for further use after which 857 µL (7.60 mmol) of 2-bromoethyl ethyl ether 3-1-1 in 2 mL of ethanol was added dropwise using a syringe. After 30 min of stirring at room temperature, the ethanol was evaporated and the crude product was extracted into dichloromethane, dried over magnesium sulfate, and concentrated. A bulb to bulb distillation using a kugelrohr gave 913 mg (79%) of diselenide 3-1-4 as a yellow oil: \( R_f \) 0.32 (9:1 hexane/ethyl acetate); \(^{1}H\) NMR (400 MHz, CDCl₃) \( \delta \) 3.71 (t, 2 H, \( J = 6.8 \) Hz), 3.53 (q, 2 H, \( J = 7.2 \) Hz), 3.11 (t, 2 H, \( J = 6.8 \) Hz), 1.21 (t, 3 H, \( J = 7.2 \) Hz); \(^{13}C\) NMR (100 MHz, CDCl₃) \( \delta \) 70.7, 66.5, 29.6, 15.4; \(^{77}Se\) NMR (76 MHz, CDCl₃) \( \delta \) 295.4 [vs PhSeSePh at 460.0 ppm as an external standard]; NI ESI-MS \( m/z \) 329 MNa⁺.
**Compound 3-1-3.** Dimethyldioxirane (total ~ 30.0 mL of a 0.30 M titrated solution of DMDO in chloroform, ~ 3.2 equiv) was added to a stirred solution of 913 mg (3.00 mmol) of diselenide 3-1-4 in 1 mL of dichloromethane. After 5 min of stirring at room temperature, the reaction mixture was concentrated and 2 mL of hexanes were added. Seleninic acid 3-1-3 precipitated out of solution to give, after filtration and drying, 1.07 g (96%) of a white solid: mp 68–69 °C; $R_f$ 0.20 (9:9:2 hexane/dichloromethane/methanol); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.86 (br s, 1 H), 3.91 (t, 2 H, $J$ = 6.0 Hz), 3.50 (q, 2 H, $J$ = 7.0 Hz), 3.33 (t, 2 H, $J$ = 6.0 Hz), 1.16 (t, 3 H, $J$ = 7.0 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 67.2, 64.0, 56.7, 15.1; $^{77}$Se NMR (76 MHz, CDCl$_3$) $\delta$ 1220.6 [vs PhSeSePh at 460.0 ppm as an external standard]; NI ESI-MS $m/z$ 185 M$^+$. 
Compound 3-1-3. Dimethyldioxirane (total ~ 1.5 mL of a 0.30 M titrated solution of DMDO in chloroform, ~ 2.1 equiv) was added to a stirred solution of 58.8 mg (0.217 mmol) of selenoester 3-1-2 in 1 mL of dichloromethane. After 5 min of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 9:9:1 hexane / dichloromethane / methanol as the eluant to give 37.7 mg (94%) of seleninic acid 3-1-3 as a white solid.
Compound 3-1-3. To a stirring suspension of 775 mg (9.80 mmol) of selenium metal in 20 mL of anhydrous ethanol cooled in an ice bath was added 263 mg (6.96 mmol) of sodium borohydride. After the initial reaction has subsided, the mixture was stirred and heated at reflux for 1.5 h with N$_2$ passing into the liquid in order to dissolve the selenium and expel hydrogen selenide. The resulting brownish red sodium diselenide solution was cooled down to room temperature and 811 µL (6.54 mmol) of 2-bromoethyl ethyl ether 3-1-1 was added dropwise using a syringe. After 2 h of stirring at room temperature, the reaction mixture was diluted with dichloromethane, washed with two portions of water, and dried over magnesium sulfate. Dimethyldioxirane (total ~ 16 mL of a 0.30 M titrated solution of DMDO in chloroform) was then added, and after 5 min of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 9:9:1 hexane / dichloromethane / methanol as the eluant to give 653 mg (54%) of seleninic acid 3-1-3 as a white solid.
Compound 3-1-6. Uridine triacetate 3-1-5 (38.5 mg, 0.104 mmol) followed by a catalytic amount of trifluoroacetic acid were added to a solution of 38.5 mg (0.208 mmol) of seleninic acid 3-1-3 in 1 mL of moist acetonitrile. After 16 h of stirring at 60 °C, the reaction mixture was concentrated and chromatographed on silica with 3:2 dichloromethane / ethyl acetate as the eluant to give 33.1 mg (61%) of selenoether 3-1-6 as a colorless oil: $R_f$ 0.46 (1:1 dichloromethane/ethyl acetate); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.95 (br s, 1 H), 7.84 (s, 1 H), 6.05 – 6.06 (m, 1 H), 5.32 – 5.34 (m, 2 H), 4.34 (app s, 3 H), 3.67 (t, 2 H, $J$ = 6.4 Hz), 3.47 (q, 2 H, $J$ = 7.2 Hz), 2.98 (t, 2 H, $J$ = 6.4 Hz), 2.22 (s, 3 H), 2.12 (s, 3 H), 2.08 (s, 3 H), 1.15 (t, 3 H, $J$ = 7.2 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.4, 169.9, 169.8, 161.6, 150.4, 143.1, 103.4, 87.3, 80.4, 73.1, 70.6, 70.0, 66.5, 63.4, 26.9, 21.2, 20.7, 20.6, 15.3; $^{77}$Se NMR (76 MHz, CDCl$_3$) $\delta$ 208.6 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS $m/z$ 545 MNa$^+$. 
**Compound 3-1-8.** 2'-Deoxyuridine diacetaate 3-1-7 (63.4 mg, 0.203 mmol) followed by a catalytic amount of trifluoroacetic acid were added to a solution of 75.2 mg (0.406 mmol) of seleninic acid 3-1-3 in 1 mL of moist acetonitrile. After 16 h of stirring at 60 °C, the reaction mixture was concentrated and chromatographed on silica with 3:2 dichloromethane / ethyl acetate as the eluant to give 52.7 mg (56%) of selenoether 3-1-8 as a colorless oil: $R_f$ 0.49 (2:3 dichloromethane/ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.67 (br s, 1 H), 7.93 (s, 1 H), 6.32 (dd, 1 H, $J = 8.5, 6.0$ Hz), 5.24 (dt, 1 H, $J = 6.5, 2.0$ Hz), 4.38 (dd, 1 H, $J = 12.0, 3.5$ Hz), 4.33 (dd, 1 H, $J = 12.0, 3.0$ Hz), 4.28 (app q, 1 H, $J = 3.0$ Hz), 3.69 (t, 2 H, $J = 6.5$ Hz), 3.48 (q, 2 H, $J = 7.0$ Hz), 3.01 (td, 1 H, $J = 13.0, 6.5$ Hz), 2.99 (td, 1 H, $J = 13.0, 6.5$ Hz), 2.50 (ddd, 14.0, 5.5, 2.0), 2.21 (ddd, $J = 14.0, 8.5, 6.5$ Hz), 2.21 (s, 3 H), 2.12 (s, 3 H), 1.17 (t, 3 H, $J = 7.5$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.6, 170.5, 161.7, 150.3, 142.9, 103.0, 85.3, 82.7, 74.4, 70.1, 66.5, 64.1, 38.2, 27.0, 21.2, 21.1, 15.4; $^{77}$Se NMR (76 MHz, CDCl$_3$) $\delta$ 206.8 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS $m/z$ 487 MNa$^+$. 
**Compound 3-1-10.** Cytidine tetraacetate 3-1-9 (20.3 mg, 0.0494 mmol) followed by a catalytic amount of trifluoroacetic acid were added to a solution of 18.3 mg (0.0988 mmol) of seleninic acid 3-1-3 in 1 mL of acetic acid. After 48 h of stirring at 70 °C, the reaction mixture was concentrated and chromatographed on silica with 3:2 dichloromethane / acetone as the eluant to give 11.8 mg (46%) of selenoether 3-1-10 as a colorless oil: $R_f$ 0.27 (3:2 dichloromethane/acetone); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.93 (s, 1 H), 7.37 (br s, 1 H), 6.98 (br s, 1 H), 6.34 (d, 1 H, $J = 4.5$ Hz), 5.36 (app quint, 2 H, $J = 5.0$ Hz), 4.33 – 4.41 (m, 3 H), 3.64 (t, 2 H, $J = 6.0$ Hz), 3.52 (q, 2 H, $J = 7.0$ Hz), 2.89 (t, 2 H, $J = 6.0$ Hz), 2.23 (s, 3 H), 2.10 (s, 6 H), 1.21 (t, 3 H, $J = 7.0$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.5, 169.8, 169.8, 165.5, 154.6, 148.1, 93.3, 88.4, 79.9, 73.9, 70.2, 68.9, 66.7, 63.1, 29.5, 21.2, 20.7, 20.7, 15.3; $^{77}$Se NMR (76 MHz, CDCl$_3$) $\delta$ 159.0 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS $m/z$ 544 MNa$^+$. 
**Compound 3-1-12.** Cytosine 3-1-11 (10.0 mg, 0.0901 mmol) followed by a catalytic amount of heptafluorobutyric acid were added to a solution of 50.0 mg (0.270 mmol) of seleninic acid 3-1-3 in 1 mL of water. After 48 h of stirring at reflux, the reaction mixture was concentrated and chromatographed on silica with 9:1 dichloromethane / methanol as the eluant to give 10.6 mg (45%) of selenoether 3-1-12 as a colorless oil: $R_f$ 0.47 (9:1 dichloromethane/methanol); $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 7.78 (s, 1 H), 3.66 (t, 2 H, $J = 6.0$ Hz), 3.50 (q, 2 H, $J = 7.0$ Hz), 2.86 (t, 2 H, $J = 6.0$ Hz), 1.18 (t, 3 H, $J = 7.0$ Hz); $^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$ 167.6, 158.4, 150.6, 91.9, 69.3, 66.0, 28.2, 14.2; $^{77}$Se NMR (76 MHz, CD$_3$OD) $\delta$ 154.8 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS $m/z$ 286 MNa$^+$. 
Compound 3-1-12. Cytosine 3-1-11 (10.0 mg, 0.0901 mmol) followed by a catalytic amount of trifluoroacetic acid were added to a solution of 33.3 mg (0.180 mmol) of seleninic acid 3-1-3 in 1 mL of acetic acid. After 48 h of stirring at 70 °C, the reaction mixture was concentrated and chromatographed on silica with 9:1 dichloromethane / methanol as the eluant to give 13.2 mg (56%) of selenoether 3-1-12 as a colorless oil.
**Compound 3-1-15.** Uridine 3-1-14 (10.0 mg, 0.0410 mmol) followed by a catalytic amount of heptafluorobutyric acid were added to a solution of 22.8 mg (0.123 mmol) of seleninic acid 3-1-3 in 1 mL of water. After 24 h of stirring at reflux, the reaction mixture was concentrated and chromatographed on silica with 19:1 dichloromethane / methanol as the eluant to give 16.2 mg (71%) of selenoether 3-1-15 as a colorless oil: $R_f$ 0.35 (9:1 dichloromethane/methanol); $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 8.01 (s, 1 H), 5.87 (d, 1 H, $J = 4.0$ Hz), 4.15 (app quint, 2 H, $J = 4.0$ Hz), 3.98 (m, 1 H), 3.85 (dd, 1 H, $J = 12.4$, 2.8 Hz), 3.72 (dd, 1 H, $J = 12.4$, 3.2 Hz), 3.64 (t, 2 H, $J = 6.8$ Hz), 3.49 (q, 2 H, $J = 7.2$ Hz), 2.87 (t, 2 H, $J = 6.8$ Hz), 1.15 (t, 3 H, $J = 7.2$ Hz); $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 173.7, 159.3, 142.1, 103.1, 90.8, 84.6, 74.8, 70.0, 70.0, 65.9, 61.1, 24.6, 14.3; $^{77}$Se NMR (76 MHz, CD$_3$OD) $\delta$ 183.2 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS $m/z$ 419 MNa$^+$. 
**Compound 3-1-15.** A solution of 12.9 mg (0.0248 mmol) of selenoether 3-1-6 in 1 mL of methanol was treated with a catalytic amount of 18.8% methanolic sodium methoxide solution. After 30 min of stirring at room temperature, the reaction was concentrated to give 9.8 mg (100%) of selenoether **3-1-15** as a colorless oil.
Compound 3-1-16. Deoxyuridine (10.0 mg, 0.0438 mmol) followed by a catalytic amount of heptafluorobutyric acid were added to a solution of 24.3 mg (0.132 mmol) of seleninic acid 3-1-3 in 1 mL of water. After 24 h of stirring at reflux, the reaction mixture was concentrated and chromatographed on silica with 19:1 dichloromethane / methanol as the eluant to give 11.6 mg (70%) of selenoether 3-1-16 as a colorless oil: $R_f$ 0.69 (4:1 dichloromethane/methanol); $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 7.98 (s, 1 H), 6.30 (t, 1 H, $J$ = 6.8 Hz), 4.36 (dt, 1 H, $J$ = 6.8, 3.6 Hz), 3.88 (app q, 1 H, $J$ = 3.6 Hz), 3.77 (dd, 1 H, $J$ = 12.4, 3.6 Hz), 3.71 (dd, 1 H, $J$ = 12.4, 4.0 Hz), 3.64 (t, 2 H, $J$ = 6.8 Hz), 3.49 (q, 2 H, $J$ = 7.2 Hz), 2.86 (t, 2 H, $J$ = 6.8 Hz), 2.27 (ddd, 1 H, $J$ = 13.6, 6.4, 3.6 Hz), 2.15 (dt, 1 H, $J$ = 13.6, 6.8 Hz), 1.15 (t, 3 H, $J$ = 7.2 Hz); $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 173.9, 159.1, 141.7, 103.1, 87.3, 85.9, 71.1, 69.9, 65.9, 61.8, 40.6, 24.6, 14.3; $^{77}$Se NMR (76 MHz, CD$_3$OD) $\delta$ 183.4 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS $m/z$ 403 MNa$^+$. 
Compound 3-1-16. A solution of 7.6 mg (0.016 mmol) of selenoether 3-1-8 in 1 mL of methanol was treated with a catalytic amount of 18.8% methanolic sodium methoxide solution. After 30 min of stirring at room temperature, the reaction was concentrated to give 6.2 mg (100%) of selenoether 3-1-16 as a colorless oil.
**Compound 3-1-17.** Cytidine (10.0 mg, 0.0412 mmol) followed by a catalytic amount of heptafluorobutyric acid were added to a solution of 22.8 mg (0.123 mmol) of seleninic acid 3-1-3 in 1 mL of water. After 48 h of stirring at reflux, the reaction mixture was concentrated and chromatographed on silica with 9:1 dichloromethane / methanol as the eluant to give 6.2 mg (38%) of selenoether 3-1-17 as a colorless oil: $R_f$ 0.27 (9:1 dichloromethane/methanol); $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 8.50 (s, 1 H), 5.81 (d, 1 H, $J$ = 2.5 Hz), 4.13 – 4.16 (m, 2 H), 4.02 (dt, 1 H, $J$ = 5.5, 3.0 Hz), 3.91 (dd, 1 H, $J$ = 12.0, 2.5 Hz), 3.77 (dd, 1 H, $J$ = 12.0, 3.5 Hz), 3.65 (t, 2 H, $J$ = 6.0 Hz), 3.50 (q, 2 H, $J$ = 7.0 Hz), 2.86 (t, 2 H, $J$ = 6.0 Hz), 1.18 (t, 3 H, $J$ = 7.0 Hz); $^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$ 166.6, 156.9, 149.4, 92.6, 91.6, 85.0, 75.6, 69.6, 69.3, 66.1, 60.6, 28.2, 14.2; $^{77}$Se NMR (76 MHz, CD$_3$OD) $\delta$ 159.7 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS $m/z$ 418 MNa$^+$. 
**Compound 3-1-17.** A solution of 11.7 mg (0.0225 mmol) of selenoether 3-1-10 in 1 mL of methanol was treated with a catalytic amount of 18.8% methanolic sodium methoxide solution. After 30 min of stirring at room temperature, the reaction was concentrated to give 8.9 mg (100%) of selenoether 3-1-17 as a colorless oil.
Compound 3-1-18. *N*-benzoyl-L-tyrosine ethyl ester (60.0 mg, 0.191 mmol) was added to a solution of 17.7 mg (0.0957 mmol) of seleninic acid 3-1-3 in 1 mL of moist dichloromethane. After 16 h of stirring at 37 °C, the reaction mixture was concentrated and chromatographed on silica with 3:2 dichloromethane / ethyl acetate as the eluant to give 14.0 mg (32%) of selenoether 3-1-18 as a colorless oil: *R*$_f$ 0.36 (3:2 dichloromethane/ethyl acetate); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.72 (d, 2 H, *J* = 8.0 Hz), 7.50 (t, 1 H, *J* = 7.6 Hz), 7.42 (t, 2 H, *J* = 8.0 Hz), 7.37 (d, 1 H, *J* = 2.4 Hz), 7.03 (dd, 1 H, *J* = 8.4, 2.4 Hz), 6.90 (d, 1 H, *J* = 8.4 Hz), 6.57 (d, 1 H, *J* = 7.2 Hz), 5.00 (dt, 1 H, *J* = 7.2, 5.2 Hz), 4.21 (q, 2 H, *J* = 7.2 Hz), 3.51 (t, 2 H, *J* = 6.4 Hz), 3.50 (q, 2 H, *J* = 6.8 Hz), 3.20 (dd, 1 H, *J* = 14.0, 5.6 Hz), 3.20 (dd, 1 H, *J* = 14.0, 5.2 Hz), 2.81 (t, 2 H, *J* = 6.4 Hz), 1.29 (t, 3 H, *J* = 7.2 Hz), 1.22 (t, 3 H, *J* = 6.8 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 171.8, 167.0, 157.0, 138.9, 134.2, 132.7, 132.0, 130.8, 128.9, 128.1, 127.2, 115.3, 68.8, 66.7, 61.9, 53.8, 37.0, 29.5, 15.1, 14.4; $^{77}$Se NMR (76 MHz, CDCl$_3$) δ 128.5 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS *m/z* 488 MNa$^+$. 
**Compound 3-1-19.** N-acetyl-L-tryptophan ethyl ester (20.0 mg, 0.0729 mmol) was added to a solution of 13.5 mg (0.0729 mmol) of seleninic acid 3-1-3 in 1 mL of moist dichloromethane. After 16 h of stirring at 37 °C, the reaction mixture was concentrated and chromatographed on silica with 3:2 dichloromethane / ethyl acetate as the eluant to give 17.4 mg (56%) of selenoether 3-1-19 as a colorless oil: $R_f$ 0.31 (3:2 dichloromethane/ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.69 (br s, 1 H), 7.48 (d, 1 H, $J$ = 8.0 Hz), 7.26 (d, 1 H, $J$ = 8.0 Hz), 7.14 (t, 1 H, $J$ = 7.5 Hz), 7.07 (t, 1 H, $J$ = 7.5 Hz), 6.03 (d, 1 H, $J$ = 8.0 Hz), 4.90 (dt, 1 H, $J$ = 8.0, 6.0 Hz), 4.17 (dq, 1 H, $J$ = 11.0, 7.0 Hz), 4.07 (dq, 1 H, $J$ = 11.0, 7.0 Hz), 3.88 (td, 1 H, $J$ = 10.0, 5.5 Hz), 3.85 (td, 1 H, $J$ = 10.0, 5.5 Hz), 3.69 (q, 2 H, $J$ = 7.0 Hz), 3.33 (d, 2 H, $J$ = 6.0 Hz), 2.98 (t, 2 H, $J$ = 5.5 Hz), 1.95 (s, 3 H), 1.42 (t, 3 H, $J$ = 7.0 Hz), 1.23 (t, 3 H, $J$ = 7.0 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.2, 169.8, 137.6, 128.4, 122.4, 122.3, 119.7, 118.5, 113.7, 110.7, 71.5, 67.2, 61.8, 53.2, 28.7, 28.6, 23.6, 15.4, 14.2; ESI-MS $m/z$ 449 MNa$^+$. 
**Compound 3-1-20.** Dimethyldioxirane (total ~ 145 µL of a 0.23 M titrated solution of DMDO in chloroform, ~ 1.0 equiv) was added to a stirred solution of 17.4 mg (0.0334 mmol) of selenoether 3-1-6 in 1 mL of moist dichloromethane. After 2 min of stirring at room temperature, the reaction mixture was concentrated to give 17.9 mg (100%) of selenoxide 3-1-20 as a colorless oil: $R_f$ 0.43 (9:9:1 hexanes/dichloromethane/methanol); $^1$H NMR (400 MHz, CDCl$_3$) δ 10.18 (br s, 2 H), 7.95 (s, 1 H), 7.93 (s, 1 H), 6.02 (d, 1 H, $J = 5.6$ Hz), 5.98 (d, 1 H, $J = 5.6$ Hz), 5.48 (t, 1 H, $J = 5.6$ Hz), 5.42 (t, 1 H, $J = 5.6$ Hz), 5.35 – 5.38 (m, 2 H), 4.29 – 4.35 (m, 6 H), 3.81 – 3.91 (m, 4 H), 3.37 – 3.52 (m, 6 H), 3.00 – 3.06 (m, 2 H), 2.24 (s, 3 H), 2.23 (s, 3 H), 2.10 (s, 6 H), 2.07 (s, 6 H), 1.14 (t, 3 H, $J = 6.8$ Hz), 1.31 (t, 3 H, $J = 7.2$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 171.0, 171.0, 169.8, 169.7, 160.7, 160.7, 150.4, 150.3, 141.7, 141.2, 114.3, 114.3, 89.4, 89.0, 80.7, 80.6, 73.1, 72.9, 70.7, 66.8, 66.8, 63.3, 63.2, 62.7, 62.5, 50.5, 50.7, 21.1, 20.7, 20.6, 15.2; $^{77}$Se NMR (76 MHz, CDCl$_3$) δ 851.4, 848.9 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS $m/z$ 561 MNa$^+$. 
**Compound 3-1-21.** Dimethyldioxirane (total ~ 81 µL of a 0.30 M titrated solution of DMDO in chloroform, ~ 1.0 equiv) was added to a stirred solution of 11.3 mg (0.0244 mmol) of selenoether 3-1-8 in 1 mL of moist dichloromethane. After 2 min of stirring at room temperature, the reaction mixture was concentrated to give 11.7 mg (100%) of selenoxide 3-1-21 as a colorless oil: $R_f$ 0.27 (9:9:1 hexanes/dichloromethane/methanol); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.80 (br s, 2 H), 8.03 (s, 1 H), 7.99 (s, 1 H), 6.33 (dd, 1 H, $J = 8.8, 5.6$ Hz), 6.31 (dd, 1 H, $J = 8.4, 5.6$ Hz), 5.24 – 5.25 (m, 2 H), 4.23 – 4.38 (m, 6 H), 3.79 – 3.90 (m, 4 H), 3.45 – 3.55 (m, 6 H), 3.04 (t, 1 H, $J = 4.8$ Hz), 3.01 (t, 1 H, $J = 4.8$ Hz), 2.29 – 2.48 (m, 4 H), 2.22 (s, 6 H), 2.10 (s, 6 H), 1.14 (t, 3 H, $J = 6.8$ Hz), 1.13 (t, 3 H, $J = 6.8$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.1, 171.1, 170.5, 160.5, 160.5, 150.3, 150.3, 141.0, 140.6, 114.0, 86.1, 85.9, 82.9, 82.8, 74.6, 74.5, 66.8, 63.9, 62.6, 62.5, 50.8, 50.6, 37.9, 37.7, 21.1, 15.3, 15.2; $^{77}$Se NMR (76 MHz, CDCl$_3$) $\delta$ 852.0, 847.9 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS $m/z$ 503 MNa$^+$. 
Compound 3-1-22. A solution of 6.3 mg (0.012 mmol) of selenoxide 3-1-20 in 1 mL of methanol was treated with a catalytic amount of 18.8% methanolic sodium methoxide solution. After 30 min of stirring at room temperature, the reaction was concentrated to give 4.8 mg (100%) of selenoxide 3-1-22 as a colorless oil: \( R_f \) 0.24 (9:9:1 hexanes/dichloromethane/methanol); \(^1\)H NMR (400 MHz, CD\(_3\)OD) \( \delta \) 8.02 (s, 1 H), 8.00 (s, 1 H), 5.92 (d, 1 H, \( J = 4.4 \) Hz), 5.90 (d, 1 H \( J = 4.4 \) Hz), 4.09 – 4.17 (m, 4 H), 3.98 – 4.01 (m, 2 H), 3.82 – 3.89 (m, 6 H), 3.73 (dd, 2 H, \( J = 12.4, 3.6 \) Hz), 3.51 – 3.61 (m, 6 H), 2.96 – 3.06 (m, 2 H), 1.18 (t, 3 H, \( J = 7.2 \) Hz), 1.18 (t, 3 H, \( J = 7.2 \) Hz); \(^{13}\)C NMR (100 MHz, CD\(_3\)OD) \( \delta \) 171.7, 171.7, 159.4, 140.3, 140.1, 112.1, 112.1, 91.2, 91.0, 85.1, 75.1, 75.1, 70.3, 70.2, 66.4, 63.2, 63.1, 61.6, 61.5, 51.2, 14.2, 14.2; \(^{77}\)Se NMR (76 MHz, CD\(_3\)OD) \( \delta \) 840.0, 839.9 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS m/z 435 MNa\(^+\).
**Compound 3-1-23.** A solution of 8.0 mg (0.017 mmol) of selenoxide 3-1-21 in 1 mL of methanol was treated with a catalytic amount of 18.8% methanolic sodium methoxide solution. After 30 min of stirring at room temperature, the reaction was concentrated to give 6.6 mg (100%) of selenoether 3-1-23 as a colorless oil: *R*<sub>f</sub> 0.46 (4:1 dichloromethane/methanol); <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.00 (s, 2 H), 6.29 (t, 1 H, *J* = 5.6 Hz), 6.27 (t, 1 H, *J* = 5.6 Hz), 4.34 (app sext, 2 H, *J* = 3.2 Hz), 3.83 – 3.93 (m, 6 H), 3.78 (dd, 1 H, *J* = 12.0, 5.6 Hz), 3.77 (dd, 1 H, *J* = 12.0, 5.6 Hz), 3.70 (dd, 2 H, *J* = 12.0, 4.4 Hz), 3.50 – 3.62 (m, 6 H), 3.02 (app q, 1 H, *J* = 5.2 Hz), 2.99 (app q, 1 H, *J* = 5.2 Hz), 2.36 (app quint, 1 H, *J* = 3.2 Hz), 2.32 (app quint, 1 H, *J* = 3.2 Hz), 2.12 (app sext, 2 H, *J* = 6.4 Hz), 1.17 (t, 3 H, *J* = 7.2 Hz), 1.17 (t, 3 H, *J* = 7.2 Hz); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD) δ 171.7, 171.7, 159.1, 139.7, 139.6, 111.9, 111.8, 87.7, 87.6, 86.6, 86.5, 71.2, 66.4, 66.3, 63.1, 61.9, 61.9, 51.4, 51.3, 40.9, 40.9, 14.2, 14.2; <sup>77</sup>Se NMR (76 MHz, CD<sub>3</sub>OD) δ 842.9, 841.3 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS *m/z* 419 MNa<sup>+</sup>.
**Compound 3-1-24.** Dimethyldioxirane (total ~ 362 µL of a 0.23 M titrated solution of DMDO in chloroform, ~ 3.0 equiv) was added to a stirred solution of 14.9 mg (0.0277 mmol) of selenoxide 3-1-20 in 1 mL of moist dichloromethane. After 6 h of stirring at -10 °C, the reaction mixture was concentrated and chromatographed on silica with 2:3 dichloromethane / acetone as the eluant to give 11.9 mg (78%) of selenone 3-1-24 as a colorless oil: $R_f$ 0.55 (2:3 dichloromethane/acetone); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.44 (s, 1 H), 6.08 (d, 1 H, $J$ = 5.2 Hz), 5.38 (t, 1 H, $J$ = 5.6 Hz), 5.35 (dd, 1 H, $J$ = 5.6, 3.6 Hz), 4.40 (app q, 1 H, $J$ = 3.6 Hz), 4.40 (dd, 1 H, $J$ = 13.2, 3.2 Hz), 3.29 (dd, 1 H, $J$ = 13.2, 3.2 Hz), 4.10 – 4.16 (m, 1 H), 4.00 – 4.06 (m, 3 H), 3.47 (dq, 2 H, $J$ = 7.2, 1.2 Hz), 2.26 (s, 3 H), 2.12 (s, 3 H), 2.01 (s, 3 H), 1.07 (t, 3 H, $J$ = 7.2 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.0, 169.7, 169.7, 157.9, 149.1, 144.7, 118.7, 88.5, 81.2, 73.6, 70.5, 67.1, 63.1, 62.9, 60.9, 21.1, 20.7, 20.6, 15.0; $^{77}$Se NMR (76 MHz, CDCl$_3$) $\delta$ 983.0 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS m/z 577 MNa$^+$. 
Compound 3-1-25. Dimethyldioxirane (total ~ 1.09 mL of a 0.23 M titrated solution of DMDO in chloroform, ~ 3.0 equiv) was added to a stirred solution of 40.0 mg (0.0835 mmol) of selenoxide 3-1-21 in 1 mL of moist dichloromethane. After 6 h of stirring at 10 °C, the reaction mixture was concentrated and chromatographed on silica with 2:3 dichloromethane / acetone as the eluant to give 33.9 mg (82%) of selenone 3-1-25 as a colorless oil: Rf 0.52 (2:3 dichloromethane/acetone); ¹H NMR (400 MHz, CDCl₃) δ 9.66 (br s, 1 H), 8.49 (s, 1 H), 6.27 (dd, 1 H, J = 8.4, 6.0 Hz), 5.25 (dt, 1 H, J = 6.4, 2.0 Hz), 4.38 (dd, 1 H, J = 12.0, 3.2 Hz), 4.31 (app q, 1 H, J = 2.8 Hz), 4.27 (dd, 1 H, J = 12.0, 2.8 Hz), 4.12 – 4.20 (m, 1 H), 3.96 – 4.06 (m, 3 H), 3.47 (q, 2 H, J = 7.2 Hz), 2.59 (ddd, 1 H, J = 14.4, 6.0, 2.0 Hz), 2.29 (ddd, 1 H, J = 14.4, 8.0, 6.4 Hz), 2.21 (s, 3 H), 2.10 (s, 3 H), 1.07 (t, 3 H, J = 6.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 171.0, 170.5, 158.3, 149.3, 144.6, 118.1, 86.8, 83.5, 74.6, 67.1, 63.8, 63.2, 60.7, 38.7, 21.1, 15.0; ⁷⁷Se NMR (76 MHz, CDCl₃) δ 983.1 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS m/z 519 MNa⁺.
**Compound 3-1-26.** Sodium azide (4.0 mg, 0.061 mmol) was added to a stirred solution of 6.8 mg (0.012 mmol) of selenone 3-1-24 in 1 mL of dimethylformamide. After 4 h of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 9:9:1 hexanes/dichloromethane/methanol as the eluant to give 5.0 mg (85%) of seleninic acid 3-1-26 as a colorless oil: $R_f$ 0.15 (9:9:1 hexanes/dichloromethane/methanol); $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 8.24 (s, 1 H), 8.23 (s, 1 H), 6.12 (d, 1 H, $J = 5.6$ Hz), 6.07 (d, 1 H, $J = 5.2$ Hz), 5.39 – 5.49 (m, 4 H), 4.35 – 4.44 (m, 6 H), 4.29 (dd, 2 H, $J = 12.4$, 2.8 Hz), 2.22 (s, 3 H), 2.17 (s, 3 H), 2.12 (s, 3 H), 2.10 (s, 3 H), 2.07 (s, 3 H), 2.06 (s, 3 H); $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 171.2, 171.2, 170.3, 143.1, 142.8, 89.2, 88.0, 80.9, 80.7, 73.6, 73.3, 71.0, 70.6, 63.3, 63.0, 19.7, 19.6, 19.2, 19.2, 19.1, 19.1; $^{77}$Se NMR (76 MHz, CD$_3$OD) $\delta$ 1204.1, 1200.2 [vs PhSeSePh at 460.0 ppm as an external standard]; NI ESI-MS $m/z$ 481 M$^+$. 
**Compound 3-1-27.** Sodium azide (8.2 mg, 0.13 mmol) was added to a stirred solution of 12.5 mg (0.0253 mmol) of selenone 3-1-25 in 1 mL of dimethylformamide. After 4 h of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 9:9:1 hexanes/dichloromethane/methanol as the eluant to give 9.6 mg (90%) of seleninic acid 3-1-27 as a colorless oil: $R_f$ 0.15 (9:9:1 hexanes/dichloromethane/methanol); $^1$H NMR (400 MHz, CD$_3$OD) δ 8.29 (s, 1 H), 8.29 (s, 1 H), 6.27 (dd, 1 H, $J = 5.6, 4.0$ Hz), 6.25 (dd, 1 H, $J = 5.6, 4.0$ Hz), 5.26 – 5.29 (m, 2 H), 4.32 – 4.38 (m, 4 H), 4.29 (dd, 1 H, $J = 13.2, 4.0$ Hz), 4.26 (dd, 1 H, $J = 13.2, 4.0$ Hz), 2.58 (ddd, 1 H, $J = 14.4, 5.6, 2.0$ Hz), 2.54 (ddd, 1 H, $J = 14.4, 5.6, 2.0$ Hz), 2.37 (ddd, 1 H, $J = 14.4, 8.4, 6.4$ Hz), 2.35 (ddd, 1 H, $J = 14.4, 8.4, 6.4$ Hz), 2.17 (s, 3 H), 2.14 (s, 3 H), 2.09 (s, 6 H); $^{13}$C NMR (100 MHz, CD$_3$OD) δ 171.4, 171.4, 170.9, 161.2, 150.4, 142.6, 142.4, 118.6, 118.4, 86.7, 86.6, 83.2, 83.1, 74.9, 74.8, 63.9, 63.9, 37.8, 37.6, 19.7, 19.6; $^{77}$Se NMR (76 MHz, CD$_3$OD) δ 1204.1, 1200.6 [vs PhSeSePh at 460.0 ppm as an external standard]; NI ESI-MS $m/z$ 423 M$^+$. 
**Compound 3-1-28.** A solution of 5.0 mg (0.010 mmol) of seleninic acid 3-1-26 in 1 mL of methanol was treated with 4 µL of 18.8% methanolic sodium methoxide solution. After 30 min of stirring at room temperature, the reaction was concentrated to give 3.9 mg (100%) of seleninate 3-1-28 as a colorless oil: $^1$H NMR (400 MHz, D$_2$O) δ 8.90 (s, 1 H), 5.78 (d, 1 H, $J = 5.2$ Hz), 4.16 (t, 1 H, $J = 4.8$ Hz), 4.00 (t, 1 H $J = 5.2$ Hz), 3.92 (dt, 1 H, $J = 5.2$, 3.2 Hz), 3.75 (dd, 1 H, $J = 12.4$, 3.2 Hz), 3.67 (dd, 1 H, $J = 12.4$, 5.2 Hz); $^{13}$C NMR (100 MHz, D$_2$O) δ 173.4, 159.9, 139.8, 125.2, 90.7, 84.6, 74.7, 70.5, 61.8; $^{77}$Se NMR (76 MHz, D$_2$O) δ 1130.7 [vs PhSeSePh at 460.0 ppm as an external standard]; NI ESI-MS $m/z$ 355 M$^-$. 
**Compound 3-1-19.** A solution of 9.0 mg (0.021 mmol) of seleninic acid 3-1-27 in 1 mL of methanol was treated with 7 µL of 18.8% methanolic sodium methoxide solution. After 30 min of stirring at room temperature, the reaction was concentrated to give 7.7 mg (100%) of seleninate 3-1-29 as a colorless oil: \(^1\)H NMR (400 MHz, D\(_2\)O) \(\delta\) 7.94 (s, 1 H), 6.12 (t, 1 H, \(J = 6.8\) Hz), 4.32 (dt, 1 H, \(J = 6.8, 3.6\) Hz), 3.90 (dt, 1 H, \(J = 5.6, 3.6\) Hz), 3.71 (dd, 1 H, \(J = 12.4, 3.6\) Hz), 3.64 (dd, 1 H, \(J = 12.4, 5.6\) Hz), 2.27 (ddd, 1 H, \(J = 14.0, 6.4, 3.6\) Hz), 2.20 (dt, 1 H, \(J = 14.0, 6.8\) Hz); \(^{13}\)C NMR (100 MHz, D\(_2\)O) \(\delta\) 173.4, 159.6, 139.6, 125.1, 86.8, 86.3, 70.9, 61.7, 39.5; \(^{77}\)Se NMR (76 MHz, D\(_2\)O) \(\delta\) 1130.8 [vs PhSeSePh at 460.0 ppm as an external standard]; NI ESI-MS \(m/z\) 339 M\(^+\).
**Compound 3-1-31.** Diisopropylethylamine (52.6 µL, 0.302 mmol) followed by chloromethyl ethyl ether (14.0 µL, 0.151 mmol) were added to a solution of 14.0 mg (0.0302 mmol) of selenoether 3-1-18 in 1 mL dichloromethane. After 4 h of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 3:2 hexanes/ethyl acetate as the eluant to give 13.3 mg (85%) of selenoether 3-1-31 as a colorless oil: \( R_f \) 0.49 (3:2 hexanes/ethyl acetate); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.75 (d, 2 H, \( J = 7.5 \) Hz), 7.51 (t, 1 H, \( J = 7.5 \) Hz), 7.43 (t, 2 H, \( J = 7.5 \) Hz), 7.13 (d, 1 H, \( J = 2.0 \) Hz), 7.01 (d, 1 H, \( J = 8.0 \) Hz), 6.94 (dd, 1 H, \( J = 8.0, 2.0 \) Hz), 6.61 (d, 1 H, \( J = 7.5 \) Hz), 5.25 (s, 2 H), 5.03 (dt, 1 H, \( J = 7.0, 5.5 \) Hz), 4.23 (dq, 2 H, \( J = 7.0, 2.0 \) Hz), 3.75 (q, 2 H, \( J = 7.0 \) Hz), 3.61 (t, 2 H, \( J = 7.0 \) Hz), 3.45 (q, 2 H, \( J = 7.0 \) Hz), 3.23 (dd, 1 H, \( J = 14.0, \) 6.0 Hz), 3.17 (dd, 1 H, \( J = 14.0, 5.0 \) Hz), 2.97 (td, 1 H, \( J = 13.0, 7.0 \) Hz), 2.95 (td, 1 H, \( J = 13.0, 7.0 \) Hz), 1.30 (t, 3 H, \( J = 7.0 \) Hz), 1.22 (t, 3 H, \( J = 7.0 \) Hz), 1.17 (t, 3 H, \( J = 7.0 \) Hz); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 171.8, 167.0, 155.1, 134.2, 132.1, 132.0, 130.2, 128.9, 128.7, 127.3, 120.9, 114.6, 93.8, 70.0, 66.4, 64.7, 61.9, 53.8, 37.2, 24.6, 15.4, 15.3, 14.4; ESI-MS \( m/z \) 546 MNa\(^+\).
**Compound 3-1-32.** Dimethyldioxirane (total ~ 77 µL of a 0.30 M titrated solution of DMDO in chloroform, ~ 1.0 equiv) was added to a stirred solution of 12.0 mg (0.0230 mmol) of selenoether 3-1-31 in 1 mL of moist dichloromethane. After 2 min of stirring at room temperature, the reaction mixture was concentrated to give 12.4 mg (100%) of selenoxide 3-1-32 as a colorless oil: $R_f$ 0.20 (19:1 dichloromethane/methanol); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.78 (d, 2 H, $J = 7.5$ Hz), 7.75 (d, 2 H, $J = 8.0$ Hz), 7.71 (d, 1 H, $J = 2.5$ Hz), 7.69 (d, 1 H, $J = 2.5$ Hz), 7.47 (m, 2 H), 7.42 (t, 2 H, $J = 8.0$ Hz), 7.42 (t, 2 H, $J = 8.0$ Hz), 7.27 (dd, 1 H, $J = 8.5, 2.0$ Hz), 7.22 (dd, 1 H, $J = 8.5, 2.5$ Hz), 7.10 (d, 1 H, $J = 8.0$ Hz), 7.08 (d, 1 H, $J = 8.0$ Hz), 6.78 (d, 1 H, $J = 7.5$ Hz), 6.72 (d, 1 H, $J = 7.5$ Hz), 5.28 (d, 1 H, $J = 7.0$ Hz), 5.27 (d, 1 H, $J = 6.5$ Hz), 5.24 (d, 1 H, $J = 7.0$ Hz), 5.23 (d, 1 H, $J = 6.5$ Hz), 5.06 (dt, 1 H, $J = 7.0, 5.5$ Hz), 5.05 (app q, 1 H, $J = 7.0, 5.5$ Hz), 4.27 (app q, 4 H, $J = 7.0$ Hz), 3.92 (ddd, 1 H, $J = 10.5, 10.0, 4.5$ Hz), 3.85 (ddd, 1 H, $J = 10.5, 10.0, 4.5$ Hz), 3.74 (ddd, 1 H, $J = 10.0, 5.5, 4.5$ Hz), 3.71 (q, 4 H $J = 7.0$ Hz), 3.64 (ddd, 1 H, $J = 10.0, 5.5, 4.5$ Hz), 3.42 $-$ 3.57 (m, 4 H), 3.28 $-$ 3.38 (m, 3 H), 3.17 $-$ 3.27 (m, 3 H), 2.77 (dt, 1 H, $J = 12.0, 4.5$ Hz), 2.66 (dt, 1 H, $J = 12.0, 4.5$ Hz), 1.34 (t, 3 H, $J = 7.0$ Hz), 1.32 (t, 3 H, $J = 7.0$ Hz), 1.22 (t, 3 H, $J = 7.0$ Hz), 1.22 (t, 3 H, $J = 7.0$ Hz), 1.18 (t, 3 H, $J = 7.0$ Hz), 1.17 (t, 3 H, $J = 7.0$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 171.8, 171.7, 167.2, 154.0, 154.0, 134.2,
134.2, 133.6, 132.0, 131.5, 131.3, 129.2, 129.1, 128.8, 127.4, 127.3, 127.3, 127.3, 114.3, 114.2, 93.8, 66.9, 66.9, 65.2, 63.4, 63.4, 62.3, 62.2, 53.9, 53.8, 51.5, 51.4, 37.7, 37.3, 15.3, 14.4; ESI-MS m/z 562 MNa\(^+\).
**Compound 3-1-33.** Dimethyldioxirane (total ~ 230 µL of a 0.30 M titrated solution of DMDO in chloroform, ~ 3.0 equiv) was added to a stirred solution of 12.4 mg (0.0230 mmol) of selenoxide 3-1-32 in 1 mL of moist dichloromethane. After 6 h of stirring at -10 °C, the reaction mixture was concentrated and chromatographed on silica with 3:2 dichloromethane / acetone as the eluant to give 10.3 mg (81%) of selenone 3-1-33 as a colorless oil: \( R_f \) 0.60 (3:2 dichloromethane/acetone); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.85 (d, 1 H, \( J = 2.5 \) Hz), 7.77 (d, 2 H, \( J = 8.0 \) Hz), 7.51 (t, 1 H, \( J = 7.5 \) Hz), 7.44 (t, 2 H, \( J = 7.5 \) Hz), 7.41 (dd, 1 H, \( J = 8.5, 2.5 \) Hz), 7.24 (d, 1 H, \( J = 8.5 \) Hz), 6.74 (d, 1 H, \( J = 7.0 \) Hz), 5.35 (s, 2 H), 5.03 (dt, 1 H, \( J = 7.5, 5.5 \) Hz), 4.27 (dq, 2 H, \( J = 7.0, 2.5 \) Hz), 3.91 – 3.96 (m, 4 H), 3.79 (q, 2 H, \( J = 7.0 \) Hz), 3.36 (dd, 1 H, \( J = 14.0, 5.5 \) Hz), 3.29 (q, 2 H, \( J = 7.0 \) Hz), 3.24 (dd, 1 H, \( J = 14.0, 5.5 \) Hz), 1.34 (t, 3 H, \( J = 7.0 \) Hz), 1.22 (t, 3 H, \( J = 7.0 \) Hz), 0.83 (t, 3 H, \( J = 7.0 \) Hz); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 171.4, 167.3, 154.3, 136.8, 134.0, 132.1, 131.2, 131.0, 129.2, 128.9, 127.3, 116.3, 94.3, 66.9, 65.5, 63.2, 62.4, 60.4, 53.8, 37.1, 15.2, 14.8, 14.4; ESI-MS \( m/z \) 578 MNa\(^+\).
**Compound 3-1-34.** Sodium azide (5.9 mg, 0.090 mmol) was added to a stirred solution of 10.0 mg (0.0181 mmol) of selenone 3-1-33 in 1 mL of dimethylformamide. After 4 h of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 9:1 dichloromethane/methanol as the eluant to give 7.7 mg (88%) of seleninic acid 3-1-34 as a colorless oil: $R_f$ 0.37 (9:1 dichloromethane/methanol); $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 7.80 (d, 1 H, $J = 2.0$ Hz), 7.78 (d, 1 H, $J = 2.0$ Hz), 7.76 (d, 2 H, $J = 7.5$ Hz), 7.74 (d, 2 H, $J = 7.5$ Hz), 7.49 – 7.54 (m, 4 H), 7.43 (t, 4 H, $J = 7.5$ Hz), 7.27 (dd, 2 H, $J = 8.5$, 2.5 Hz), 5.37 (d, 1 H, $J = 7.0$ Hz), 5.36 (d, 1 H, $J = 7.0$ Hz), 5.29 (d, 2 H, $J = 7.0$ Hz), 4.86 – 4.90 (m, 2 H), 4.22 (q, 2 H, $J = 7.0$ Hz), 4.22 (dq, 2 H, $J = 7.0$, 1.0 Hz), 3.73 (q, 2 H, $J = 7.0$ Hz), 3.73 (q, 2 H, $J = 7.0$ Hz), 3.37 (dd, 2 H, $J = 14.0$, 5.0 Hz), 3.18 (dd, 1 H, $J = 14.0$, 8.0 Hz), 3.16 (dd, 1 H, $J = 14.0$, 8.0 Hz), 1.28 (t, 3 H, $J = 7.0$ Hz), 1.27 (t, 3 H, $J = 7.0$ Hz), 1.17 (t, 3 H, $J = 7.0$ Hz), 1.16 (t, 3 H, $J = 7.0$ Hz); $^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$ 171.7, 171.6, 169.1, 168.9, 155.3, 155.3, 135.3, 135.2, 134.0, 133.8, 132.2, 131.9, 131.7, 131.7, 131.5, 131.4, 128.4, 127.3, 126.9, 126.6, 114.9, 114.8, 93.5, 64.7, 61.4, 54.7, 54.6, 36.3, 36.2, 14.2, 13.3; NI ESI-MS $m/z$ 482 M$. 

![Diagram of compounds 3-1-33 and 3-1-34].
**Compound 3-1-35.** A solution of selenoxide 3-1-35 (8.0 mg, 0.015 mmol) in 1 ml of acetonitrile was stirred at 60 °C for 16 h and then concentrated to give 7.3 mg (100%) of aldehyde 3-1-35 as a colorless oil: \( R_f \) 0.37 (9:1 dichloromethane/methanol); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 9.49 (t, 1 H, \( J = 3.6 \) Hz), 8.67 (br s, 1 H), 7.79 (s, 1 H), 6.06 (d, 1 H, \( J = 4.8 \) Hz), 5.30 – 5.35 (m, 2 H), 4.32 – 4.43 (m, 3 H), 3.49 (d, 2 H, \( J = 3.6 \) Hz), 2.20 (s, 3 H), 2.13 (s, 3 H), 2.10 (s, 3 H); \(^{13}\)NMR (100 MHz, CDCl\(_3\)) \( \delta \) 192.7, 170.4, 169.8, 169.8, 161.1, 150.0, 144.3, 101.6, 87.4, 80.6, 73.1, 70.5, 63.4, 35.3, 21.2, 20.7, 20.6; \(^{77}\)Se NMR (76 MHz, CDCl\(_3\)) \( \delta \) 186.3 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS \( m/z \) 515 MNa\(^+\).
Compound 3-1-36. Sodium borohydride (1.1 mg, 0.029 mmol) was added to a stirred solution of 14.4 mg (0.0293 mmol) of selenoaldehyde 3-1-35 in 1 mL of methanol. Once all the starting material was consumed (~ 5 min of stirring at room temperature – monitored by TLC), a catalytic amount of 18.8% methanolic sodium methoxide solution was added. After 30 min of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 2:3 dichloromethane / ethyl acetate as the eluant to give 9.1 mg (84%) of selenoalcohol 3-1-36 as a colorless oil: \( R_f \) 0.36 (2:3 dichloromethane/ethyl acetate); \(^1\)H NMR (500 MHz, CD\(_3\)OD) \( \delta \) 8.37 (s, 1 H), 5.90 (d, 1 H, \( J = 4.0 \) Hz), 4.20 (t, 1 H, \( J = 4.5 \) Hz), 4.17 (t, 1 H, \( J = 4.5 \) Hz), 4.02 (dt, 1 H, \( J = 4.5, 2.5 \) Hz), 3.87 (dd, 1 H, \( J = 12.5, 2.5 \) Hz), 3.75 (dd, 1 H, \( J = 12.5, 2.5 \) Hz), 3.74 (t, 2 H, \( J = 6.5 \) Hz), 2.88 (t, 2 H, \( J = 6.5 \) Hz); \(^{13}\)C NMR (100 MHz, CD\(_3\)OD) \( \delta \) 163.7, 151.3, 144.2, 101.5, 89.7, 85.2, 74.8, 70.0, 61.2, 60.9, 28.9; \(^{77}\)Se NMR (76 MHz, CDCl\(_3\)) \( \delta \) 180.9 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS \( m/z \) 391 MNa\(^+\).
**Compound 3-1-40.** N,N-dimethylaniline (9.6 µL, 0.075 mmol) was added to a solution of 13.5 mg (0.0251 mmol) of selenoxide 3-1-20 in 1 mL of acetonitrile. After 12 h of stirring at 80 °C, the reaction mixture was concentrated and chromatographed on silica with 7:3 dichloromethane / ethyl acetate as the eluant to give 8.1 mg (57%) of selenoether 3-1-40 as a colorless oil: Rf 0.33 (7:3 dichloromethane/ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.32 (br s, 1 H), 7.48 (d, 2 H, $J$ = 8.5 Hz), 7.25 (s, 1 H), 6.65 (d, 2 H, $J$ = 9.0 Hz), 6.03 (d, 1 H, $J$ = 5.5 Hz), 5.23 (t, 1 H, $J$ = 5.5 Hz), 5.20 (dd, 1 H, $J$ = 6.0, 4.0 Hz), 4.28 (q, 1 H, $J$ = 4.0 Hz), 4.18 (dd, 1 H, $J$ = 12.5, 4.0 Hz), 4.13 (dd, 1 H, $J$ = 12.5, 3.5 Hz), 2.96 (s, 6 H), 2.16 (s, 3 H), 2.12 (s, 3 H), 2.09 (s, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.4, 169.8, 169.8, 161.0, 151.1, 150.1, 138.8, 136.9, 113.5, 111.5, 109.2, 87.4, 80.2, 73.1, 70.8, 63.5, 40.5, 21.2, 20.8, 20.7; ESI-MS m/z 592 MNa$^+$. 
**Compound 3-1-41.** A solution of 6.8 mg (0.012 mmol) of selenoether 3-1-40 in 1 mL of methanol was treated with a catalytic amount of 18.8% methanolic sodium methoxide solution. After 30 min of stirring at room temperature, the reaction was concentrated to give 5.3 mg (100%) of selenoether 3-1-41 as a colorless oil: $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 7.42 (d, 2 H, $J = 8.5$ Hz), 7.01 (s, 1 H), 6.75 (d, 2 H, $J = 9.0$ Hz), 5.82 (d, 1 H, $J = 4.0$ Hz), 3.93 (dd, 1 H, $J = 5.5$, 4.0 Hz), 3.88 (dt, 1 H, $J = 5.5$, 3.5 Hz), 3.76 (t, 1 H, $J = 5.5$ Hz), 3.54 (dd, 1 H, $J = 12.0$, 3.5 Hz), 3.33 (dd, 1 H, $J = 12.0$, 5.5 Hz), 2.96 (s, 6 H); $^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$ 173.2, 159.4, 151.1, 137.6, 136.6, 113.6, 113.0, 109.2, 91.1, 84.5, 74.9, 70.8, 62.4, 39.5; NI ESI-MS m/z 442 M$^+$.
Compound 3-1-42. Diisopropylamine (2.4 µL, 0.017 mmol) was added to a solution of 3.1 mg (0.0058 mmol) of selenoxide 3-1-20 in 1 mL of acetonitrile. After 12 h of stirring at 80 °C, the reaction mixture was concentrated and chromatographed on silica with 2:3 dichloromethane / ethyl acetate as the eluant to give 2.5 mg (95%) of diselenide 3-1-42 as a colorless oil: \( R_f \) 0.25 (2:3 dichloromethane/ethyl acetate); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.74 (br s, 1 H), 8.03 (s, 1 H), 6.13 (d, 1 H, \( J = 4.5 \) Hz), 5.45 (t, 1 H, \( J = 5.0 \) Hz), 5.41 (t, 1 H, \( J \) = 5.0 Hz), 4.45 (dd, 1 H, \( J = 12.0, 2.5 \) Hz), 4.35 – 4.38 (m, 1 H), 4.34 (dd, 1 H, \( J = 12.0, 3.5 \) Hz), 2.17 (s, 6 H), 2.13 (s, 6 H), 2.12 (s, 6 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 170.6, 169.9, 169.9, 161.4, 149.8, 146.2, 104.5, 87.5, 80.1, 73.5, 70.1, 63.1, 21.2, 20.8, 20.7; \(^{77}\)Se NMR (76 MHz, CDCl\(_3\)) \( \delta \) 436.9 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS \( m/z \) 921 MNa\(^+\).
Compound 3-1-43. A solution of 5.0 mg (0.0056 mmol) of diselenide 3-1-42 in 1 mL of methanol was treated with a catalytic amount of 18.8% methanolic sodium methoxide solution. After 30 min of stirring at room temperature, the reaction was concentrated to give 3.6 mg (100%) of selenoether 3-1-43 as a colorless oil: $^1$H NMR (500 MHz, D$_2$O) $\delta$ 7.65 (s, 1 H), 5.69 (d, 1 H, $J$ = 4.0 Hz), 4.01 (t, 1 H, $J$ = 4.5 Hz), 3.97 (t, 1 H, $J$ = 4.5 Hz), 3.91 – 3.93 (m, 1 H), 3.76 (dd, 1 H, $J$ = 12.5, 3.0 Hz), 3.61 (dd, 1 H, $J$ = 12.5, 4.0 Hz); $^{13}$C NMR (125 MHz, D$_2$O) $\delta$ 147.9, 102.5, 90.1, 83.2, 74.9, 68.9, 60.4; NI ESI-MS $m/z$ 645 M$^+$. 
Compound 3-1-44. Sulfuryl chloride (1.2 µL, 0.014 mmol) was added to a solution of 12.8 mg (0.0202 mmol) of diselenide 3-1-42 in 1 mL of dichloromethane. After 30 min of stirring at room temperature, 6.3 µL (0.043 mmol) of trimethylsilyl-imidazole was added. The reaction solution was stirred for an additional 30 min and then was concentrated and chromatographed on silica with 6:3:1 dichloromethane / hexanes / methanol as the eluant to give 8.7 mg (59%) of selenoether 3-1-44 as a colorless oil: $R_f$ 0.27 (6:3:1 dichloromethane/hexanes/methanol); $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 7.78 (d, 1 H, $J = 1.0$ Hz), 7.55 (s, 1 H), 7.34 (br s, 1 H), 5.94 (d, 1 H, $J = 4.5$ Hz), 5.40 (t, 1 H, $J = 5.0$ Hz), 5.33 (t, 1 H, $J = 5.0$ Hz), 4.32 (q, 1 H, $J = 5.0$ Hz), 4.26 (dd, 1 H, $J = 12.5, 4.5$ Hz), 4.23 (dd, 1 H, $J = 12.5, 3.5$ Hz), 2.11 (s, 3 H), 2.09 (s, 3 H), 2.07 (s, 3 H); $^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$ 170.9, 170.1, 170.1, 162.5, 150.6, 140.7, 138.1, 105.8, 88.7, 80.1, 73.3, 70.6, 63.1, 19.6, 19.2, 19.1; ESI-MS $m/z$ 517 MH$^+$. 
Compound 3-1-44. A solution of 8.7 mg (0.017 mmol) of selenoether 3-1-44 in 1 mL of methanol was treated with a catalytic amount of 18.8% methanolic sodium methoxide solution. After 30 min of stirring at room temperature, the reaction was concentrated to give 6.6 mg (100%) of selenoether 3-1-45 as a colorless oil: $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 7.69 (s, 1 H), 7.22 (d, 1 H, $J$ = 1.0 Hz), 7.12 (br s, 1 H), 5.84 (d, 1 H, $J$ = 4.0 Hz), 3.98 (t, 1 H, $J$ = 4.5 Hz), 3.86 – 3.92 (m, 2 H), 3.65 (dd, 1 H, $J$ = 12.0, 3.5 Hz), 3.47 (dd, 1 H, $J$ = 12.0, 4.5 Hz); $^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$ 173.1, 159.4, 140.6, 137.1, 129.8, 121.4, 108.4, 90.8, 84.4, 74.7, 70.6, 62.1; ESI-MS m/z 413 M$^+$.
**Compound 3-1-46.** Bromine (1.0 µL, 0.020 mmol) was added to a solution of 18.1 mg (0.0202 mmol) of diselenide 3-1-42 in 1 mL of dichloromethane. After 30 min of stirring at room temperature, 4.2 µL (0.024 mmol) of triethylphosphite was added. The reaction solution was stirred for an additional 30 min and then was concentrated and chromatographed on silica with 1:1 acetone / hexanes as the eluant to give 17.5 mg (74%) of selenophosphonate 3-1-46 as a colorless oil: \(R_f \) 0.33 (1:1 acetone/hexanes); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta \) 9.00 (br s, 1 H), 7.99 (d, 1 H, \(J = 3.0\) Hz), 6.06 (d, 1 H, \(J = 4.5\) Hz), 5.34 – 5.38 (m, 2 H), 4.40 (app s, 3 H), 4.15 – 4.29 (m, 4 H), 2.23 (s, 3 H), 2.13 (s, 3 H), 2.11 (s, 3 H), 1.36 (t, 3 H, \(J = 7.0\) Hz), 1.36 (t, 3 H, \(J = 7.0\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta \) 170.5, 169.8, 169.7, 161.0, 150.0, 145.7 (d, \(J = 4.5\) Hz), 99.6 (d, \(J = 8.2\) Hz), 87.8, 80.5, 73.3, 70.5, 64.9 (d, \(J = 6.0\) Hz), 64.7 (d, \(J = 5.9\) Hz), 63.4, 21.2, 20.7, 20.6, 16.2, 16.1; \(^{31}\)P NMR (202 MHz, CDCl\(_3\)) \(\delta \) 16.8 [vs Phosphoric acid at 0.0 ppm as an external standard]; \(^{77}\)Se NMR (76 MHz, CDCl\(_3\)) \(\delta \) 175.1 (d, \(J = 456\) Hz) [vs PhSeSePh at 460.0 ppm as an external standard]; NI ESI-MS \(m/z \) 585 M\(^+\).
Compounds 4-2-2. 4-Ethoxybenzeneboronic acid 4-2-1 (20.0 mg, 0.120 mmol) was added to a solution of hydrogen peroxide (13.6 µL of a 30% solution in water, 0.120 mmol) in 1 mL of water. After 16 h of stirring at room temperature, the reaction solution was extracted into dichloromethane (6 x 3 mL), dried over sodium sulfate, and concentrated to give a spectroscopic yield of 86% of 4-ethoxyphenol 4-2-2 (% yield was calculated based on crude NMR using 2,6-ditertbutyl-4-methyl phenol as an internal standard): Rf 0.46 (3:7 ethyl acetate/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) δ 6.78 (m, 4 H), 4.71 (s, 1 H), 3.98 (q, 2 H, $J = 7.0$ Hz), 1.39 (t, 3 H, $J = 7.0$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 153.3, 149.6, 116.3, 115.9, 64.4, 15.2.
Compounds 4-2-1. 4-Ethoxybenzeneboronic acid 4-2-1 (20.0 mg, 0.120 mmol) was added to a flask charged with in 1 mL of water. After 16 h of stirring at room temperature, the reaction solution was extracted into dichloromethane (6 x 3 mL), dried over sodium sulfate, and concentrated to recover 95% of 4-ethoxybenzeneboronic acid 4-2-1: \( R_f 0.17 \) (3:7 ethyl acetate/hexanes); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta 8.16 \) (d, 2 H, \( J = 8.5 \) Hz), 7.01 (d, 2 H, \( J = 8.5 \) Hz), 4.14 (q, 2 H, \( J = 7.0 \) Hz), 1.57 (br s, 2 H), 1.47 (t, 3 H, \( J = 7.0 \) Hz); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta 162.8, 137.7, 135.5, 114.2, 63.6, 15.0. \)
Compounds 4-2-2. Hydrogen peroxide (13.6 μL of a 30% solution in water, 0.120 mmol) was added to a flask containing 1 mL of dichloromethane and the mixture was stirred vigorously at room temperature for 10 min before it was washed with 1 mL of water. The water layer was subsequently added to a flask charged with 4-ethoxybenzeneboronic acid 4-2-1 (20.0 mg, 0.120 mmol). After 16 h of stirring at room temperature, the reaction solution was extracted into dichloromethane (6 x 3 mL), dried over sodium sulfate, and concentrated to give a spectroscopic yield of 77% of 4-ethoxyphenol 4-2-2 (% yield was calculated based on crude NMR using 2,6-ditertbutyl-4-methyl phenol as an internal standard).
**Compound 4-2-1.** Neat commercial N-(**tert**-butoxycarbonyl)-L-cysteine methyl ester (97%, d = 1.143 g/mL, 12.8 µL, 0.060 mmol) was added by micropipette over a 10 sec period to a stirred solution of 25.0 mg (0.060 mmol) of seleninic acid 2-2-3 and 6.8 µL (0.378 mmol) of water in 1 mL of moist dichloromethane. After 1 min of stirring at room temperature, TLC analysis indicated that 2-2-3 was consumed, and the reaction mixture was washed with 1 mL of water. The water layer was subsequently added to a flask charged with 4-ethoxybenzeneboronic acid 4-2-1 (10.0 mg, 0.060 mmol). After 16 h of stirring at room temperature, the reaction solution was extracted into dichloromethane (6 x 3 mL), dried over sodium sulfate, and concentrated to to recover 96% of 4-ethoxybenzeneboronic acid 4-2-1.
Compounds 4-2-3, 4-2-4, & 3-1-4. A solution of 11.1 mg (0.060 mmol) of seleninic acid 3-1-3 in 0.5 mL of dichloromethane was treated dropwise with 0.5 mL solution of p-thiocresol (22.4 mg, 0.180 mmol) in dichloromethane. After 5 min of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 9:1 hexanes / ethyl acetate as the eluant to give 13.4 mg (81%) of selenosulfide 4-2-3 as a colorless oil, 15.3 mg (69%) of disulfide 4-2-4 as a colorless oil, and 1.5 mg (17%) of diselenide 3-1-4 as a yellow oil. Selenosulfide 4-2-3: \( R_f \) 0.13 (1:9 hexane/ethyl acetate); \( ^1H \) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.44 (d, 2 H, \( J = 8.4 \) Hz), 7.08 (d, 2 H, \( J = 8.4 \) Hz), 3.71 (t, 2 H, \( J = 6.8 \) Hz), 3.46 (q, 2 H, \( J = 7.2 \) Hz), 3.09 (t, 2 H, \( J = 6.8 \) Hz), 2.32 (s, 3 H), 1.17 (t, 3 H, \( J = 7.2 \) Hz); \( ^{13}C \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 137.6, 133.8, 130.5, 129.9, 69.4, 66.5, 31.8, 21.2, 15.4; \(^{77}\text{Se} \) NMR (76 MHz, CDCl\(_3\)) \( \delta \) 437.4 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS \( m/z \) 299 MNa\(^+\). Disulfide 4-2-4: \( R_f \) 0.64 (1:9 hexane/ethyl acetate); \( ^1H \) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.40 (d, 4 H, \( J = 8.0 \) Hz), 7.12 (d, 4 H, \( J = 7.5 \) Hz), 2.33 (s, 6 H); \( ^{13}C \) NMR (125 MHz, CDCl\(_3\)) \( \delta \) 137.7, 134.2, 130.0, 128.8, 21.3; ESI-MS \( m/z \) 269 MNa\(^+\).
Compounds 4-2-5, 4-2-6, 4-2-3, 4-2-4, & 3-1-4. A solution of 20.6 mg (0.111 mmol) of seleninic acid 3-1-3 in 1 mL of dichloromethane was treated with 13.8 mg (0.111 mmol) of thiocresol. After 5 min of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 9:1 hexanes / ethyl acetate as the eluant to give 14.9 mg (44%) of selenosulfonate 4-2-5 as a colorless oil, 1.7 mg (11%) of thiosulfonate 4-2-5 as a white solid, 3.7 mg (12%) of selenosulfide 4-2-3 as a colorless oil, 4.3 mg (32%) of disulfide 4-2-4 as a colorless oil, and 6.6 mg (39%) of diselenide 3-1-4 as a yellow oil. Similar results were obtained upon scaling up the reaction to 1.5 mmol scale.

Selenosulfonate 4-2-5: $R_f$ 0.13 (1:9 hexane/ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.77 (d, 2 H, $J = 8.5$ Hz), 7.33 (d, 2 H, $J = 8.5$ Hz), 3.76 (t, 2 H, $J = 6.5$ Hz), 3.46 (q, 2 H, $J = 7.0$ Hz), 3.38 (t, 2 H, $J = 6.5$ Hz), 2.45 (s, 3 H), 1.15 (t, 3 H, $J = 7.0$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 144.8, 144.7, 130.0, 126.7, 69.1, 66.8, 33.3, 21.9, 15.2; $^{77}$Se NMR (76 MHz, CDCl$_3$) $\delta$ 857.2 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS m/z 331 MNa$^+$. Thiosulfonate 4-2-6: $R_f$ 0.27 (1:9 hexane/ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.47 (d, 2 H, $J = 8.0$ Hz), 7.25 (d, 2 H, $J = 8.5$ Hz), 7.22 (d, 2 H, $J = 8.0$ Hz), 7.15 (d, 2 H, $J = 8.0$ Hz), 2.43 (s, 3 H), 2.38 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 144.8, 142.3, 140.7, 136.7, 130.4, 129.6, 127.8, 124.9, 21.9, 21.7; ESI-MS m/z 301 MNa$^+$. 
Compounds 4-2-5. Seleninic acid 3-1-3 (8.4 mg, 0.045 mmol) in 1 mL of dichloromethane was added dropwise using a syringe to a solution of 9.3 mg (0.05 mmol) of p-toluenesulfonyl hydrazide in dichloromethane. After 30 min of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 4:1 hexanes / ethyl acetate as the eluant to give 13.9 mg (100%) of selenosulfonate 4-2-5 as a white solid.
Compounds 4-2-5. Compounds 4-2-6. Dimethyldioxirane (total ~ 196 µL of a 0.30 M titrated solution of DMDO in chloroform, ~ 2.0 equiv) was added to a stirred solution of 8.1 mg (0.029 mmol) of selenosulfide 4-2-3 in 1 mL of moist dichloromethane. After 2 min of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 4:1 hexanes / ethyl acetate as the eluant to give 6.8 mg (76%) of selenosulfonate 4-2-5 as a white solid.
**Compounds 4-2-6.** Dimethyldioxirane (total ~ 366 µL of a 0.30 M titrated solution of DMDO in chloroform, ~ 2.0 equiv) was added to a stirred solution of 13.5 mg (0.0549 mmol) of disulfide 4-2-4 in 1 mL of moist dichloromethane. After 2 min of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 9:1 hexanes / ethyl acetate as the eluant to give 14.1 mg (92%) of thiolsulfonate 4-2-6 as a white solid.
Compounds 3-1-6 & 4-3-1. Ethoxyethaneseleninic acid (7.1 mg, 0.038 mmol) was added to a solution of 20.5 mg (0.0382 mmol) of selenoxide 3-1-20 in 1 mL of acetonitrile. After 16 h of stirring at 60 °C, the reaction mixture was concentrated and dichloromethane was added to triturate 2.4 mg (57%) of selenium dioxide as a white solid. The dichloromethane solution was chromatographed on silica with 1:1 dichloromethane / ethyl acetate then 19:1 dichloromethane / methanol to give 11.3 mg (57%) of selenoether 3-1-6 as a colorless oil, 1.2 mg (9%) of ethoxyethane diselenide 3-1-4 as a yellow oil, 6.8 mg (20%) of uridine diselenide 3-1-42 as a colorless oil, and 3.2 mg (14%) of mixed diselenide 4-3-3 as a colorless oil. 1.4 mg (20%) of ethoxyethaneseleninic acid was recovered. Selenium dioxide 4-3-1: $^{77}$Se NMR (76 MHz, CD$_3$OD) $\delta$ 1341.1 [vs PhSeSePh at 460.0 ppm as an external standard]. Diselenide 4-3-3: $R_f$ 0.60 (3:2 ethyl acetate/dichloromethane); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.12 (br s, 1 H), 7.87 (s, 1 H), 6.06 (d, 1 H, $J = 5.0$ Hz), 5.35 – 5.37 (m, 2 H), 4.38 (app s, 3 H), 3.76 (t, 2 H, $J = 6.5$ Hz), 3.53 (q, 2 H, $J = 7.0$ Hz), 3.37 (t, 2 H, $J = 7.0$ Hz), 2.22 (s, 3 H), 2.12 (s, 3 H), 2.11 (s, 3 H), 1.20 (t, 3 H, $J = 7.0$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.4, 169.8, 169.8, 161.0, 149.9, 142.9, 105.2, 87.8, 80.4, 73.2, 70.5, 70.3, 66.5, 63.3, 31.3, 21.3, 20.7, 20.6, 15.4; ESI-MS m/z 625 MNa$^+$. 
**Compound 3-1-6.** Uridine triacetate 3-1-5 (50.0 mg, 0.135 mmol) followed by a catalytic amount of trifluoroacetic acid were added to a solution of 50.0 mg (0.270 mmol) of seleninic acid 3-1-3 in 1 mL of moist acetonitrile. After 16 h of stirring at 60 °C, the reaction mixture was concentrated and dichloromethane was added to triturate 7.6 mg (25% – based on 3-1-3) of selenium dioxide as a white solid. The dichloromethane solution was chromatographed on silica with 1:1 dichloromethane / ethyl acetate then 19:1 dichloromethane / methanol to give 41 mg (58%) of selenoether 3-1-6 as a colorless oil, 8.6 mg (21% – based on 3-1-3) of ethoxyethane diselenide 3-1-4 as a yellow oil, 2.4 mg (4%) of uridine diselenide 3-1-42 as a colorless oil, and 1.0 mg (1%) of mixed diselenide 4-3-3 as a colorless oil. 12.2 mg (24%) of uridine triacetate 3-1-5 and 11.6 mg (23% – based on 3-1-3) of ethoxyethaneseleninic acid were recovered.
Compound 4-3-1. Dimethyldioxirane (total ~ 541 µL of a 0.30 M titrated solution of DMDO in chloroform, ~ 3.0 equiv) was added to a stirred solution of 10.0 mg (0.0541 mmol) of seleninic Acid 3-1-3 in 1 mL of moist dichloromethane. After 30 min of stirring at room temperature, the white precipitate was filtered to give 5.6 mg (93%) of selenium dioxide 4-3-1.
Compounds 3-1-6 & 4-3-5. Dodecyl sulfide 4-3-4 (4.0 mg, 0.010 mmol) followed by a catalytic amount of trifluoroacetic acid were added to a solution of 5.4 mg (0.010 mmol) of selenoxide 3-1-20 in 1 mL of dichloromethane. After 2 h of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 3:2 dichloromethane / ethyl acetate as the eluant to give 5.2 mg (100%) of selenoether 3-1-6 as a colorless oil and 4.2 mg (100%) of dodecyl sulfoxide 4-3-5 as a white solid. Dodecyl sulfoxide 4-3-5: mp 88–89 °C; Rf 0.45 (3:2 hexane/ethyl acetate); ¹H NMR (500 MHz, CDCl₃) δ 2.59 – 2.71 (m, 2 H), 1.73 – 1.80 (m, 2 H), 1.38 – 1.51 (m, 2 H), 1.26 – 1.37 (m, 16 H), 0.88 (t, 3 H, J = 7.0 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 52.7, 32.1, 29.8, 29.8, 29.6, 29.6, 29.4, 29.1, 22.9, 22.8, 14.3; ESI-MS m/z 387 MH⁺.
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Sulfur Proton

[Chemical structure image with peaks labeled H1, H2, H3, H4, H5, H6, and CH3]

[Graph showing peaks at various ppm values]
NOE: H1

NOE: H2
332

Na+ Se
O
O

HO

2-2-42

ppm (δ°)

ppm (δ°)
\[ \text{Et}_3\text{NH} \]

\[ \text{O} \]

\[ \text{SO}_2 \]

\[ \text{CH}_3 \]

\[ \text{H} \]

\[ \text{NHCO}_2\text{-Bu} \]

2-2-68
424
4-2-2
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