# Templates for Intramolecular O,N-Acyl Transfer via Cyclic Intermediates Derived from Mercury Derivatives of L-Cysteine: Progress toward a Mercury-Based Thiol Capture Strategy

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A first study is reported of optimization of a template bridging an oxygen ester with mercury that facilitates intramolecular O,N-acyl transfer from a phenolic oxygen to the amino group of a cysteine residue that is functionalized at sulfur as an arylmercuri complex. Respective effective molarities (EM values) of 0.28, ca. 0.6, and 0.0 are observed for the following three arylmercuri complexes: methyl S-((4-acetoxy-6-phenoxathiinyl)-mercuri)-L-cysteinate (**9**), methyl S-((5-acetoxy-1,3-dimethoxy-2-methyl-9-oxoxanth-4-yl)mercuri)-L-cysteinate (**10**), and methyl S-((4-acetoxydibenzofuran-6-yl)mercuri)-L-cysteinate (**11**). Syntheses of these compounds are reported, and the structural significance of the EM values for transition states of the acyl-transfer reactions is discussed. The observed reactivity pattern is consistent with a linear geometry at the mercury atom and a geometry about the forming C–N bond of other than the trans, anti relationship that has been observed for intermolecular acyl-transfer reactions.

## Introduction

In a previous report we described a design strategy for finding and optimizing templates that facilitate intramolecular acyl transfer across an unsymmetrical cysteine disulfide framework.[1] A key premise for the application of these results to the practical coupling of polypeptides is a reliable methology for generating unsymmetrical disulfides from precursors at low concentrations in a protic solvent. Elsewhere we have described the successful application of the (methoxycarbonyl)sulfenyl (Scm) group of Brois[2] to this problem.[3]

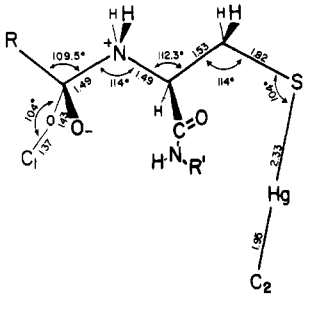
A thiol-capture methodology that involves mercury–sulfur bond formation as a capture step has many potentially attractive features. Equilibrium constants for formation of methylmercury complexes of cysteine derivatives appear to be adequate for capture in dilute solution,[4] and the rapid displacement of thiolate from mercury by stronger ligands such as phosphines or iodide ion should permit cleavage of the spent template once acyl transfer is complete.

The special chemical features of organomercury derivatives constrain synthetic manipulations of peptides that are to be coupled by a mercury–mercaptan tactic. The electrophilicity of the R–Hg–X function varies by many orders of magnitude with changes in the soft nucleophilicity of the leaving group X,[5] and highly reactive leaving groups that might be generated under strongly acidic conditions must be avoided to prevent mercuration of Tyr, His, or Trp functionalities. Moreover, arylmercury derivatives undergo rapid solvolysis of the C–Hg bond in trifluoroacetic acid solution. Two general tactics thus suggest themselves: use of the more acid-resistant alkylmercury derivatives, blocked at the metal by a good ligand that can be selectively removed just prior to the capture step, or use of an arylmercuric capture site that is itself introduced just prior to that step. Mercury introduction by a century-old reaction of dilute aqueous mercuric chloride with arylboronic acids,[6] which have previously been shown to be compatible with the operations of peptide synthesis,[7] is a promising candidate.

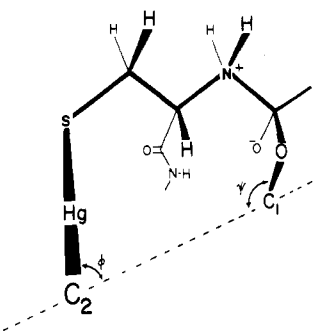
This paper reports an attempt to establish a relationship between template structure and effective molarity for the intramolecular O,N-acyl transfer **1** → **3** of a series of mercury derivatives (Scheme I). Our design approach is similar to that used for the previously reported disulfide study: important conformations of the cysteine framework of the intermediate **2** are identified, and the subclass of these that can be bridged by easily accessible templates are singled out. Although this project has yet to yield a testable correlation between structure and EM, important conclusions can be drawn from present results, and these are the substance of this paper.[8]

## Bridgeable Conformations of 2

As noted previously, we have not been able to realize a rapid intramolecular O,N-acyl transfer involving an aliphatic ester, and weakly activated (i.e., electron-rich) phenolic esters are therefore the natural structural candidates for **1**. For a combination of tactics and preparative convenience, we restricted this first mercury design exercise to arylmercury derivatives. The appropriate templates therefore were rigid, readily preparable arenes or heteroarenes with oxygen and mercury functions at a separation corresponding to that of a stable conformation of the mercury–cysteine backbone of **2**, as redrawn in **4**.




**4**




**5**

The geometry at bivalent mercury is linear, and the C–Hg and Hg–S distances can be estimated from X-ray crystallographic structural studies as 1.95 and 2.33 Å, re-

(1) Kemp, D.; Carey, R.; Dewan, J.; Galakatos, N.; Kerkman, D.; Leung, S.-L. *J. Org. Chem.* **1989**, *54*, 1589.
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(6) Michaelis, A.; Becker, P. *Chem. Ber.* **1882**, *15*, 182.
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(8) For a preliminary report of some of the present results, see: Kemp, D.; Kerkman, D. *Tetrahedron Lett.* **1981**, *22*, 185.

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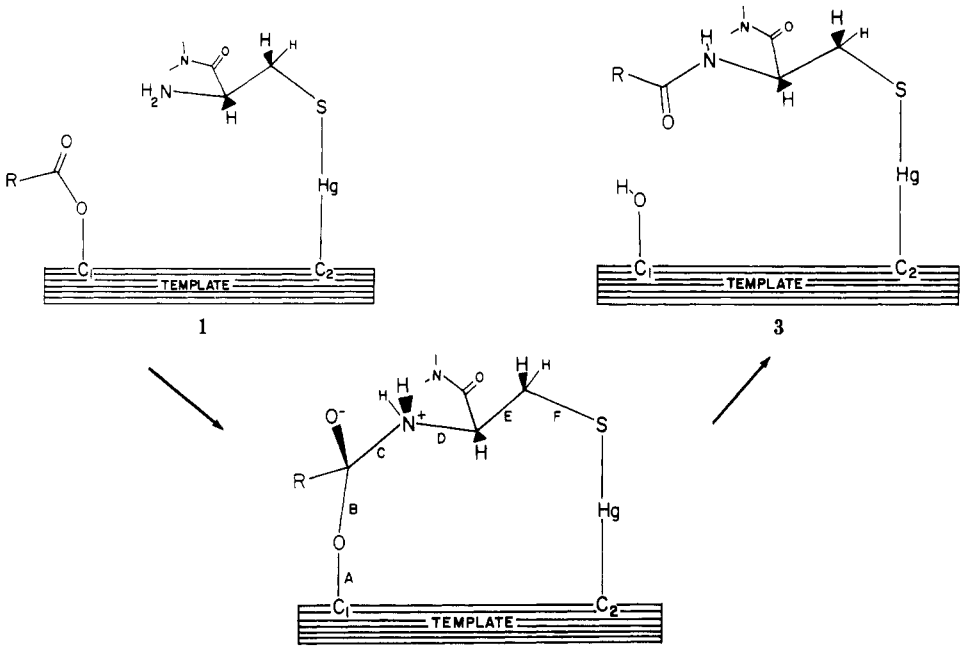
Scheme I




1 3 2

spectively.[9] The thiomercury subunit therefore behaves as an exceptionally long bond of 4.28 Å. As previously noted,[1] the bond distances, bond angles, and torsional angles of **4** can be approximated from literature values, with the exception of the region of breaking or forming bonds for which assumptions must be made. In the cysteine disulfide studies, the torsional angle at the forming C–N bond was assumed to be 60°, in accord with a previous study of steric effects for intermolecular acyl transfer.[10] As will be seen, the torsional angle at this bond poses special problems for modeling of the mercury-based intramolecular acyl-transfer reactions.

Examination of the five most stable conformations of **4** with the restraint of 60° torsional angle at the forming bond reveals that none is capable of accommodating a planar arene or heteroarene template. The problem is typified by conformation **5**, characterized by internal dihedral angles of 120, −60, 180, 180, and 60°. The terminal atoms of this linkage are defined by a tetrahedron with $C_1$–$C_2$ distance of 5.98 Å and an O–S distance of 5.52 Å. The angles labeled Φ and Ψ in this structure are 66.6° and 80.5°, respectively, and the dihedral angle defined by the S–Hg–$C_2$ and O–$C_1$ linkages is 72.9°. Because this dihedral angle is large, no planar template can bridge this conformation. In fact, for all of the more stable conformations of **5**, angles Φ and Ψ lie in the range of 60–80°, and the dihedral angles between terminal bonds are significantly greater than zero. Since these features result from the structural tilt generated by the long, linear S–Hg–C subunit, these small angles Φ and Ψ at the site of template attachment are shared with any structure generated from the initial structure by small changes in internal torsional angles. Unfortunately the geometry of prospective heteroarene templates requires that angles of attachment be in excess of 90° and that dihedral angles between terminal bonds be zero.

An alternative is to explore the conformations that result if the torsional angle at the forming C–N bond is 120° or greater. Previously we have argued[10] that the observed steric effects for peptide coupling reactions are best explained by a torsional angle at this bond of ca. 60°, and it is therefore likely that conformations with larger torsional angles must belong to less stable transition states that do not correspond to normal acylation processes. An increase in the torsional angle at the forming bond to 120° effectively rotates the aryl-cysteine framework away from the heteroarene template. Subsequent adjustments of internal angles create a structural class where the long $C_2$–Hg–S bonds constitute one side of a trapezoid which must be complimented by the opposing side defined by the bonding array between $C_1$ and the β-C of cysteine. This structural class can accommodate the geometric requirements of Φ, Ψ angles near 90° or 120° as well as $HgC_2,C_1O$ dihedral angles near zero.

For example, if the distance $C_1$–$C_2$ is maximized while constraining the Φ, Ψ angles to 90°, **6** is generated, with internal angles 140, 180, 170, −120, and 20° and $C_1$–$C_2$ distance 5.47 Å. This conformation is best suited to 1,8-difunctionalized derivatives of heteroatom equivalents of the anthracene ring system such as **9** and **10** with respective $C_1$–$C_2$ distances of 4.72 and 4.41 Å. Conversely, if within this class $C_1$–$C_2$ distances are minimized to roughly the aryl C–C bond length of 1.4 Å while constraining Φ and Ψ to 120°, structures such as **7** can be generated. Internal angles of 130, −130, 115, −100, and 40° give a $C_1$–$C_2$ distance of 1.51 Å, constituting a conformation which is best suited to 1,2-difunctionalized benzene derivatives such as **8**. Both **6** and **7** share the feature of an exceptionally low value for the torsional angle at the $CH_2$–S bond. However, it is expected that this bond should show an unusually low rotational barrier.[11]

## Synthesis of Templates

The four templates employed in this study were **8**, **9**, **10**, and **11**. The precursor of **8** is a literature compound,[12] and precursors of **9** and **11** were prepared by reactions of

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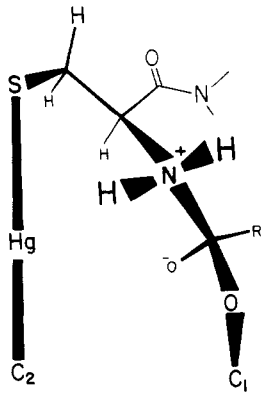
(12) Whitmore, F.; Middleton, E. *J. Am. Chem. Soc.* **1921**, *43*, 619.



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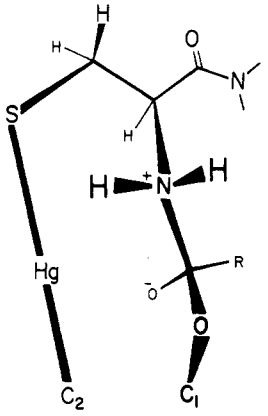

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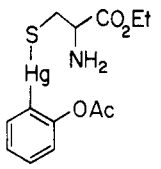
mercuric salts with the previously described, analogous heteroarene trimethylsilyl derivatives, which were in turn generated by silylation of the appropriate aryllithium reagent.



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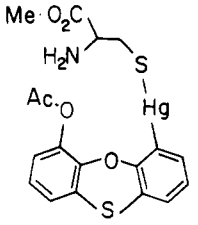

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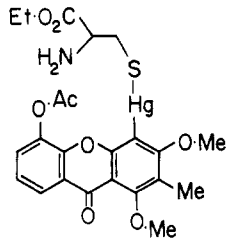
Template **10** and its precursor xanthone **13** posed special synthetic problems. It was expected that **13** could be generated as a sole product of the mercuration of **12**, a highly functionalized structure that was relatively easily available. In fact, attempts to generate the highly hindered **13** from **12** under a wide variety of standard mercuration conditions led only to recovery of starting material, and this reaction could be achieved only by heating mercuric acetate with **12** in a vacuum in which the coformed acetic acid can be volatilized. In solution in the presence of acidic reagents **13** is quantitatively demercurated to form **12**. In this highly hindered case the aromatic mercuration reaction, which is normally reversible, actually has an unfavorable equilibrium constant.



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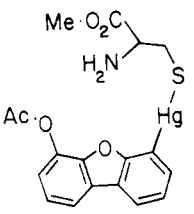

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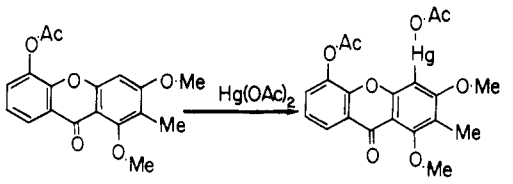


12 13

## Results of Intramolecular, *O,N*-Acyl-Transfer Experiments

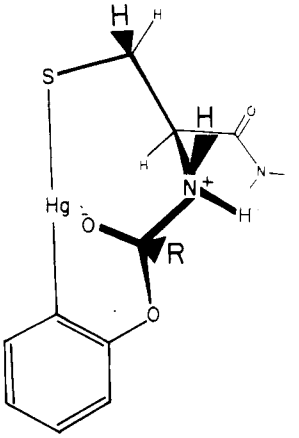
The cysteine derivatives **8**–**11** were prepared from the corresponding mercury halides or acetates by reaction with an equivalent of cysteine methyl or ethyl ester in the presence of tertiary amine. By $^1$H NMR analysis at 25 °C, **8** at 0.01 M in DMSO-$d_6$ over 48 h showed no evidence of *O,N*-acyl transfer. Clean, concentration-independent acyl transfer for **9** (0.006–0.02 M in DMSO, 25 °C) was observed with a rate constant of $1.9 \times 10^{-2}$ h$^{-1}$. The model 4-acetoxyphenoxathiin was found to react with H-Cys(Bzl)-OMe under the above conditions with a second-order rate constant of $6.9 \times 10^{-2}$ M$^{-1}$ h$^{-1}$, and the EM value for **9** is accordingly 0.28 M.

With **10**, acyl transfer was accompanied by demercuration as evidenced by separation of a gray precipitate and isolation in good yield of the demercurated template. The rate of acyl transfer for **10** was followed by $^1$H NMR spectroscopy at ca. $1 \times 10^{-3}$ M and by UV spectroscopy at $7 \times 10^{-5}$ M; a consistent first-order rate constant of $2.9 \times 10^{-2}$ h$^{-1}$ was obtained in DMF, and a rate constant of $8.3 \times 10^{-2}$ h$^{-1}$ was observed in DMSO. An attempt was made to follow the reaction in methanol, but only 10% reaction was observed after 40 h. Iodine oxidation of the *O,N*-acyl-transfer product generated diethyl *N,N'*-diacetylcystinate. Since 1,3-dimethoxy-2-methyl-5-acetoxyxanthone reacts with ethyl *S*-benzylcysteinate at 25 °C with a second-order rate constants of $4 \times 10^{-2}$ M$^{-1}$ h$^{-1}$ in DMF and $4.3 \times 10^{-1}$ M$^{-1}$ h$^{-1}$ in DMSO,[1] estimates of EM values for **10** are 0.7 M in DMF and 0.2 M in DMSO. Because of the uncertainties in measurements of rate constants, these values must be regarded as estimates.

When **11** was maintained at 25 °C in DMSO for 20 h, less than 5–8% of the expected amide product could be detected by NMR. From the known intermolecular reactivity of 4-acetoxydibenzofuran, an upper bound on the EM value of **12** can be calculated as 0.05 M, which is effectively zero within the error of the experiment.

## Discussion of Results

The *o*-phenylene case **8** shows no evidence whatsoever of intramolecular acyl transfer. Although the two hairpin-like conformations **14** and **15** that could allow intramolecular acyl transfer with this template have relatively small torsional strain, each requires that mercury and hydrogen atoms approach within 2 Å. Appropriate potential functions are not available, particularly for an edge-wise mercury interaction, but almost certainly this close separation results in large van der Waals repulsions, and the inertness of **8** provides experimental confirmation of their importance.



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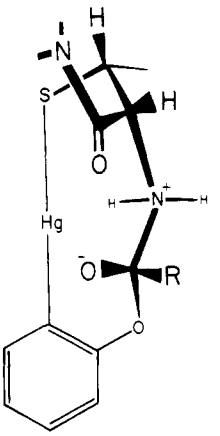

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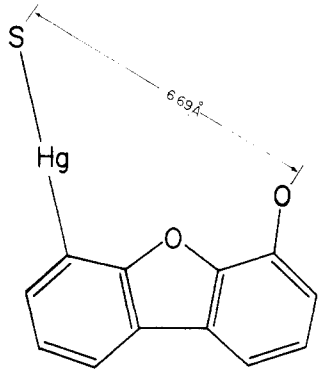
As noted previously, the heteroarene cases **9**, **10**, and **11** provide a "tuned" series in which the geometry of the *o,o'*-diphenyl ether functionality is varied by small amounts. In our previous study, we observed intramo-

lecular acyl transfer with the xanthone **10**, but as noted in the preceding section, the kinetic measurements were complicated by the demercuration of the heteroaryl function at a rate comparable with the acyl transfer itself, and the EM value therefore has a large uncertainty. In the planning stages of this work the prime structural candidate was the phenoxathiin **9**, which appears to allow a relatively strain-free accommodation of the conformation **7**, and it was expected that **9** would show unequivocal evidence for intramolecular acyl transfer.

The dibenzofuran case **11** was prepared and examined to test a point intrinsic to the molecular modeling process itself, for even though there is relatively little change in bond distances and angles for the three cognate heteroarene templates, the long linear C–Hg–S linkage acts as an amplifying lever arm. As noted in **16**, the distance between S and template O is 6.69 Å, but the equivalent distance measured through the backbone of the transition state model **17** in its fully extended conformation is only 6.51 Å, or ca. 0.2 Å less than that required to accommodate a strainless dibenzofuran functionalized with a linear C–Hg–S array. Should this array be expected to be linear

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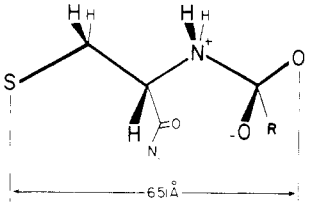


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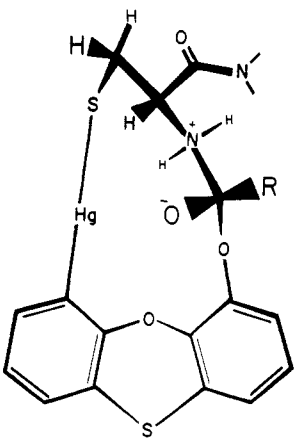
in DMSO solution? From crystal data it is evident that a continuous series of geometries may exist that span linear bivalent mercury derivatives (e.g. $Hg(CN)_2$) and tetrahedral complexes (e.g. $HgI_4^{2-}$).[12] DMSO as a solvent is expected to act as a soft ligand with weak coordinating capacity, and therefore might enforce a C–Hg–S angle of less than 180°. Only a small deviation from linearity at Hg results in large changes in O–S distance (thus for 175° at C–Hg–S, the O–S distance of **16** is 6.53 Å; for 170°, the O–S distance is 6.31 Å). The absence of detectable intramolecular *O,N*-acyl transfer with **11** is probably best understood in terms of little deviation from linearity for the C–Hg–S array, even in the moderately strongly coordinating solvent DMSO.

As indicated in **18** and **19** both the phenoxathiin and xanthone templates can be assigned transition states in which the C–Hg–S linkage is linear and the mercury atom is relatively free of transannular interactions. Although the unavailability of key energetic parameters for this atom render molecular mechanics simulations of energies premature, qualitative observations do permit these two systems to be distinguished. The $\Phi$, $\Psi$ angles and $C_1$–$C_2$ distance of the xanthone template cause the bridging $C_1$–$C\beta$ backbone of the cysteine framework to stretch to nearly maximum extension, while the corresponding parameters for the phenoxathiin allow more flexibility to this backbone. Other than the mercury and sulfur, the largest atomic cluster in these transition states is the tetrahedral acyl carbon with its three linked heteroatoms, and the effective van der Waals radius of each of these is likely to be enlarged by solvation. The transition state for the xanthone derivative is expected to be destabilized by repulsion between this atomic cluster and the heteroaryl oxygen atom, while that for the more flexible phenoxathiin should be destabilized to a much smaller degree. It is therefore surprising to find that similar EM values are seen for these two templates. A stiffer C–Hg bond in the ortho buttressed xanthone case may conceivably compensate for the greater strain.

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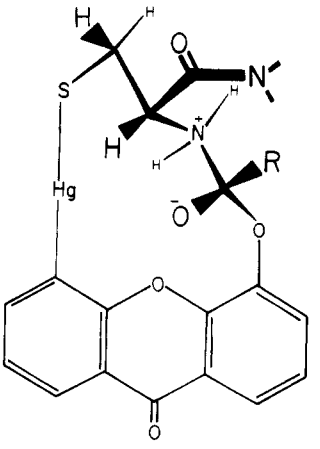


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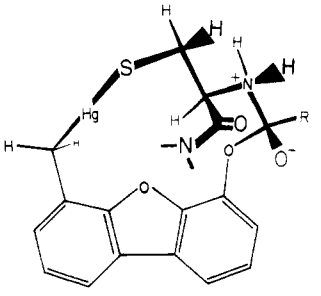


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In summary, this work has demonstrated that EM values close to the catalytically useful range of 1 M can be obtained by bridging the acylmercuricysteine framework of **1** with suitable heteroaromatic templates. The observed reactivity pattern is consistent with a linear geometry at the mercury atom and a geometry about the forming C–N bond of other than the trans, anti relationship that has been observed for intermolecular acyl-transfer reactions; however, reliance on this less favored geometry must result in a reduction in EM values. A qualitative analysis of strain in the transition states suggests that the acyl transfer observed in the phenoxathiin case must be nearly optimal, and it appears unlikely that further exploration of this structural class can lead to markedly more efficient intramolecular reactivity in the series **1** → **2** → **3**. Other structural classes may prove more versatile, as revealed by a comparison between **5** and **20**, which contains the strain-free linkage of **5**, without significant destabilizing van der Waals interactions.

## Experimental Section

High-resolution $^1H$ NMR spectra were obtained on either a Bruker WM-250, a Bruker WM-270, or a Varian XL-300 instrument. Chemical shifts are reported in ppm downfield from tetramethylsilane, and splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. Low-resolution, high-resolution, and field desorption mass spectra were recorded on Varian MAT-44, CEC-110, and Finnigan MAT-731 mass spectrometers, respectively. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN.

Preparative-layer chromatography was performed on Analtech 1000 $\mu$ GF plates, and flash chromatography was carried out on

silica gel 60 (230–400 mesh) with 100% dichloromethane as eluent. HPLC was performed on a Waters system consisting of two Model 6000-A pumps, a Model 680 automated gradient controller, a Model U6K injector, a Model 440 dual-channel UV detector (280,254), and a Model 730 data module. HPLC runs were conducted in the reverse-phase mode on Whatman Partisil columns. For kinetics runs DMSO was fractionally distilled and stored for at least 24 h over 4-Å molecular sieves, and DMSO-$d_6$ from Aldrich was used from freshly opened 1-mL ampoules. Unless otherwise specified, chemicals were reagent grade. Solutions of butyllithium in hexane were obtained from Alpha.

Bond angles, torsional angles, and bond distances were determined as described in the discussion section and in the related paper by Kemp et al.[1]

**Ethyl *S*-((2-Acetoxyphenyl)mercuri)-L-cysteinate (8). A. (2-Acetoxyphenyl)mercuric Chloride.** A solution of 1 mL of acetic anhydride of 0.5 g (1.5 mmol) of (2-hydroxyphenyl)mercuric chloride, prepared from mercuric acetate, phenol, and sodium chloride by the procedure of Whitemore and Middleton,[13] was treated with 0.35 mL of pyridine. After 2 h at 25 °C the solvent was evaporated, and the residue was repeatedly taken up in ethyl acetate and evaporated until a solid was obtained, which was then washed with water and vacuum-dried to give 0.46 g (82%) of a white solid, mp 160–161 °C. $^1$H NMR (60 MHz, $CDCl_3$): δ 2.33 (s, 3 H); 7.35 (b s, 4 H). MS *m/e*: 372 ($M^+$, 0.12), 135 (6), 43 (100).

Anal. Calcd for $C_8H_7O_2HgCl$: C, 25.89; H, 1.90; Hg, 54.04; Cl, 9.55. Found: C, 25.63; H, 1.99; Hg, 54.07; Cl, 9.31.

**B. Preparation and Acyl Transfer of 8.** To a solution of 17.2 mg (0.046 mmol) of the above compound in 0.4 mL of DMSO-$d_6$ was added ethyl L-cysteinate (6.85 μL, 0.046 mmol) and triethylamine (6.43 μL, 0.049 mmol). $^1$H NMR spectra taken over a 12-day period showed no change in the chemical shift of the acetyl peak and no appearance of the resonances of the product of acyl transfer. After 2 days, decomposition of the mercury derivative was evidenced by appearance of traces of a black precipitate.

**Methyl *S*-((4-Acetoxy-6-phenoxathiinyl)mercuri)-L-cysteinate (9). A. 4-(Trimethylsilyl)-6-acetoxyphenoxathiin.** As reported previously,[14] phenoxathiin was sequentially converted to 4-hydroxyphenoxathiin and thence to 4-(trimethylsilyl)-6-hydroxyphenoxathiin. A solution of 135 mg (0.47 mmol) of the latter in 0.6 mL of acetic anhydride was treated with 2 mg of 4-(dimethylamino)pyridine. After 3 h at 25 °C the solution was evaporated, and the residue was partitioned between 0.5 M citric acid and dichloromethane. The combined organic extracts were washed with 5% $NaHCO_3$ and water, dried, and evaporated to yield 155 mg (100%) of a white solid, mp 112–113 °C. $^1$H NMR (250 MHz, $CDCl_3$): δ 0.40 (9 H, s), 2.37 (3 H, s), 6.9–7.0 (4 H, m), 7.09 (1 H, dd, *J* = 8.2 Hz), 7.22 (1 H, dd, *J* = 7.2 Hz).

**B. 4-(Bromomercuri)-6-acetoxyphenoxathiin.** To a solution of 33 mg (0.10 mmol) of the above compound in 3 mL of trifluoroacetic acid was added a solution of 42.3 mg (0.10 mmol) of mercuric trifluoroacetate in 3 mL of the same solvent. After 10 min at 25 °C the solvent was evaporated, and the resulting white residue was dissolved in 2 mL of acetone and treated with a solution of 21 mg of sodium bromide in 0.5 mL of water. The resulting precipitate was collected after 5 min, washed with water, and dried under high vacuum to yield 38 mg (71%) of the title compound as a white powder, mp 194–195 °C. The compound was recrystallized from dichloromethane–pentane. $^1$H NMR (270 MHz, $CDCl_3$): δ 2.53 (3 H, s), 6.90 (1 H, dd, *J* = 7.2 Hz), 6.9–7.05 (2 H, m), 7.1–7.15 (3 H, m). Field desorption mass spectrum: *m/e* 538 ($M^+$).

Anal. Calcd for $C_{14}H_9O_3BrHg$: C, 31.27; H, 1.69; Hg, 37.30. Found: C, 31.12; H, 1.80; Hg, 36.96.

**C. Calculation of Second-Order Rate Constant for 4-Acetoxyphenoxathiin.** The aminolysis of 4-acetoxyphenoxathiin with methyl *S*-benzylcysteinate was used as the model system for determining the second-order rate constant in effective molarity calculations. Rate studies were carried out at 25 °C in DMSO under pseudo-first-order conditions in amine at two concentrations. Disappearance of 4-acetoxyphenoxathiin was measured by HPLC (70% $Me_3CN$, 30% 0.1% aqueous TFA) with biphenyl as internal standard. Six or seven data points were recorded for each run and were measured up to 1.1 and 1.5 half-lives. First-order plots ($R > 0.99$ for each run) at amine concentrations of 0.267 M and 0.386 M gave $k_{obsd}$ values of $1.89 \times 10^{-2}$ h$^{-1}$ and $7.1 \times 10^{-2}$ h$^{-1}$, respectively. A plot of $k_{obsd}$ vs [amine] including the zero point gave $k_2 = 6.9 \times 10^{-2}$ M$^{-1}$ h$^{-1}$ ($R = 0.999$).

**D. Formation and Acyl Transfer Reaction of 9.** The rate studies were carried out at three concentrations to confirm the first-order nature of acyl transfer. For example, 6.6 mg (0.012 mmol) of 4-(bromomercuri)-6-acetoxyphenoxathiin was dissolved in 2.0 mL of DMSO-$d_6$ (ca. $6.2 \times 10^{-3}$ M) at 25 °C to which 2.1 mg (0.012 mmol) of methyl L-cysteinate hydrochloride was added followed by 3.4 μL (0.024 mmol) of $Et_3N$. The rate of disappearance of acetate was followed by $^1$H NMR spectroscopy by integration of ester and amide acetyl singlet resonances. Five data points for each run were recorded up to 1 half-life at 0.0062, 0.014, and 0.023 M and gave first-order plots with the following rate constants and correlation coefficients: $1.9 \times 10^{-2}$ h$^{-1}$ (0.99), $2.1 \times 10^{-2}$ h$^{-1}$ (0.98), $1.9 \times 10^{-2}$ h$^{-1}$ (0.96), respectively. Using the second-order rate constant from *C*, an effective molarity of 0.019 h$^{-1}$/0.069 M h$^{-1}$ = 0.28 M can be calculated.

A purified sample of the product of acyl transfer was isolated after 6 days by combining the samples, evaporating the solvent, and subjecting one quarter of the residue to preparative TLC (9:1 $CHCl_3$), $R_f = 0.08$; 2.5 mg (34% extrapolated yield) of acyl transfer product was isolated from this chromatographic separation. $^1$H NMR (300 MHz, $CDCl_3$): δ 2.12 (s, 3 H, CONMe), 3.48 (dd, 1 H, *J* = 14, 5.8 Hz, Cys β-$CH_2$), 3.67 (dd, 1 H, *J* = 13.9 Hz, 4.1), 3.83 (s, 3 H, OMe), 5.98 (m, 1 H, α-CH), 6.67 (dd, 1 H, *J* = 7.1, 1.3 Hz), 6.81 (dd, 1 H, *J* = 8.0, 1.8 Hz), 6.91 (t, 1 H, *J* = 7.8 Hz), 7.12 (m, 3 H), 7.85 (s, 1 H, NH).

**Methyl *S*-((5-Acetoxy-1,3-dimethoxy-2-methyl-9-oxoxanth-4-yl)mercuri)-L-cysteinate (10). A. 5-Acetoxy-1,3-dimethoxy-2-methylxanthone.** The title compound was prepared in three steps following the general procedure of Shah.[15] A mixture of 2,3-dihydroxybenzoic acid (15 g, 97 mmol), 2-methyl-3,5-dimethoxyphenol (15 g, 89 mmol), fused zinc chloride (50 g, 0.37 mol), and 100 mL of phosphorus oxychloride was stirred at 75 °C for 2 h, poured hot onto 700 g of ice, and swirled vigorously for 3 min. After 1 h, the precipitate was collected on a large Büchner funnel and washed with saturated sodium bicarbonate solution. Recrystallization from methanol gave 2.28 g (9.5%) of 1,5-dihydroxy-3-methoxy-2-methylxanthone, mp 165–170 °C. The compound gave the green color with ferric chloride that is characteristic of 1-hydroxyxanthones. $^1$H NMR (250 MHz, DMSO-$d_6$): δ 2.00 (s, 3 H), 3.97 (s, 3 H), 6.75 (s, 1 H), 7.35 (m, 2 H), 7.65 (dd, 1 H, *J* = 4.6 Hz), 10.3 (b s, 1 H), 12.9 (s, 1 H).

A solution of 50 mg (0.18 mmol) of the above compound and 0.1 mL (1.0 mmol) of acetic anhydride in 2 mL of pyridine was stirred at 25 °C for 1.3 h, poured into 1 M HCl, and extracted with dichloromethane. The organic phases were combined, washed with water, dried ($MgSO_4$), and evaporated to give 46 mg (80%) of 5-acetoxy-1-hydroxy-3-methoxy-2-methylxanthone, mp 225–226 °C; this gave a green color reaction with ferric chloride. $^1$H NMR (250 MHz, DMSO-$d_6$): δ 1.80 (s, 3 H), 2.25 (s, 3 H), 3.65 (s, 3 H), 6.30 (s, 1 H), 7.15 (m, 2), 7.60 (dd, 1 H, *J* = 2.7 Hz), 12.50 (s, 1 H).

To a solution of 309 mg (0.98 mmol) of the above compound in 25 mL of warm acetone was added 0.20 g (1.45 mmol) of granular $K_2CO_3$ and 0.5 mL (8 mmol) of methyl iodide. The mixture was stirred at reflux until a test sample no longer gave a positive ferric chloride test (20 h). The mixture was evaporated, water was added to the residue, and the resulting mixture was extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated to give 320 mg (99%) of 5-acetoxy-1,3-dimethoxy-2-methylxanthone, mp 195.5–197.5 °C. $^1$H NMR (250 MHz, $CDCl_3$): δ 2.16 (s, 3 H), 2.45 (s, 3 H), 3.94 (s, 6 H), 6.60 (s, 1 H), 7.35 (m, 2 H), 8.17 (dd, 1 H, *J* = 2.6 Hz). MS (70 ev): *m/e* 328 ($M^+$, 0.5), 168 (6), 92 (100), 43 (84).

Anal. Calcd for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91. Found: C, 65.70; H, 5.10.

**B. 5-Acetoxy-4-(acetoxymercuri)-1,3-dimethoxy-2-methylxanthone.** A mixture of 65 mg (0.20 mmol) of 5-acet-

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oxy-1,3-dimethoxy-2-methylxanthone and 63 mg (0.20 mmol) of mercuric acetate was heated neat under aspirator vacuum at 170 °C for exactly 4 min. After cooling the mixture, it was recrystallized from a minimum volume of tetrahydrofuran to give 54 mg (47%) of the title compound, mp 219–221 °C dec. The compound gave a deep violet color with diphenylcarbazone. $^1$H NMR (250 MHz, $CDCl_3$): δ 2.10 (s, 3 H), 2.17 (s, 3 H), 3.88 (s, 3 H), 4.00 (s, 3 H), 7.30 (mm, 2), 8.08 (m, 1 H).

Anal. Calcd for $C_{20}H_{18}HgO_8 \cdot 2H_2O$: C, 38.56; H, 3.56; Hg, 32.20. Found: C, 38.58; H, 3.34; Hg, 32.08.

**C. Formation and Acyl Transfer Reaction of Ethyl *S*-((5-Acetoxy-1,3-dimethoxy-2-methyl-9-oxoxanth-4-yl)-mercuri)-L-cysteinate (10).** To a solution of xanthone (23 mg, 0.039 mmol) prepared in B in 1.25 mL of DMF-$d_7$ was added triethylamine (5.3 μL, 0.38 mmol) and 5.6 μL of ethyl L-cysteinate. After 4 days at 25 °C the solution was poured into 1 M HCl and extracted with dichloromethane. The pooled extracts were washed, dried, and evaporated, and the residue was taken up in chloroform and treated with sufficient iodine to retain a purple color for 1 h. The resulting solution was washed with aqueous ascorbic acid, dried ($MgSO_4$), and evaporated. Preparative-layer chromatography (1:1 chloroform–ethyl acetate) gave 2 mg (28%) of diethyl *N,N'*-diacetyl-LL-cystinate, mp 122–123 °C, identical by mixture melting point, IR, and $^1$H NMR data with an authentic sample.

Identical rate constants (±5%) were obtained by $^1$H NMR and UV methods. The NMR experiments were carried out as described for **9**. The UV experiments were carried out by combination of the xanthone prepared in B at $7 \times 10^{-3}$ M in DMSO or DMF with 1 equiv each of triethylamine and ethyl cysteinate. (After addition of the cysteine ester, the solution no longer gave a colored diphenylcarbazone.) The solution was then diluted 100-fold and the absorbance at 282 nm was followed with time. Rate constants at 25 °C of $2.94 \times 10^{-2}$ h$^{-1}$ in DMF and $8.3 \times 10^{-2}$ h$^{-1}$ in DMSO were seen. A corresponding intermolecular reaction is that of 1.25 M ethyl *S*-benzyl-L-cysteinate with 5-acetoxy-1,3-dimethoxy-2-methylxanthone in DMF at 25 °C. By NMR a half-time of 13.5 h under pseudo-first-order conditons was observed, corresponding to a second-order rate constant of $4 \times 10^{-2}$ M$^{-1}$ h$^{-1}$. The calculated EM value is therefore 0.7 M = $(2.9 \times 10^{-2})/(4 \times 10^{-2})$.

**Methyl *S*-((4-Acetoxydibenzofuran-6-yl)mercuri)-L-cysteinate (11). A. 4-(Trimethylsilyl)-6-hydroxydibenzofuran.** To a solution of 4-hydroxydibenzofuran (88 mg, 0.47 mmol) in 3 mL of tetrahydrofuran under $N_2$ was added 0.20 mL (1.3 mmol) of tetramethylethylenediamine, and the mixture was cooled to −12 °C and stirred as 0.45 mL (1.0 mmol) of *n*-butyllithium in *n*-hexane was added dropwise over 5 min. The mixture was stirred at −12 °C for 12 h, treated with trimethylsilyl chloride (0.19 mL, 1.35 mmol), and warmed to 25 °C over 4 h. The dark-yellow solution was poured into 5% $NaHCO_3$ and extracted with dichloromethane. The pooled organic extracts were washed with $NaHCO_3$ solution and water, dried ($MgSO_4$), and evaporated to 113 mg of residue, which was dissolved in 4 mL of methanol containing a trace of HCl. After 5 min the mixture was diluted with 5% $NaHCO_3$ and extracted with dichloromethane. Residual starting material was extracted into cold 1 M NaOH, and the organic phase was washed, dried, evaporated, and dried under high vacuum to yield the title compound as a pale yellow oil, 43 mg (36%). $^1$H NMR (270 MHz, $CDCl_3$): δ 0.48 (s, 9 H), 5.32 (s, 1 H), 7.04 (d, 1 H, *J* = 8 Hz), 7.24 (t, 1 H, *J* = 8 Hz), 7.53 (d, 1 H, *J* = 8 Hz), 7.55 (d, 1 H, *J* = 8 Hz), 7.96 (d, 1 H, *J* = 8 Hz). High-resolution mass spectrum: calcd for $C_{15}H_{16}O_2Si$ 256.0920, found 256.0922.

A substance with identical properties was formed in 12% yield by boron tribromide treatment of 4-(trimethylsilyl)-6-methoxydibenzofuran.[15]

**B. 4-(Trimethylsilyl)-6-acetoxydibenzofuran.** To a solution of 4-(trimethylsilyl)-6-hydroxydibenzofuran (121 mg, 0.47 mmol) in 0.6 mL of acetic anhydride was added 2 mg of 4-(dimethylamino)pyridine. After 4 h at 25 °C the solution was evaporated, and the residue was treated with 0.5 M citric acid and dichloromethane. The organic phases were washed with $NaHCO_3$ and water, dried, and evaporated. The residue was dried by two evaporations of acetonitrile and then dried under high vacuum to yield 133 mg (94%) of a viscous oil. $^1$H NMR (270 MHz, $CDCl_3$): δ 0.40 (s, 9 H), 2.42 (s, 3 H), 7.16 (d, 1 H), 7.28 (t, 1 H, *J* = 8 Hz), 7.33 (t, 1 H, *J* = 8 Hz), 7.51 (d, 1 H, *J* = 8 Hz), 7.78 (d, 1 H, *J* = 8 Hz), 7.93 (d, 1 H, *J* = 8 Hz). High-resolution mass spectrum: calcd for $C_{17}H_{18}O_3Si$ 298.1025, found 298.1021.

**C. 4-(Acetoxymercuri)-6-acetoxydibenzofuran.** To a solution of 59.3 mg (0.20 mmol) of 4-(trimethylsilyl)-6-acetoxydibenzofuran in 0.3 mL of 99% acetic acid was added 63.0 mg (0.2 mmol) of mercuric acetate in 0.75 mL of acetic acid. Trifluoroacetic acid (0.1 mL) was added, and the solution was stirred at 25 °C for 1 h and then filtered into ice water. The residue was collected, washed with acetic acid, and dried to constant weight in high vacuum to yield 29 mg (30%) of the title compound as a shiny white powder, mp 190–192 °C. A further 48 mg (50%) could be recovered by chilling the filtrates. $^1$H NMR (250 MHz, $CDCl_3$) 1.60 (s, 3 H), 2.51 (s, 3 H), 7.20 (d, 1 H, *J* = 8 Hz), 7.33–7.39 (m, 3 H), 7.80 (d, 1 H, *J* = 8 Hz), 7.89 (d, 1 H, *J* = 8 Hz).

Anal. Calcd for $C_{16}H_{12}O_5Hg$: C, 39.63; H, 2.49; Hg, 41.37. Found: C, 39.43; H, 2.29; Hg, 41.46.

**D. EM Limits for Acyl Transfer of Methyl *S*-((4-Acetoxydibenzofuran-6-yl)mercuri)-L-cysteinate (11).** Acyltransfer rate studies were attempted by $^1$H NMR at three concentrations (0.0047, 0.0146, and 0.0235 M) as described for **9**. Thus, in each run the mercury derivative prepared in C was combined with 1 equiv of methyl L-cysteinate hydrochloride and dissolved in 1–2 mL of DMSO-$d_6$ at 25 °C, and 2.1 equiv of $Et_3N$ was added. After 21 h any peaks appearing in the acetamide spectral region (1.8–2.0) were integrated, and for runs at 0.0047, 0.042, and 0.082 M these peaks accounted for 8.5%, 6.4%, and 12%, respectively, of the initial amount of ester. From these values upper limits on EM could be calculated as 0.056, 0.042, and 0.082 M, respectively.

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**Registry No.** **8**, 121270-23-3; **9**, 121270-24-4; **10**, 77849-39-9; **11**, 121270-26-6; **12**, 77834-07-2; **13**, 77834-06-1; 2-$HOC_6H_4HgCl$, 90-03-9; 2-$AcOC_6H_4HgCl$, 121288-67-3; H-Cys-OEt, 3411-58-3; H-Cys($CH_2Ph$)-OMe, 22728-88-7; H-Cys-OMe, 2485-62-3; 2,3-$(HO)_2C_6H_3COOH$, 303-38-8; 2-Me-3,5-$(MeO)_2C_6H_2OH$, 39828-36-9; Ac-Cys(Ac-Cys-OEt)-OEt, 24037-21-6; H-Cys-OMe·HCl, 18598-63-5; 4-(trimethylsilyl)-6-hydroxyphenoxathiin, 101762-12-3; 4-(trimethylsilyl)-6-acetoxyphenoxathiin, 121288-68-4; 4-(bromomercuri)-6-acetoxyphenoxathiin, 121288-69-5; 4-acetoxyphenoxathiin, 101762-41-8; 1,5-dihydroxy-3-methoxy-2-methylxanthone, 118143-54-7; 5-acetoxy-1-hydroxy-3-methoxy-2-methylxanthone, 121270-27-7; 4-hydroxydibenzofuran, 19261-06-4; 4-(trimethylsilyl)-6-hydroxydibenzofuran, 121270-28-8; 4-(trimethylsilyl)-6-acetoxydibenzofuran, 121270-29-9; 4-(acetoxymercuri)-6-acetoxydibenzofuran, 121270-30-2.