Costello of Prof. K. Biemann's laboratory for high resolution and field desorption mass spectra, N. Fotouhi for optimization of experimental conditions for the solid-phase protocol, and Dr. M. Kolovos for optimization of the conversion of 7 to 8.

Peptide Synthesis by Prior Thiol Capture. 2. Design of Templates for Intramolecular O,N-Acyl Transfer. 4,6-Disubstituted Dibenzofurans as Optimal Spacing Elements

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A central feature of the strategy for amide bond formation by prior thiol capture is an intramolecular acyl transfer across a template that links the phenolic ester function of one peptide with an unsymmetrical disulfide involving the side chain of the N-terminal cysteine residue of a second peptide. The structures of 4-hydroxy-6-mercaptodibenzofuran (3) and 4-hydroxy-6-mercaptophenoxythiin (4) are established by ¹H NMR spectra of deuterated dibenzofuran and phenoxythiin derivatives. On the basis of the criterion of effective molarity, a dibenzofuran template for intramolecular acyl transfer is shown to be approximately 2 orders of magnitude more efficient than a phenoxythiin. An effective local concentration of ca. 5 M and a Hammett ρ value of 2.6 are observed for the intramolecular acyl-transfer reaction 1 → 2.

In the accompanying paper we have described general features of a strategy of prior thiol capture, which provides a new methodology for forming amide bonds between medium to large sized peptide fragments.[1] A key step in this strategy is the intramolecular O,N-acyl transfer reaction 1 → 2, which is facilitated by the selection of a
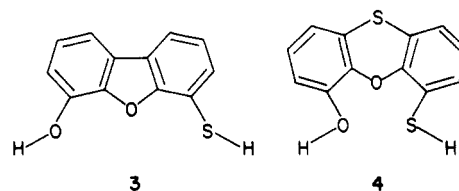

1

2

X = H, Cl, NO₂; Z = H, Cl
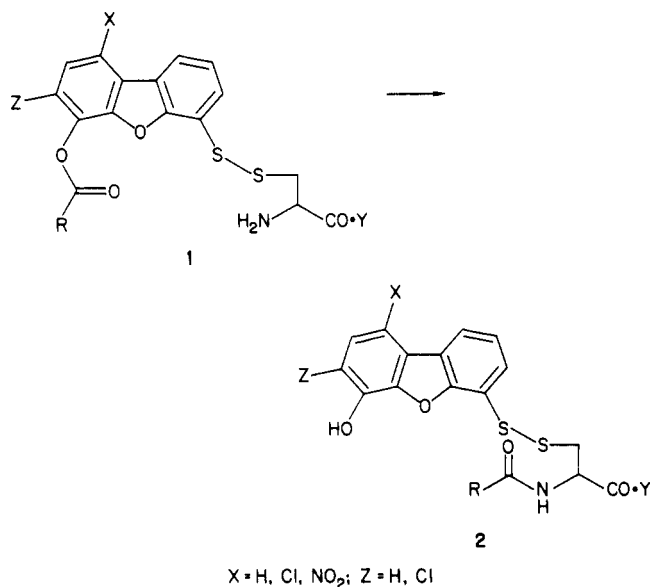
4,6-substituted dibenzofuran as an optimal linking element.[2] In earlier report[3] we have described our general approach to the design of molecular frameworks that facilitate intramolecular acyl transfer, and in that report we have noted advantages of large, rigid templates over smaller frameworks that result in acyl transfer through intermediates containing the more orthodox five- or six-membered rings.

In this paper we give a brief account of the reasoning and experiments that have led us to a selection of a dibenzofuran as a template for the acyl-transfer step of the thiol capture strategy. An unambiguous proof of structure is given for 3 and 4, key precursors in our optimization experiments, and the acyl-transfer reaction 1 → 2 is defined by proof of intramolecularity and studies of the effects of solvent and substituents on its rate.

Structural Characterization of 3 and 4. In the accompanying paper we report a synthesis of 3 from 4-methoxydibenzofuran by metalation with *n*-butyllithium followed by oxidation with elemental sulfur and demethylation. Gilman and co-workers established[4] that di-

benzofuran itself undergoes preferential metalation at the 4-position owing to the directing effect of the furanoid oxygen, and in the course of their work they assigned the structures of 4-hydroxy and 4-methoxydibenzofuran unambiguously.[5] We have noted that when lithiated 4-methoxydibenzofuran gives a mixture of lithio derivatives, presumably as a result of competitive coordination by the

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(1) Kemp, D. S. *Biopolymers* 1981, *20*, 1793.
(2) Kemp, D.; Leung, S.-L.; Kerkman, D.; Galakatos, N. In *Peptides—1980*; Brunfeldt, K., Ed., Scriptor: Copenhagen, 1981; pp 191–195.
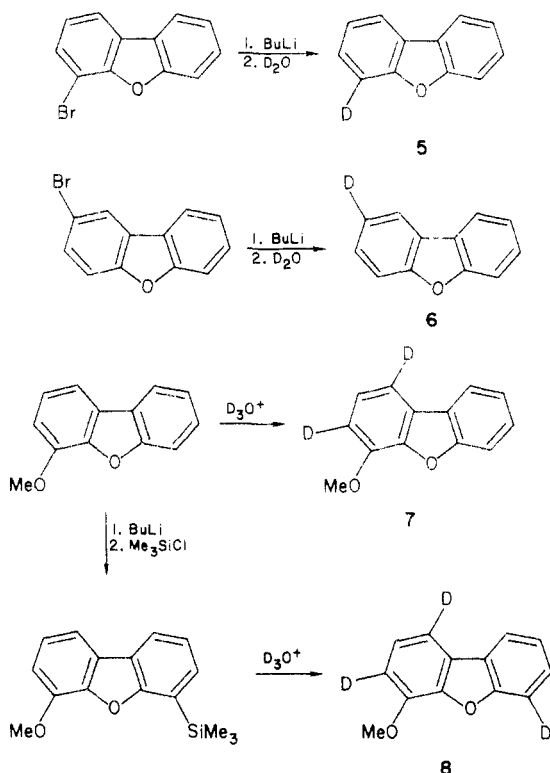(3) Kemp, D.; Kerkman, D.; Leung, S.-L.; Hanson, G. *J. Org. Chem.* 1981, *46*, 490.
(4) Gilman, H.; Cheney, L.; Willis, H. *J. Am. Chem. Soc.* 1929, *51*, 951.
(5) Gilman, H.; van Ess, P. *J. Am. Chem. Soc.* 1939, *61*, 1365. Gilman, H.; Swiss, J. *Ibid.* 1944, *66*, 1884.

Scheme I. Deuterated Derivatives of Dibenzofuran and 4-Methoxydibenzofuran


two oxygen atoms. Although it is likely that the major product is the desired 4-methoxy-6-lithiodibenzofuran, we sought independent confirmation of this assignment, relying on ¹H NMR data for dibenzofuran and for the deuterated derivatives shown in Scheme I.

As noted by Black and Heffernan,[6] the ¹H NMR spectrum of dibenzofuran at high field consists of four separated resonances at δ 7.17, 7.29, 7.42, and 7.78. Since the former two appear as triplets of doublets (J = 8, 1 Hz) and the latter as doublets of multiplets, the 4-hydrogen must be assigned either the δ 7.42 or the 7.78 resonance. The ambiguity is resolved by examination of the deuterated species 5 and 6, which are formed from bromodibenzofurans of unambiguous structure. In the ¹H NMR spectrum of 5 the δ 7.42 resonance has half its normal area, and with 6 the δ 7.17 resonance is similarly reduced, allowing the following C_x–H assignments to be made: 1, δ 7.78; 2, 7.17; 3, 7.29; 4, 7.42.

Reaction of 4-methoxydibenzofuran with 35% deuterium chloride in deuterium oxide at reflux for 15 gave dideuterated product 7 in which the unexchanged 2-hydrogen remained as a singlet and the remaining four hydrogens were each deshielded by ca. δ 0.15 relative to the corresponding hydrogen in dibenzofuran. Thus the two doublets appear at δ 7.91 and 7.61 and are assigned to the 9- and 6-hydrogens respectively. Metalation of 4-methoxydibenzofuran followed by reaction with trimethylsilyl chloride and deuterolysis generates a trideutero-4-methoxydibenzofuran with an ¹H NMR spectrum that lacks the δ 7.61 resonance. Accordingly this must be 1,3,6-trideutero-4-methoxydibenzofuran (8), and the major product of lithiation of 4-methoxydibenzofuran must therefore be the 6-isomer.

A 4,6-disubstituted phenoxythiin (4) was also of interest for studies of acyl transfer, and an analogous preparative route and structure proof was achieved. Hydroxylation

of phenoxythiin following the procedure of Gilman and Esmay[7] generated the phenol 9 which was lithiated by reaction with 2 equiv of n-butyllithium in the presence of tetramethylethylenediamine. Quenching with trimethylsilyl chloride generated 10 in a remarkable yield of 90%, while oxidation with excess elemental sulfur followed by a reductive workup generated a thiol in 65% yield.
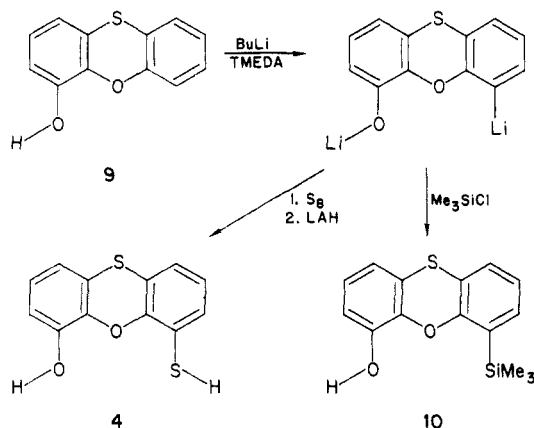
The structures of 10 and therefore of 4 were established by methylation of the phenol function of 10, followed by silane cleavage with tetrabutylammonium fluoride in tetrahydrofuran containing deuterium oxide. Inspection of the proton-decoupled ¹³C NMR spectrum of this product showed a change in the resonance at δ 117.5 from a singlet to a broad triplet. Since this resonance appears in the spectrum of phenoxythiin and 9 and has been assigned by Isbrandt et al.[8] to the 4- or 6-carbon of phenoxythiin, the structures of 4 and 10 are established as 4,6-disubstituted phenoxythiins.

Design of Templates for the O,N-Acyl Transfer Step. The fundamental premise of the strategy of amide bond formation by prior thiol capture rests on the rational design of systems that can induce rapid intramolecular acyl transfer to a weakly basic (pK_a ca. 7.0) cysteine amino function from a very weakly activated phenyl ester across a span of at least nine atoms. Acyl transfers of this type must almost certainly involve transition states that are similar in structure to the presumed acyl-transfer tetrahedral intermediate, which necessarily bears a medium-sized ring. Although the art of generating medium-sized lactones and lactams has been refined by recent synthetic work in the macrolide field, we are not aware of precedents in which the acylating agent is as unreactive as a simple phenyl ester, as it must be if the features implicit in the thiol capture strategy are to be realized. In effect, the acyl transfer of the type 1 → 2 must be driven by a relatively favorable entropy of ring closure, rather than by the enthalpic driving force provided by a reactive O-acyl derivative.

A convenient measure of entropic activation for a reaction of this kind is *effective molarity* (EM) which has been recently reviewed by Kirby[9] and which is defined as the ratio of a first-order rate constant for an intramolecular reaction to a second-order rate constant for an analogous intermolecular reaction involving the same functional groups. Typical effective molarities for the frequently studied ω-oxyalkyl halides range from above 10^4 for the most favorable reactions such as cyclization of 4-bromobutanol to below 10^{-1} for formation of saturated alicyclic

(6) Black, P. J.; Heffernan, M. L. *Austr. J. Chem.* 1965, *18*, 353.

(7) Gilman, H.; Esmay, D. *J. Am. Chem. Soc.* 1954, *76*, 5787.

(8) Isbrandt, L. R.; Jensen, R. K.; Petrakis, L. *J. Magn. Reson.* 1973, *12*, 143.

(9) Kirby, A. J. *Adv. Phys. Org. Chem.* 1980, *17*, 183.

systems with rings of 9 to 12 atoms.[9] We set an EM of 1 M as the lower limit of acceptability for the design of templates for the thiol capture reaction.

In an earlier report[3] we listed a set of design principles for template construction and illustrated these through demonstration of rapid, efficient intramolecular acyl transfer in the model systems **11** and **12**. The latter is


11

12
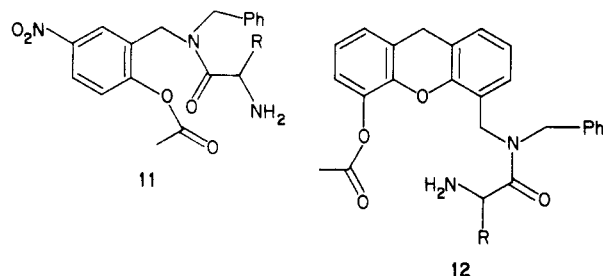
particularly noteworthy in that acyl transfer occurs via a ring of 12 members with a half-life of 10 min in Me$_2$SO at 25 °C with an EM value of 18 M. It was then necessary to show that this result could be generalized to a conformationally looser backbone containing a disulfide bond.

The design process that led to **11** and **12** contains three conceptual steps. First, a structure is identified that is a likely major conformation for the transition state for the acyl transfer reaction. Second, a very rigid template is found that permits a strain-free spanning of the end atoms of that conformation. The appropriately functionalized template is then synthesized and examined for evidence of intramolecular O,N-acyl transfer. Third, if acyl transfer is seen, the model for the template-bridged transition state is reexamined to identify structural changes in the template that might further facilitate reaction. A structural family of templates is then synthesized and tested for optimal transfer efficiency using the EM value as a criterion. The starting point for application of this process to the thiol capture problem is a likely structure of the rate-determining transition state **13** for acyl transfer to an S-sulfenyl cysteine derivative.


13
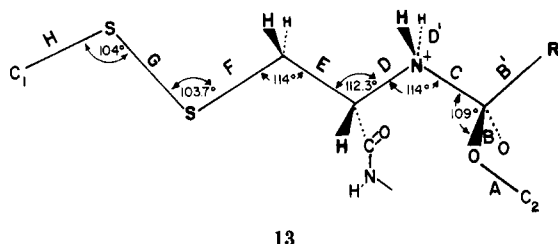
From several studies[10] it is likely that the transition states for aminolysis of phenyl esters in dipolar aprotic solvents have nearly tetrahedral character at amine nitrogen and acyl carbon, a fully formed N–C bond (bond C of **13**) and a pair of partially broken NH and CO bonds (bonds B and D' of **13**). The resulting cysteine structure **13** consists of a pair of terminal atoms C$_1$ and C$_2$ linked by no fewer than eight single bonds. It might be supposed that the number of conformations of **13** with similar energy is too large to permit efficient acyl transfer across a rigid template that has been designed to span the C$_1$–C$_2$ distance of a single conformation. In fact, there is a likely, significant restriction of the conformational population of **13**, first as a result of the preference of the S–S bond for a dihedral angle near 90°,[12] and second by a strong prefer-

ence of bonds B' and D for a trans,anti relationship about the forming bond C, as we have noted in an earlier study of ester aminolysis.[11] Although the conformational bias is likely not as strong at bonds D and E, the Newman projections **14** and **15**, which show local dihedral environ-

bond D

14

bond E

15

bond F

16
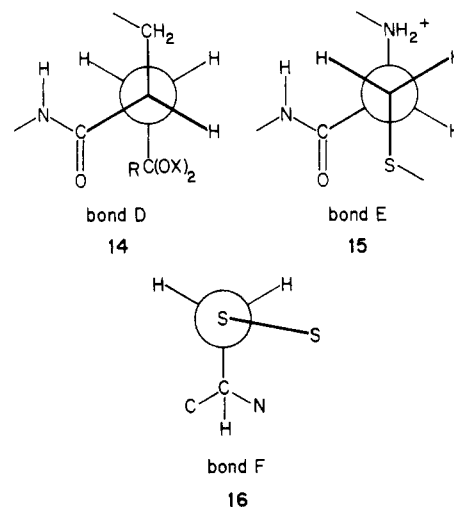
ments of the conformation **13**, demonstrate that each of these is probably the more stable of two energetically favored conformers.[11] The remaining bond F has been assigned a gauche conformation (**16**), similar to those seen in the X-ray structures of two crystalline forms of *LL*-cystine.[12]

If these conformational restrictions are applied to structure **13**, five bonds (B', C, D, E, F) are found to define a plane, and the bonds A and H which must join the template lie roughly speaking in a neighboring, parallel plane as seen in **17**. From X-ray data for the cysteine moiety and some assumed torsional angles for the region of changing bonds (see Experimental Section), the OS$_2$ distance of **17** can be calculated to be 5.3 Å and the C$_1$–C$_2$ distance (if both are aryl carbons) as 4.8 Å. Variation of bond angles by 1° or torsional angles by 2° results in an average change in these distances of only 0.03 Å, and, significantly, the OS$_2$ and C$_1$–C$_2$ distances are relatively insensitive (0.3 Å per Å) to changes in the length of the breaking bond B.

17
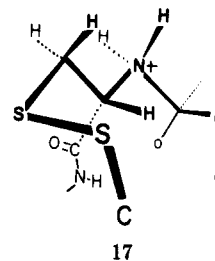
In the transition state for the reaction, bond B is likely to be longer and bond C shorter than those in the corresponding tetrahedral intermediate modeled by **17**. Therefore to a large extent the influence of these changes on the OS$_2$ and C$_1$–C$_2$ distances should cancel. The ideal template to bridge C$_1$ and C$_2$ of the transition state corresponding to **17** is thus seen to be a rigid, planar structure that introduces no major van der Waals interactions with the cysteine α-hydrogen and that places C–O and C–S bonds with an O–S distance of ca. 5.3 Å and a C$_1$–C$_2$ distance that is significantly shorter.

(10) Menger, F. M.; Smith, J. H. *J. Am. Chem. Soc.* **1972**, *24*, 3824. Fersht, A. R.; Jencks, W. P. *Ibid.* **1972**, *94*, 4733. Johnson, S. L. *Adv. Phys. Org. Chem.* **1967**, *5*, 237.

(11) Kemp, D.; Choong, S.-L.; Pekaar, J. *J. Org. Chem.* **1974**, *39*, 3841.
(12) Jones, D. D.; Bernal, I.; Frey, M.; Koetzle, T. *Acta Crystallogr., Sect. B* **1974**, *30*, 1220.

**Table I. Intramolecular O,N-Acyl Transfer with
o,o'-Bridged Diphenyl Ether Derivatives 19 and 20 as
Templates**

| template	Me$_2$SO $t_{1/2}$, h	25 °C EM,^{a} M	OS$_2$ distance, Å
19b	ca. 100^b	≤0.1	4.5
20^c	3	0.6	4.9
19a	2	5	5.3

^{a} EM values are first-order rate constants for **19a,b** divided by second-order rate constants for reactions of 4-acetoxydibenzofuran or 4-acetoxyphenoxythiin with methyl *S*-benzyl-L-cysteinate: for **19a**, 4.6 = (9.7 × 10^{-5} s^{-1})/(2.1 × 10^{-5} s^{-1}); for **19b**, 0.1 ≐ (1.7 × 10^{-6} s^{-1})/(2.1 × 10^{-5} M^{-1} s^{-1}). ^{b} Estimated for the component of the reaction that is concentration-independent. ^{c} Reference 13.

As a template, **18** lacks rigidity, owing to the presence of a benzylic methylene group, but it was readily available from precursors of **12**, and in some of its conformation it can accommodate an OS$_2$ distance of ca. 5.3 Å. We therefore examined it first. As reported previously by

18
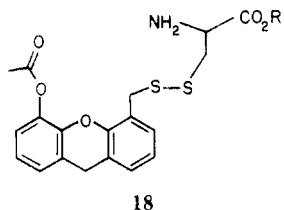
Kemp and Kerkman,[13] this substance gave the first evidence for intramolecular O,N-acyl transfer that is consistent with geometry **17**. Not surprisingly, the reaction is slow ($t_{1/2}$ ca. 15 h in Me$_2$SO, 25 °C) and complicated by competing disulfide interchange. Since the rate data for this messy reaction were imprecise, only a range of effective local concentrations of 0.1 to 0.5 M could be estimated.

With this lead we were encourated to examine the more rigid templates **19a**, **19b**, and **20**, for which OS$_2$ distances vary by 0.7 Å. In effect this series has given us three examples of *o,o'*-bridged diphenyl ether derivatives **19** for

**19a, x = no atom**
19b, X = S

20
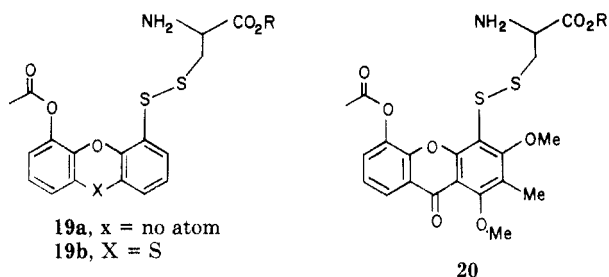
which we can coontrol the O–S$_2$ distance by varying the size of the spacing atom X. The ether oxygen common to this series selected in preference to other, larger bridging atoms (NH or CH$_2$) because models and crude energy calculations for **14** show that the bridging atom must be small to minimize van der Waals interaction with the α-CH of the cysteine residue.

As noted in preliminary reports, Kemp and Kerkman[13] and subsequently Kemp and Galakatos[2] have observed clean O,N-acyl transfer with concentration-independent rates for **20** and for **19a** as templates. With **19b** a slow, concentration-dependent acyl transfer is seen for which a unimolecular component can be estimated. Half times and EM values for these cases are listed in Table I.

From these data it is evident that the efficiency of acyl transfer as measured by EM values is highly sensitive to geometry within a series of structurally related, rigid

(13) Kemp, D.; Leung, S.-L.; Kerkman, D. *Tetrahedron Lett.* **1981**, *22*, 181.

templates. In the case of **19b**, the rate data are not sufficiently precise to prove the occurrence of an intramolecular acyl-transfer reaction, and the EM value cited must therefore be regarded only as an upper limit. The phenoxythiin molecule is butterfly-shaped;[14] although we regard the small OS$_2$ distance as the best explanation for the failure of this template to permit acyl transfer, some contribution from the lesser rigidity of this system is difficult to exclude.

21a   **21b**
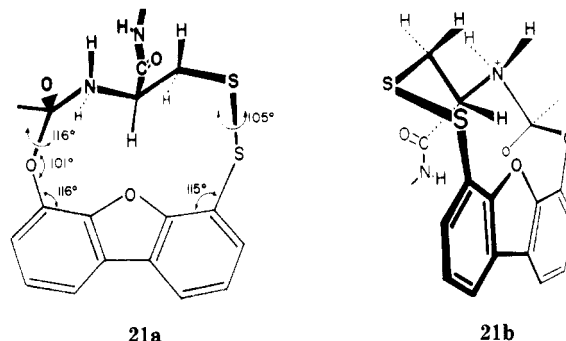
As seen in **21** the dibenzofuran template provides a remarkably precise accommodation of the structural features of the major conformation **17** of the tetrahedral intermediate for the acyl-transfer reaction. Although we regard the impressive and practical EM value of 5 M for **1 = 19a** as a legitimization of the assumptions of the model, we stress that the model, though useful and plausible, is not yet proven. It is unfortunate that within the *o,o'*-bridged diphenyl ether series one cannot construct a template **19** with an OS$_2$ distance significantly greater than 5.3 Å. Observation of a sharp maximum in EM at this distance would provide a compelling demonstration of the relevance of **17** as a transition-state model, and we are exploring other structural series to examine this point. These and other results with templates will be reported in more detail subsequently.

Effects of Solvent and Substituent on the Reaction 1 → 2. Generally speaking, the aminolysis reactions of phenyl esters obey a termolecular rate law, with first-order terms in ester, amine, and a catalyst which is a hydrogen-bond acceptor whose role is often served by the solvent.[15] The solvent effects we have observed for the reaction **1 → 2** fit this generalization; the reaction proceeds fastest in aprotic solvents that display strong hydrogen-bond-accepting character. At 25 °C the reaction **1 → 2** (X = Z = H, R = Y = Me) shows no detectable progress in 30 h in acetonitrile, while half-lives of 23 h, 2 h, and 2 h are seen in DMF, Me$_2$SO, and a mixture of Me$_2$SO and hexamethylphosphoramide (1:5). In a mixture of the unusual protic solvent hexafluoroisopropyl alcohol and Me$_2$SO (5:1) a half-life of 23 h is seen.

The Hammett ρ values for the hydrolysis of phenyl esters with good nucleophiles are frequently small, reflecting a rate-determining addition step with little or no C–O bond cleavage in the transition state.[16] By contrast, those for aminolyses of phenyl esters can be very large, particularly for reactions carried out in dipolar aprotic solvents. For example, Menger[10] reports a rate ratio of nearly 10^5 for the reactions of phenyl and *p*-nitrophenyl acetates with pyrrolidine in acetonitrile. It was therefore of interest to determine the corresponding ratio for the intramolecular acyl transfer reaction, as well as the vari-

(14) Hosoya, S. *Acta Crystallogr., Sect. B* **1966**, *20*, 429.

(15) Kemp, D. In *Peptides–1971*; Nesvadba, H., Ed.; North Holland, 1973; p 1. Su, C.; Watson, J. *J. Am. Chem. Soc.* **1974**, *96*, 1854.

(16) Bruice, T.; Benkovic, S. *Bioorganic Chemistry*; Benjamin: New York, 1966; Vol. 1, p 20.

Table II. Influence of 1- and 3-Substituents on the Rates and Effective Molarities (EM) for the Reaction 1 → 2 (Me₂SO, 25 °C)

| ring substituent	acyloxy R-group	$k_1(s^{-1})$	$t_{1/2}$	k_1/k_H (rel rate)	EM^a
1-H	acetoxy	9.7×10^{-5}	2.0h	1 (ref)	4.6
1-Br	acetoxy	4.8×10^{-4}	24 min	4.9	
1-Cl	acetoxy	1.1×10^{-3}	10 min	11	4.5
1-H	Z-L-Ala-O	7.6×10^{-5}	2.5h	1 (ref)	5.1
1-Br	Z-L-Ala-O	7.8×10^{-4}	15 min	10	
1-Cl	Z-L-Ala-O	1.2×10^{-3}	10 min	15	5.7
1-NO₂	Z-L-Ala-O	2.4×10^{-1}	2.8s	3200	8.6
3-Cl	Z-L-Ala-O	3.5×10^{-3}	3.3 min	45	4.9
1,3-di-Cl	Z-L-Ala-O	7.6×10^{-3}	1.5 min	100	2.7

^{a}Equal to the ratio k_1/k_2, where k_2 is the second-order rate constant for aminolysis of a corresponding 1- and/or 3-functionalized 4-(acyloxy)dibenzofuran in Me₂SO at 25 °C containing ethyl S-benzyl-L-cysteinate. See Experimental Section for k_2 values.

ation of EM with change of activating substituent. The appropriate derivatives were prepared by electrophilic substitution on the S-blocked phenol **22a**, followed by
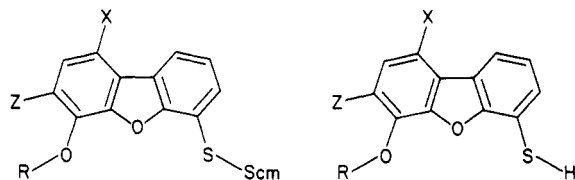

22a, X=Z=H; R=H
22b, H=Z=H; R=Ac
22c, H=Z=H; R=Z-L-Ala
23, X=Br; Z=H
24, X=Cl; Z=H
25, X=H; Z=Cl
26, X=Z=Cl
27, X=NO₂; Z=H

33b, X=H=Z; R=Ac
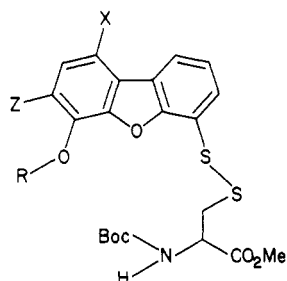
34b, X=Z=H; R=Ac
34c, X=Z=H; R=Z-L-Ala
35b, X=Cl; Z=H; R=Ac
36b, X=NO₂; Z=H; R=Ac
36c, X=NO₂; Z=H; R=Z-L-Ala

phosphine cleavage of the Scm group to form thiols (e.g., **33**) which were usually not characterized but were converted directly by reaction with Boc-L-Cys(Scm)-OMe to the unsymmetrical disulfides (e.g., **34**). Removal of the Boc group with HCl or trifluoroacetic acid generated a salt of **1**, suitable for the acyl-transfer studies. EM values were estimated as ratios of first-order rate constants for the acyl-transfer reactions of **1** to second-order rate constants for the aminolysis of corresponding esters **28–32** in the presence of ethyl S-benzyl-L-cysteinate.
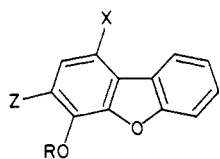
28b, X=H=Z; R=Ac
29b, X=Cl; Z=H; R=Ac
29c, X=Cl; Z=H; R=Z-L-Ala
30, X=H; Z=Cl
31, X=Z=Cl
32, X=NO₂; Z=H

As seen by the data of Table II, a respectable substituent effect is seen for the reactions of **1** bearing electron-withdrawing 1-substituents. The 1-nitro derivative of **1** is more than 3000 times more reactive than **1** itself, and using a σ⁻ value of 1.27 for the nitro substituent we calculate a Hammett σ for this reaction of 2.6.

Although the nitro derivative is probably too reactive to be used in preparative work, the bromo and chloro derivatives are likely to be useful when dealing with β-branched amino acid esters, and we are currently exploring these applications. It is striking that the values for EM are moderately consistent over 3 orders of magnitude of reactivity, supporting the view that this parameter does indeed provide a measure of the efficiency of entropic activation, independent of the degree of activation of the acylating agent.

Inspection of model **21a** for the transition state of the reaction **1 → 2** suggests an intriguing role for a buttressing 3-substituent. In **21** the oxygens and carbon derived from the acyloxy function of **1** occupy a plane perpendicular to that of the dibenzofuran, but in **1** itself one might expect a planar conformation to be preferred. Introduction of a 3-substituent should restrict the geometry of the starting material to that required by **21**. A larger EM value would then be expected for a 3-chloro derivative of **1**. In fact this substance was prepared and studied (Table II) but was found to have a somewhat smaller EM value than that seen for the 1-chloro derivative. Clearly a rate-accelerating buttressing effect, if present, is outweighed by other steric factors.

Summary

By a process of rational design we have prepared the dibenzofuran derivative **1** as our prime candidate for the intramolecular acyl-transfer step of the thiol capture strategy. This weakly activated acyl derivative owes its acylating capacity primarily to an effective positioning of the cysteine amine substituent near the electrophilic carbon of the weakly electrophilic acyloxy function. In effect, given a means of forming **1** from separate peptide fragments by a disulfide bond-generating reaction, the amide-forming step is expected to occur with an efficiency equivalent to an intermolecular reaction run at 5 M concentration. In the accompanying paper we have demonstrated a convenient, efficient synthesis of peptide esters with structure **1**. In later papers in this series we will address the problem of the disulfide-forming capture chemistry as well as practical aspects of amide bond formation between peptide fragments in the acyl-transfer step.

Experimental Section

IR spectra were recorded on a Perkin-Elmer Model 283-B spectrometer. High resolution ¹H NMR and ¹³C NMR spectra

were obtained on either a Bruker WM-250 or a Bruker WM-270 instrument. Chemical shifts are reported in ppm downfield from Me₄Si and splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad; only major or simple peaks are reported for peptide spectra. 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.

Analytical thin layer chromatography was performed on glass precoated silica gel 60 plates (Merck F-254). Preparative layer chromatography was performed on Analtech GF plates, and flash chromatography was carried out on silica gel 60 (230–400 mesh) using 100% CH_2Cl_2 as eluent.

HPLC was performed on a Waters system consisting of two Model 6,000-A pumps, a Model 680 automated gradient controller, a Model U6K injector, a Model 440 dual channel UV detector (280, 254 nm), an extended wavelength module (229, 214 nm) and a Model 730 data module. HPLC runs were conducted in the reverse-phase mode on Whatman Partisil columns. Unless otherwise specified, chemicals used were reagent grade. Solutions of butyllithium in hexane were obtained from Alpha. Methoxycarbonylsulfenyl chloride was prepared by literature procedures[18] and purified by careful spinning-band distillation.

2-Deuteriodibenzofuran (6). Literature procedures[17] were used to convert dibenzofuran to 2-bromodibenzofuran in 76% yield, mp 106–107 °C (lit. 107 °C). To a solution of the latter (0.80 g, 3.2 mmol) in 20 mL of anhydrous ether was added a solution of n-butyllithium (3.35 mmol) in 1.42 mL of n-hexane in one portion at 25 °C under nitrogen. The mixture was heated at reflux for 0.5 h, then cooled to 0 °C and quenched with 10 mL of a 20% solution of DCl in D_2O. Extraction of the aquous phase with ether, pooling of organic phases drying, and evaporation gave 2-deuteriodibenzofuran (6), 0.48 g, 88%: mp 78–79 °C after recrystallization (MeOH); ¹H NMR (250 MHz, CDCl₃) δ 7.17 (1 H, t, J = 8 Hz, C₈-H), 7.29 (2 H, tm, C₃-H and C₇-H), 7.42 (2 H, d, J = 8 Hz, C₄-H and C₆-H), 7.78 (2 H, dm, C₁-H and C₉-H); ¹³C NMR (62.83 MHz, CDCl₃) δ 111.7 (d, C₄ and C₆), 120.6 (d, C₁), 120.7 (d, C₉), 122.5 (t, C₂), 122.7 (d, C₈), 124.3 (s, C₄ₐ and C₆ₐ), 127.1 (d, C₃), 127.2 (d, C₇), 156.3 (s, C₄ₐ and C₆ₐ); mass spectrum (70 eV), m/e 169 (M⁺).

Anal. Calcd for C₁₂H₇DO: C, 85.21; (H + D), 4.14. Found: C, 84.94; (H + D), 4.30.

4-Deuteriodibenzofuran (5). A procedure similar to that described for 6 was used. Dibenzofuran was converted first to 4-bromodibenzofuran,[19] then to the organomagnesium complex, and then to 5 (92%) by treatment with DCl–D₂O: mp 81–82 °C; ¹H NMR (250 MHz, CDCl₃) δ 7.17 (2 H, t, J = 8 Hz, C₂-H and C₈-H), 7.29 (2 H, tm, C₃-H and C₇-H), 7.42 (1 H, d, J = 8 Hz, C₆-H), 7.78 (2 H, dd, J = 8,1 Hz, C₁-H and C₉-H); ¹³C NMR (62.83 MHz, CDCl₃) δ 111.6 (t, C₄), 111.7 (d, C₆), 120.7 (d, C₁ and C₉), 122.7 (d, C₂ and C₈), 124.3 (s, C₄ᵦ and C₆ᵦ), 127.1 (d, C₃), 127.2 (d, C₇), 156.2 (s, C₄ₐ), 156.3 (s, C₆ₐ); mass spectrum (70 eV), m/e 169 (M⁺).

Anal. Calcd for C₁₂H₇DO: C, 85.21; H, 4.14. Found: C, 85.03; H, 4.38.

4-Methoxy-6-(trimethylsilyl)dibenzofuran and 1,3,6-Trideuterio-4-methoxydibenzofuran (8). To a solution of 4-methoxydibenzofuran (2.00 g, 10.1 mmol) in 50 mL of diethyl ether was added under nitrogen at 25 °C 10.3 mmol of n-butyllithium in 4.70 mL of n-hexane. The mixture was heated at reflux for 10 h, then chilled to −78 °C, quenched with 1.35 mL (10.6 mmol) of trimethylsilyl chloride, and allowed to warm to 25 °C over 6 h. Water (50 mL) was added, and the resulting aqueous phase was extracted with ether. The organic phases were pooled, washed, dried, and evaporated to yield 2.5 g of yellow oil which was subjected to flash chromatography on silica gel (9:1 cyclohexane–CH₂Cl₂) to yield the title compound (1.15 g, 42%): mp 59.5–61.5 °C; ¹H NMR (250 MHz, CDCl₃) δ 0.46 (9 H, s), 4.08 (3

H, s), 6.97 (1 H, dd, J = 8, 1 Hz), 7.23 (1 H, t, J = 8 Hz), 7.32 (1 H, t, J = 8 Hz), 7.50–7.55 (2 H, m), 7.93 (1 H, dd, J = 8, 1 Hz); high resolution mass spectrum, calcd for C₁₆H₁₈O₂Si 270.1076, found 270.1059.

To a solution of the above silyl derivative (7.1 mg, 26 μmol) in 0.60 mL of methanol-d was added a 35% solution of DCl in D₂O. The mixture was heated at reflux for 15 h, then poured into water, and extracted 3× with CH₂Cl₂. The pooled extracts were washed, dried, evaporated, and dried under vacuum to yield 6.1 mg of oil, purified by preparative layer chromatography to give 3.8 mg of 8 (72%): ¹H NMR (250 MHz, CDCl₃) δ 4.06 (3 H, bt, C₇-H), 7.92 (1 H, dd, J = 8, 1 Hz, C₁-H); high resolution mass spectrum, calcd for C₁₃H₇D₃O₂ 201.0869, found 201.0860.

1,3-Dideuterio-4-methoxydibenzofuran (7). When 4-methoxydibenzofuran was subjected to the above conditions the dideutero 7 was obtained, contaminated with monodeuterated derivatives: ¹H NMR (250 MHz, CDCl₃) δ 4.03 (3 H, s, Ar OCH₃), 6.95 (0.16 H, d, J = 8 Hz, C₃-H), 7.24 (1 H, bs, C₂-H), 7.33 (1 H, t, J = 8 Hz, C₈-H), 7.44 (1 H, t, J = 8 Hz, C₇-H), 7.52 (0.32 H, d, J = 8 Hz, C₁-H), 7.61 (1 H, d, J = 8 Hz, C₆-H), 7.91 (1 H, d, J = 8 Hz, C₉-H).

4-(Trimethylsilyl)-6-hydroxyphenoxythiin (10). By literature procedures,[20] diphenyl ether was converted to phenoxythiin and thence to 4-hydroxyphenoxythiin (9). Reaction of 9 (101 mg, 0.47 mmol) in 3 mL of THF containing 0.20 mL (1.3 mmol) of tetramethylethylenediamine at −12 °C with 0.45 mL (1.0 mmol) of n-butyllithium in n-hexane was carried out for 12 h at −12 °C. The solution was then quenched with 0.2 mL (1.4 mmol) of trimethylsilyl chloride and allowed to warm to 25 °C (4 h). The mixture was poured into 5% NaHCO₃ and extracted 3× with CH₂Cl₂; the pooled organic phases were extracted with NaHCO₃, dried, and evaporated. The oily residue was dissolved in 4 mL of methanol containing 50 μL 1 N HCl. After 5 min, the mixture was partitioned between CH₂Cl₂ and excess 1 N NaOH. Separation of the CH₂Cl₂ layer, washing, drying, and evaporation gave 117 mg of 10, 90%, as a viscous yellow oil: ¹H NMR (250 MHz, CDCl₃) δ 0.50 (9 H, s), 5.53 (1 H, bs), 6.69 (1 H, dd, J = 8, 1 Hz), 6.86 (1 H, dd, J = 8, 1 Hz), 6.97 (1 H, t, J = 8 Hz), 7.0. (1 H, t, J = 8 Hz), 7.191 (1 H, dd, J = 8, 1 Hz), 7.29 (1 H, dd, J = 8, 1 Hz); mass spectrum (70 eV), m/e (relative intensity) 288 (M⁺, 100), 257 (79), 242 (48), 136 (47), 75 (65).

4-(Trimethylsilyl)-6-methoxyphenoxythiin and 6-Deuterio-4-methoxyphenoxythiin. To a solution of 100 mg of 10 (0.35 mmol) in 4 mL of acetone at 40 °C was added 72 mg (0.52 mmol) of anhydrous K₂CO₃ and 0.2 mL (3 mmol) of methyl iodide. After 11h at reflux, the solvent was evaporated, and the residue was partitioned between CH₂Cl₂ and water. The organic phases were combined, extracted with 1 N NaOH, washed, dried, and evaporated. Kugelrohr distillation of the oily residue gave a solid: mp 97–99 °C, 98 mg, 93%; ¹H NMR (250 MHz, CDCl₃) δ 0.42 (9 H, s, TMS), 3.87 (3 H, s, Ar OCH₃), 6.69 (1 H, dd, J = 8, 1 Hz), 6.75 (1 H, dd, J = 8, 1 Hz), 6.96 (1 H, t, J = 8 Hz), 7.01 (1 H, t, J = 8 Hz), 7.12 (1 H, dd, J = 8, 1 Hz), 7.26 (1 H, d d, J = 8, 1 Hz); mass spectrum (70 eV), m/e (relative intensity) 302 (M⁺, 100), 287 (87), 244 (27), 144 (60), 136 (30).

Anal. Calcd for C₁₆H₁₈O₂₂SSi: C, 63.54; H, 6.00; S, 10.60; Si, 9.29. Found: C, 63.66; H, 5.97; S, 10.45; Si, 9.09.

To a solution of 54 mg (0.18 mmol) of the above silyl derivative in 2 mL of THF was added at 25 °C 10 μL (0.45 mmol) of D₂O and 180 mg (0.66 mmol) of tetrabutylammonium fluoride in 0.2 mL of THF. After 1 h of stirring the solution was quenched with D₂O and extracted 3× with CH₂Cl₂. The pooled extracts were washed, dried, and evaporated to give 6-deuterio-4-methoxyphenoxythiin as an oil, 39 mg, 94%: ¹H NMR (250 MHz, CDCl₃) δ 3.89 (3 H, s), 6.69 (1 H, dd, J = 8, 1 Hz), 6.73 (1 H, dd, J = 8 Hz), 6.90–7.04 (2 H, m), 6.07–7.11 (2 H, m); ¹³C NMR (67.93 MHz, CDCl₃) δ 56.3 (Ar OCH₃), 111.1 (d), 117.5 (t, C₆), 118.7 (d), 120.4 (s), 121.4 (s), 124.0 (d), 124.5 (d), 126.6 (d), 127.5 (d), 141.8 (s), 149.2 (s), 152.3 (s); mass spectrum (70 eV), m/e 231 (M⁺).

4-Hydroxy-6-mercaptophenoxythiin (4). To a solution of 9 (0.51 g, 2.35 mmol) in 15 mL of THF containing 1 mL (6.6 mmol) of tetramethylethylenediamine at −15 °C under nitrogen was added 2.4 mL (5 mmol) of a solution of n-butyllithium in n-hexane.

(17) Buu-Hoi, N. P.; Royer, R. *Recl. Trav. Chim. Pays-Bas* 1948, 67, 175.

(18) Weiss, W. Ger. Pat. 1 224 720, Farbenfabriken Bayer A.G., 1966; Mühlbauer, E.; Weiss, W. Ger. Pat. 1 568 632, Farbenfabriken Bayer A.G., 1969. Zupancic, B. *Synthesis.* 1975, 169.

(19) Gilman, H.; Parker, P.; Baile, J.; Brown, G. *J. Am. Chem. Soc.* 1938, 61, 2836.

(20) Suter, C. M.; Maxwell, C. E. *Org. Synth. (N.Y.)* 1938, 18, 64.

After 5 h at −15 °C the solution was treated with 0.24 g (7.5 mmol) of sulfur and allowed to warm to 25 °C (4 h). The resulting black mixture was added to 1 g of lithium aluminum hydride slurried in 5 mL of THF, and after 10 min, excess hydride was decomposed cautiously with methanol. The mixture was acidified (1 N HCl) and extracted 3× with CH_2Cl_2. The pooled extracts were washed with 1 N HCl and water, dried, and evaporated to yield 0.37 g of orange solid, 65%, which was used directly in the synthesis of **19b** (X = S).

4-Acetoxyphenoxythiin. A solution of 1.0 g (4.6 mmol) of 4-hydroxyphenoxythiin (9) in 3.2 mL of pyridine was treated with 2.3 mL of acetic anhydride and stirred 20 h at 25 °C. The mixture was then poured on a slurry of ice and 1 N hydrochloric acid which was extracted with dichloromethane. The pooled extracts were washed with 1 N hydrochloric acid, water, and brine, then dried, and evaporated to yield 1.1 g, 93%, mp 88 °C. Recrystallization from ethanol gave 0.88 g, 74%, mp 88.5–90 °C. Anal. Calcd for $C_{14}H_{10}O_3S$: C, 65.10; H, 3.90. Found: C, 64.92; H, 4.01.

4-Hydroxy-6-(methoxycarbonyldithio)phenoxythiin, 4-Acetoxy-6-(methoxycarbonyldithio)phenoxythiin, and Methyl *N-tert*-Butoxycarbonyl-*S*-[4-acetoxy-6-phenoxythiinylthio]-L-cysteinate (19b) (NH → N-Boc). To a solution of 0.38 g (1.5 mmol) of 4-hydroxy-6-mercaptophenoxythiin (4) in 2.5 mL of methanol was added with stirring 0.16 mL (1.7 mmol) of methoxycarbonylsulfenyl chloride. After 2 h only a trace of starting material could be detected by TLC, and the 0.37 g of orange oil obtained after evaporation was dissolved in 5.5 mL of acetic anhydride and treated at 25 °C with a drop of concentrated sulfuric acid. After 3 h the solution was poured onto ice–aqueous sodium bicarbonate and extracted with dichloromethane. After washes with sodium bicarbonate, brine, and water, drying, and evaporation, the resulting residue was further dried by azeotropic evaporation of acetonitrile (2 × 25 mL). The oily product, 0.43 g, was homogeneous by TLC and HPLC and was dissolved in 7 mL of a 4:1 dioxane–water mixture and added under nitrogen to 0.3 mL (ca. 1.07 equiv) of freshly distilled tri-*n*-butylphosphine. After 35 min the solvent was evaporated, and the oily residue was dissolved in 5 mL of 14:1 hexafluoroisopropyl alcohol–chloroform and added to a solution of 0.25 g (ca. 0.75 equiv) of methyl *N-tert*-butoxycarbonyl-*S*-(methoxycarbonylthio)-L-cysteinate[21] in 4 mL of hexafluoroisopropyl alcohol. After 0.5 h the solvent was evaporated, and the oily residue was purified by preparative layer chromatography (Analtech GF 1000 μm silica gel; 9:1 chloroform–ethyl acetate) to give **19b (NH → N-Boc)** homogeneous to TLC and HPLC, as a white powder, 120 mg, 30% from 4; mp 108.5–112.0 °C; ^{1}H NMR (90 MHz, CD_2Cl_2) δ 7.52–7.59 (2 H, overlapping doublets), 7.46–7.50 (4 H, m), 4.19 (3 H,s), 2.93 (3 H, s), 1.90 (9 H, s).

4-Hydroxy-6-(methoxycarbonyldithio)dibenzofuran (22a), 4-Acetoxy-6-(methoxycarbonyldithio)dibenzofuran (22b), and 4-(Benzyloxycarbonyl-L-alanyloxy)-6-(methoxycarbonyldithio)dibenzofuran (22c). To a solution of 4-hydroxy-6-mercaptodibenzofuran (3) (1.02 g, 4.72 mmol) in 10 mL of methanol was added in one portion with vigorous stirring 0.5 mL (5.45 mmol) of methoxycarbonylsulfenyl chloride. The mixture was stirred at 25 °C for 2 h and then was concentrated, and the residue was dried by azeotropic distillation with acetonitrile (2 × 25 mL) to yield 1.64 g of a viscous oil. Flash chromatography (eluant dichloromethane) yielded an oil that solidified on standing (1.13 g, 78%). Trituration with 1:1 ether–hexane gave 1.01 g of **22a**, white powder: mp 106–108 °C, 70%; high resolution mass spectrum, calcd for $C_{14}H_{10}O_4S_2$ 306.002, found 306.005. Anal. Calcd for $C_{14}H_{10}O_4S_2$: C, 54.89; H, 3.29; S, 20.93. Found: C, 54.89; H, 3.42; S, 21.07.

To a solution of **22a** (176 mg, 0.575 mmol) in 2.5 mL of acetic anhydride at 25 °C was added 5 μL of sulfuric acid (concentrated). After 4 h the solution was poured onto ice–sodium bicarbonate (5%), and the mixture was extracted with dichloromethane. The combined extracts were washed with 5% sodium bicarbonate, water, and brine, then dried, and evaporated. The oily residue was dried by azeotropic distillation at reduced pressure of acetonitrile (2 × 25 mL) and further dried under vacuum to yield 194 mg of a white powder, **22b**: mp 95–96 °C, 97%; high resolution

mass spectrum, calcd for $C_{16}H_{12}O_5S_2$ 348.0126, found 348.0115.

A solution of 1.43 g (4.67 mmol) of **22a** and 1.05 g (5.1 mmol) of *N*-benzyloxycarbonyl-L-alanine in 35 mL of dichloromethane was cooled to 0 °C and treated with 1.2 g (5.8 mmol) of dicyclohexylcarbodiimide. The resulting mixture was stirred at 0 °C, for 2 h, then at 25 °C, for 16 h, when the precipitate was filtered and washed with cold dichloromethane. The combined filtrates were washed with cold citrate buffer (pH 3.5, 0.5 M), with cold sodium bicarbonate solution, and with water. After drying and evaporation the solution yielded a white residue that was suspended in 50 mL of ethyl acetate and warmed briefly to leave residual urea undissolved. The solution was cooled, filtered, concentrated to 25 mL, and again filtered to remove urea. After repetition of this sequence, the solution was evaporated to leave 2.17 g, 97%, of a residue that was recrystallized from 10 mL of ethyl acetate to give 1.33 g of **22c**, white needles, mp 148–149 °C, 60%. Cooling to −20 °C and concentration yielded a second crop, 11%: mp 146–148 °C; field desorption mass spectrum, *m/e* 4/6 (M^+ − 1). Anal. Calcd for $C_{22}H_{23}O_7NS_2$: C, 55.33; H, 4.85; N, 2.94; S, 13.43. Found: C, 55.53; H, 5.01; N, 2.94; S, 13.69.

1-Bromo-4-hydroxy-6-(methoxycarbonyldithio)dibenzofuran (23a), 1-Bromo-4-acetoxy-6-(methoxycarbonyldithio)dibenzofuran (23b), and 1-Bromo-4-(benzyloxycarbonyl-L-alanyloxy)-6-(methoxycarbonyldithio)dibenzofuran (23c). To a solution of 34 mg (0.11 mmol) 4-hydroxy-6-(methoxycarbonyldithio)dibenzofuran (22a) in 1 mL of glacial acetic acid was added dropwise over 2 min 224 μL (0.11 mmol) of a 0.5 M solution of bromine in acetic acid. After 30 min of stirring at 25 °C the solution was poured into water and extracted with chloroform. The combined extracts were pooled, washed with water and brine, dried, and evaporated. Purification of the resulting oil by preparative layer chromatography (1000 μm; 9:1 chloroform–ethyl acetate) afforded a white foam, **23a**, 33 mg, 76%: high resolution mass spectrum, calcd for $C_{14}H_9O_4S_2Br$ 383.9126 and 385.9105, found 383.9122 and 385.9124.

A solution of **23a** was acetylated as described for **22b** to give a 99% yield of crude product. Trituration with hexane gave 79% of a fluffy white solid, **23b**, mp 136–139 °C; ^{1}H NMR (270 MHz, CDCl₃) δ 8.49 (1 H, d, *J* = 7.8 Hz), 7.80 (1 H, d, J = 7.8 Hz), 7.5 (1 H, d, *J* = 8.3 Hz), 7.41 (1 H, t, *J* = 7.8 Hz), 7.15 (1 H, d, *J* = 8.8 Hz), 2.50 (3 H, s); high resolution mas spectrum, calcd for $C_{16}H_{11}O_5S_2Br$ 425.9231 and 427.9211, found 425.9245 and 427.9224.

Reaction of 109 mg (0.28 mmol) of **23a** with 63.0 mg (0.28 mmol) of Z-L-Ala-OH and 58.3 mg (0.28 mmol) of DCC was carried out as described for **22c**. Recrystallization of the resulting clear glass from dichloromethane–petroleum ether yielded 98.7 g of **23c**, 57%, white needles, mp 135–136 °C.

1-Chloro-4-hydroxy-6-(methoxycarbonyldithio)dibenzofuran (24a), 1-Chloro-4-acetoxy-6-(methoxycarbonyldithio)dibenzofuran (24b), and 1-Chloro-4-(benzyloxycarbonyl-L-alanyloxy)-6-(methoxycarbonyldithio)dibenzofuran (24c). A solution of 84 mg (0.27 mmol) of **22a** in 2 mL of chloroform and 24 μL (0.3 mmol) of sulfuryl chloride was stirred for 2 h at 25 °C and then heated to reflux for 1.5 h. The solution was evaporated, and the oily residue was purified by preparative layer chromatography (1000 μm, 9:1 chloroform–ethyl acetate) to give 43 mg of **24a** as a clear oil, 47%: ^{1}H NMR (250 MHz, CDCl₃) δ 8.26 (1 H, dd, *J* = 7.7, 1.1 Hz), 7.71 (1 H, dd, *J* = 7.7, 1.1 Hz), 7.36 (1 H, t, *J* = 7.7 Hz), 7.14 (1 H, d, *J* = 8.4 Hz), 6.97 (1 H, d, *J* = 8.4 Hz) high resolution mass spectrum, calcd for $C_{14}H_9O_4S_2Cl$ 339.9631, found 339.9638.

The resulting **24a** was acetylated as described for **22b** to give the acetyl ester **24b** in 72% yield after trituration with cold acetonitrile: mp 124.0–126.5 °C; high resolution mass spectrum, calcd for $C_{16}H_{11}O_5S_2Cl$ 381.9736, found 381.9712.

Using the dicyclohexylcarbodiimide procedure described for **22c** the Z-L-Ala-OH ester **24c** was obtained in 55% yield, homogeneous by HPLC and TLC.

3-Chloro-4-hydroxy-6-(methoxycarbonyldithio)dibenzofuran (25a) and 3-Chloro-4-(benzyloxycarbonyl-L-alanyloxy)-6-(methoxycarbonyldithio)dibenzofuran (25c). The general ortho-chlorination procedure of Watson[22] was followed. Under a current of dry nitrogen 183 mg (0.596 mmol) of **22a** was

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(22) Watson, W. D. *J. Org. Chem.* **1974**, *39*, 1160.

heated to reflux in 4 mL of carbon tetrachloride. To this solution was added every 15–20 min 100-μL aliquots of a 0.9 M solution of chlorine in carbon tetrachloride until an HPLC assay revealed disappearance of the starting phenol (nine aliquots were required). Preparative layer chromatography (Analtech GF 1000 μm, 9:1:0.05 chloroform, ethyl acetate, acetic acid) gave two principal bands; the upper band yielded 80.7 mg of product which was further purified by preparative HPLC (Magnum 9 ODS-2 Column, 92% methanol/8% aqueous/1% acetic acid) to yield 43.6 mg of **25a**: ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.88 (1 H, d, J = 7.7 Hz), 7.71 (1 H, dd, J = 8.3, 0.8 Hz), 7.24–7.35 (4 H, m), 3.91 (3 H, s).

Using the dicyclohexylcarbodiimide procedure described for **22c** the Z-L-Ala-OH ester **25c** was obtained in 62% yield, mp 121.5–122 °C.

1,3-Dichloro-4-hydroxy-6-(methoxycarbonyldithio)dibenzofuran (26a) and 1,3-Dichloro-4-(benzyloxycarbonyl-alanyloxy)-6-(methoxycarbonyldithio)dibenzofuran (26c). Following the procedure described for **25a** but using 2 equiv of chlorine, the dichlorophenol **26a** was isolated by HPLC (Lobar column (Merck), 4:1 methanol–aqueous 0.1% trifluoroacetic acid): mp 150–153 °C; ^{1}H NMR (250 mHz, CDCl$_3$) δ 8.27 (1 H, dd, J = 8.0, 1.0 Hz), 7.75 (1 H, dd, J = 8.0, 1.2 Hz), 7.36 (1 H, t, J = 8.0 Hz), 7.31 (1 H, s), 3.90 (3 H, s).

Using the mixed anhydride acylation procedure described for **27c** the Z-L-Ala-OH ester **26c** was obtained in 43% yield, mp 130–131.5 °C.

1-Nitro-4-hydroxy-6-(methoxycarbonyldithio)dibenzofuran (27a) and 1-Nitro-4-(benzyloxycarbonyl-L-alanyloxy)-6-(methoxycarbonyldithio)dibenzofuran (27c). The general nitration procedure of Colbert et al.[23] was followed. A solution of 269 mg (0.878 mmol) of **22a** in 3 mL of nitromethane was chilled with stirring and treated with 34.7 μL of fuming nitric acid (1 equiv). After 6 h the mixture was poured into dichloromethane–water, and the organic phase was separated and washed with water, brine, and then dried. Evaporation yielded a brown glass that was crystallized from acetone–water to give 82–87 mg of **27a**, yellow plates, 27%: mp 161–162 °C, mp 171.5 °C after a second recrystallization; ^{1}H NMR (250 mHz, CDCl$_3$) δ 8.15 (1 H, d, J = 8.5 Hz), 7.96 (1 H, dd, J = 7.5, 1.0 Hz), 7.87 (1 H, d, J = 8.5 Hz), 7.26–7.38 (2 H, m), 4.97 (3 H, s).

To a solution of 30.1 mg (0.135 mmol) of benzyloxycarbonyl-L-alanine and 17.5 μL of isobutyl chloroformate (0.135 mmol) in 1 mL of ethyl acetate at –12 °C was added 28 μL of triethylamine. After 15 min, 46.4 mg (0.132 mmol) of **27a** in 2 mL of chloroform was added at –12 °C. After 7.5 h the reaction mixture was warmed to 25 °C, filtered, and evaporated. The residue was dissolved in 20 mL of dichloromethane, washed with 0.5 M citric acid, water, and brine, then dried, and evaporated. Purification by preparative layer chromatography (Analtech GF 1000 μM, 9:1 chloroform–ethyl acetate) yielded 32.2 mg of **27c**, homogeneous by TLC and HPLC: ^{1}H NMR (250 mHz, CDCl$_3$) δ 8.17 (1 H, d, J = 8.7 Hz), 7.99 (1 H, dd, J = 6.7, 0.8 Hz), 7.90 (1 H, d, J = 8.7 Hz), 7.86 (1 H, dd, J = 7.6, 0.8 Hz), 7.26–7.54 (6 H, m), 1.83 (3 H, d, J = 6.7 Hz).

4-Acetoxydibenzofuran (28). Acetylation of 4-hydroxydibenzofuran using the procedure for **22b** gave a nearly quantitative yield of the title compound, mp 98.5–99.5 °C, recrystallized from ethanol, mp 99–100 °C. Anal. Calcd for C$_{14}$H$_{10}$O$_3$: C, 74.33; H, 4.46. Found: C, 74.23; H, 4.50.

1-Chloro-4-acetoxydibenzofuran (29b) and 1-Chloro-4-(benzyloxycarbonyl-L-alanyloxy)dibenzofuran (29c). A specimen of 1-chloro-4-hydroxydibenzofuran was prepared by literature procedures and acetylated as described for **22b** to yield 90% of a white powder, mp 122–127 °C, which was recrystallized from dichloromethane–pentane: mp 126–128 °C; ^{1}H NMR (250 MHz, Me$_2$SO-d$_6$) δ 8.34 (1 H, d, J = 7.1 Hz), 7.83 (1 H, d, J = 7.1 Hz), 7.66 (1 H, t, J = 7.1 Hz), 7.53 (1 H, t, J = 7.1 Hz). Anal. Calcd for C$_{14}$H$_9$O$_3$Cl: C, 64.51; H, 3.48; Cl, 13.60. Found: C, 64.70; H, 3.52; Cl, 13.73.

Following the dicyclohexylcarbodiimide esterification procedure reported for **26**, 28.4 mg (0.13 mmol) of **29b** and 29 mg of benzyloxycarbonyl-L-alanine (0.14 mmol) were coupled to yield 34

mg, 64% of **29c**: mp 157–158 °C; ^{1}H NMR (270 MHz, Me$_2$SO-d$_6$) δ 8.36 (1 H, d), 8.15 (1 H, d), 7.80 (1 H, d), 7.67 (1 H, t), 7.33–7.55 (7 H, m).

3-Chloro-4-hydroxydibenzofuran (30a) and 3-Chloro-4-(benzyloxycarbonyl-L-alanyloxy)dibenzofuran (30c). The general ortho-chlorination procedure of Watson[22] was followed. Under a current of dry nitrogen, 110 mg (0.596 mmol) of 4-hydroxydibenzofuran was heated to reflux in 4 mL of carbon tetrachloride. To this solution was added every 15–20 min 100-μL aliquots of a 0.9 M solution of chlorine in carbon tetrachloride until an HPLC assay revealed disappearance of the starting phenol (eight aliquots were required). Preparative layer chromatography (Analtech GF 1000 μm, 9:1:0.05 chloroform, ethyl acetate, acetic acid) gave two principal bands; the upper band yielded 50 mg of **30a**: mp 114–115 °C; ^{1}H NMR (250 MHz, acetone-d$_6$) δ 9.36 (1 H, s, exch), 8.08 (1 H, d, J = 7.0 Hz), 7.66 (1 H, d, J = 8.0 Hz), 7.60 (1 H, d, J = 8.0 Hz), 7.53 (1 H, dt, J = 7.0, 1.0 Hz), 7.40 (1 H, dt, J = 7.0, 1.0 Hz), 7.35 (1 H, d, J = 7.0 Hz).

Following the general procedure described for **22c** the phenol was converted to its Z-L-Ala-OH ester **30c**: mp 113–115 °C; ^{1}H NMR (270 MHz, CDCl$_3$) δ 7.80 (1 H, d, J = 8.0 Hz), 7.63 (1 H, d, J = 8.0 Hz), 7.11–7.46 (9 H, m), 1.64 (3 H, d, J = 8.0 Hz).

1,3-Dichloro-4-hydroxydibenzofuran (31a) and 1,3-Dichloro-4-(benzyloxycarbonyl-L-alanyloxy)dibenzofuran (31c). Following the procedure described for **30a** but using sufficient chlorine to effect nearly complete conversion to the dichlorophenol as monitored by HPLC gave **31a** as white crystals from carbon tetrachloride solution: mp 155–156.5 °C; ^{1}H NMR (250 MHz, CDCl$_3$) δ 8.31 (1 H, d, J = 7.6 Hz), 7.63 (1 H, d, J = 8.3 Hz), 7.53 (1 H, dt, J = 7.5, 1.0 Hz), 7.40 (1 H, dt, J = 8.0, 1.0 Hz), 7.32 (1 H, s).

Following the mixed anhydride procedure as described for **27c**, the Z-L-Ala-OH active ester **31c** was obtained in 63% yield as white needles: mp 167–168 °C; ^{1}H NMR (250 MHz, CDCl$_3$) δ 8.33 (1 H, d, J = 7.0 Hz), 7.30–7.67 (9 H, m), 1.78 (3 H, d, J = 8 Hz).

1-Nitro-4-hydroxydibenzofuran (32a) and 1-Nitro-4-(benzyloxycarbonyl-L-alanyloxy)dibenzofuran (32c). A solution of 4-hydroxydibenzofuran (310 mg, 1.85 mmol) in 3 mL of nitromethane at 0 °C was treated with stirring with 75 μL of fuming nitric acid. After 4 h, the reaction mixture was poured into 30 mL of dichloromethane and washed with water and brine. Drying followed by evaporation gave **32a** as a brown glass, mp 192–193 °C, after two crystallizations from acetone–water.

The above prepared nitrophenol (54 mg, 0.153 mmol) was acylated as described for **22c** to give **32c**; preparative TLC (1000 μm silica plate, 15:1 chloroform–ethyl acetate) gave 46.5 mg (68%) of **32c** as an oil: ^{1}H NMR (250 mHz, CDCl$_3$) δ 8.15 (d, J = 8.5 Hz, 1 H), 8.02 (d, J = 7.6 Hz, 1 H), 7.91 (d, J = 8.5 Hz, 1 H), 7.7–7.3 (m, 8 H).

General Procedure for Conversion of a 4-(Acyloxy)-6-(methoxycarbonyldithio)dibenzofuran to a Methyl N-(tert-Butoxycarbonyl)-S-(4-(acyloxy)dibenzofuranylsulfenyl)-L-cysteinate. A solution of the SScm derivative of the mercaptodibenzofuran in 4:1 dioxane–water under nitrogen is treated with an equivalent of tri-n-butylphosphine or triethylphosphine. The solution is lyophilized after 0.5 h, subjected to high vacuum, purged with nitrogen, and treated with sufficient hexafluoroisopropyl alcohol to dissolve the thiol. (At high concentrations 4-(acyloxy)-6-mercaptodibenzofurans undergo a slow O,S-acyl equilibration, and they are best converted immediately to the unsymmetrical disulfides without isolation.) One equivalent of Boc-L-Cys(SScm)-OMe[21] is then added under nitrogen, and after 30–40 min, the solvent is evaporated. The resulting unsymmetrical disulfide can be purified by chromatography but is usually sufficiently pure to use directly in N-deblocking and acyl transfer.

4-Acetoxy-6-mercaptodibenzofuran (33b) and Methyl N-(tert-Butoxycarbonyl)-S-(4-acetoxy-6-dibenzofuranylsulfenyl)-L-cysteinate (34b). Following the general procedure for removing the SScmn group with tri-n-butyl phosphine, **22b** was converted to **33b** in 87% yield; recrystallization from dichloromethane–pentane yielded large prisms of **33b**, mp 115–116 °C. Anal. Calcd for C$_{14}$H$_{10}$O$_3$S: C, 65.10; H, 3.90; S, 12.41. Found: C, 65.33; H, 4.05; S, 12.44.

To a solution under nitrogen of 22.5 mg (87.1 μmol) of **33b**, freshly prepared as described above, in 0.5 mL of methanol was

(23) Colbert, J. C.; Fox, D.; Matuszak, C. *J. Am. Chem. Soc.* **1955**, *77*, 2448.

added 28.3 mg (87.1 μmol) of methyl N-(*tert*-butoxycarbonyl)-S-(methoxycarbonylsulfenyl)-L-cysteinate,[21] mp 76.5–78.0 °C (lit. 78 °C), in 1 mL of 1:1 chloroform–methanol, followed by 2 μL (14 μmol) of triethylamine. After 0.5 h at 25 °C, the solution was evaporated, and the resulting oil was dissolved in dichloromethane and washed with cold 0.1 M hydrochloric acid, water, and brine, then dried, and evaporated. The residue was purified by preparative layer chromatography (1000 μm, 9:1 chloroform–ethyl acetate) to give 37.4 mg (87%) of **34b** as an oil that solidified on standing mp 63–64 °C; high resolution mass spectrum, calcd for $C_{23}H_{25}O_7NS_2$ 491.1073, found 491.1081. Anal. Calcd for $C_{23}H_{25}O_7NS_2$: C, 56.20; H, 5.13; N, 2.85; S, 13.04. Found: C, 55.99; H, 5.31; N, 2.77; S, 13.20.

Methyl N-(*tert*-Butoxycarbonyl)-S-(4-benzyloxy-carbonyl-L-alanyloxy-6-dibenzofuranylsulfenyl)-L-cysteinate (34c). To a suspension of 40.8 mg (79.8 mmol) of **22c** in 2 mL of 4:1 dioxane–water at 25 °C was added 20 μL (80.3 mmol) of tri-n-butylphosphine. After 30 min the solution was lyophilized, the 50.8-mg residue was dissolved under nitrogen in 1.5 mL of 14:1 hexafluoroisopropyl alcohol–chloroform, and the solution was added quickly to 26.1 mg (80.3 mmol) of methyl N-(*tert*-butoxycarbonyl)-S-(methoxycarbonylsulfenyl)-L-cysteinate in 0.7 mL of HFIP. After 0.5 h under nitrogen at 25 °C the solvent was evaporated, and the residue was dried in high vacuum to yield a white solid, 83 mg, which was purified by preparative layer chromatography (1000 μm, 9:1 chloroform–ethyl acetate) to give **34c**, mp 133–135 °C, 46.7 mg, 90%. For analysis a sample was recrystallized from ethyl acetate: mp 133.5–132.5 °C; ^{1}H NMR (270 MHz, CDCl$_3$) δ 7.92 (1 H, dd, J = 8.0, 1.0 Hz), 7.83 (1 H, dd, J = 8.0, 1.0 Hz), 7.70 (1 H, dd, J = 8.0, 1.0 Hz), 7.28–7.42 (8 H, m), 3.67 (3 H, s), 1.80 (3 H, d, J = 7.0 Hz), 1.40 (9 Hz, s). Anal. Calcd for $C_{32}H_{34}N_2O_9S_2$: C, 58.70; H, 5.23; N, 4.28. Found: C, 58.68; H, 5.41; N, 4.17.

Methyl N-(*tert*-Butoxycarbonyl)-S-(1-nitro-4-benzyloxycarbonyl-L-alanyloxy-6-dibenzofuranylsulfenyl)-L-cysteinate (36c). The general procedure was used with modification. The free thiol was found to be unstable in solution. The residue obtained from phosphine cleavage of **27c** after the lyophilization step was treated with N-Boc-L-Cys(SScm)-OMe[21] (3 equiv) in dichloromethane. The desired disulfide was isolated by successive preparative layer chromatograms (Analtech GF 1000, 15:1 chloroform–ethyl acetate; then Merck 1000, 1:1 ether–hexane). The resulting product, 30%, was homogeneous by TLC and HPLC: ^{1}H NMR (250 MHz, CDCl$_3$) δ 8.20 (1 H, d, J = 8.6 Hz), 7.99 (1 H, dd, J = 7.9, 0.8 Hz), 7.93 (1 H, d, J = 8.3 Hz), 7.84 (1 H, d, J = 7.9 Hz), 7.27–7.51 (6 H, m), 3.71 (3 H, s), 1.80 (3 H, d, J = 7.5 Hz), 1.43 (9 H, s).

Methyl N-(*tert*-Butoxycarbonyl)-S-(1-chloro-4-acetoxy-6-dibenzofuranylsulfenyl)-L-cysteinate (35b). The title substance was prepared by the above procedure and purified by preparative layer chromatography, 42%, as a pale oil: ^{1}H NMR (250 MHz, CDCl$_3$) δ 8.34 (1 H, dd, J = 7.7, 1.1 Hz), 7.77 (1 H, dd, J = 7.7, 1.1 Hz), 7.34 (1 H, t, J = 7.7 Hz), 7.33 (1 H, d, J = 8.5 Hz), 7.20 (1 H, d, J = 8.5 Hz), 3.77 (3 H, s), 2.50 (3 H, s), 1.43 (9 H, s); high resolution mass spectrum, calcd for $C_{23}H_{24}O_7NS_2Cl$ 525.0683, found 525.0663.

General Procedure for N-Deblocking and Observation of Intramolecular Acyl Transfer. Roughly 20 mg of the disulfide was dissolved under nitrogen at 0 °C in 0.5 mL of trifluoroacetic acid containing 1 drop of anisole. After 25 min at 0 °C the acid was removed in high vacuum, and traces were removed by two evaporations with 5 mL of toluene followed by trituration with 1:1 ether–petroleum ether.

From 4 to 10 mg of the trifluoroacetate salt of **1** was dissolved in 0.35–0.50 mL of Me$_2$SO-d_6 (0.02–0.03 M) in an NMR tube containing ca. 2 μL of tetramethylsilane. An ^{1}H NMR spectrum was immediately taken (NMR spectra of the salts often gave poorly resolved spectra). The free amine was then liberated by the addition of 1–2 equiv of triethylamine. Spectra were measured periodically by collecting data from 16 transients (40 s). The time of each such measurement was taken as the midpoint of this interval. Rates were followed at 25 °C by measurement of the areas of at least two marker peaks, such as the resonances of the 3-hydrogen of the dibenzofuran moiety. When the phenoxythiin derivative **19b** (NH → N-Boc) was subjected to Boc removal and deprotonation to give **19b** in Me$_2$SO, rate data at a series of

concentrations were found to fit the equation $k_1[19b] + k_2[19b]^2$ where $k_1 = 1.7 \times 10^{-6}$ s^{-1} and $k_2 = 4.3 \times 10^{-5}$ (M s)$^{-1}$. The dibenzofuran derivatives **1** showed no evidence of second-order rate terms.

Rates of reaction of the 1-nitro derivatives were too fast to measure by NMR; these reactions were followed at ca. 5×10^{-5} M at 360 nm using a Durrum-Gibson stopped flow spectrometer. Rate constants for **1** (X = H, Z = Cl) and **1** (X = Z = Cl) were obtained from measurements only beyond 1 half-life and are the least accurate. Rate constants for **1** (X = Cl, Z = H), **1** (X = NO$_2$, Z = H), and **1** (X = H) were calculated from runs carried out to 2–4 half-lives. Products were usually characterized by their high field ^{1}H NMR spectra. The unsymmetrical disulfide linkage undergoes slow disulfide interchange under a variety of manipulative conditions; owing to mechanical losses on small-scale chromatography and S–S interchange during manipulation, isolated yields of 30–50% are typical of these species, although spectroscopic yields are substantially higher. (In practical preparative work, the species containing unsymmetrical disulfides are carried through the reaction sequence as intermediates, without isolation or purification.)

Trifluoroacetate Salt of Methyl S-(4-Acetoxy-6-dibenzofuranylsulfenyl)-L-cysteinate (1, X = Z = H, R = Me, Y = OMe). A solution of 27.9 mg (42.7 mmol) of **34b** in trifluoroacetic acid was treated as described in the general procedure to give 23 mg of salt, 81%: mp 85–88 °C; field desorption mass spectrum, m/e 555 (M$^+$ – Tfa).

Methyl N-Acetyl-S-(4-hydroxy-6-dibenzofuranylsulfenyl)-L-cysteinate (2, X = Z = H, R = Me, Y = OMe). Salt **1** (X = Z = H, R = Me, Y = OMe) prepared as described above was partitioned between chloroform and aqueous potassium carbonate solution; the organic phases were pooled and evaporated to yield 33 mg of free amine which was dissolved in 0.4 mL of dimethyl sulfoxide. After 20 h the solvent was removed in high vacuum and the residue was purified by preparative layer chromatography (1000 μm, 1:1 chloroform–ethyl acetate) to give the title compound as an oil, 10.1 mg, 30%: ^{1}H NMR (250 MHz, CDCl$_3$) δ 8.53 (1 H, d, J = 8.0 Hz, exchange), 8.06 (1 H, dd, J = 8.0, 1.0 Hz), 7.74 (1 H, dd, J = 8.0, 1.0 Hz), 7.57 (1 H, dd, J = 8.0, 1.0 Hz), 7.43 (1 H, td, J = 8.0, 1.0 Hz), 7.22 (1 H, td, J = 8.0, 1.0 Hz), 7.02 (1 H, dd, J = 8.0, 1.0 Hz), 3.63 (3 H, s), 1.87 (3 H, s); high resolution mass spectrum, calcd for $C_{18}H_{17}O_5NS_2$ 391.0548, found 391.0549.

A substance with identical properties was obtained by reaction of Ac-L-Cys-OMe with the SScm derivative of **3**.

Methyl N-Acetyl-S-(1-chloro-4-hydroxy-6-dibenzofuranylsulfenyl)-L-cysteinate (2, X = Cl, Z = H, R = Me, Y = OMe). Species **35b** was converted to **2** (X = Cl, Z = H, R = Me, Y = OMe) by the general procedure which was purified as described above by preparative layer chromatography: mp 103–106 °C, yield 42%; ^{1}H NMR (250 MHz, CDCl$_3$) δ 10.25 (1 H, exchanges), 8.42 (1 H, dd, J = 7.7, 1.1 Hz), 7.71 (1 H, dd, J = 7.7, 1.1 Hz), 7.38 (1 H, t, J = 8.5 Hz), 7.03 (1 H, d, J = 8.5 Hz), 7.03 (1 H, d, J = 8.5 Hz), 3.83 (3 H, s), 2.30 (3 H, s); high resolution mass spectrum, calcd for $C_{18}H_{16}O_5NS_2Cl$ 425.0158, found 425.0172.

Determination of Effective Molarities. Rate constants for the reactions of species **28–32** with ethyl S-benzyl-L-cysteinate in Me$_2$SO-d_6 at 25 °C were carried out using ^{1}H NMR of appropriate resonances as described above for the intramolecular reactions. Rates were calculated from 3–5 data points obtained during the first 1–2 half-lives of the reaction, using roughly equal concentrations of amine and phenolic ester, in the range of 0.04–0.08 M. Although we did not prove a first power dependence of rate on amine concentration, this dependence has been previously established for aminolysis reactions of phenyl esters in Me$_2$SO solution.[24] Effective molarities were obtained by dividing each of these second-order rate constants into the first-order rate constant for the analogous dibenzofuran derivative lacking 6-thia substitution. The following rate constants were observed (M^{-1} S^{-1}): 4-acetoxyphenoxythiin, 2.1×10^{-5}; **28b**, 2.1×10^{-5}; **29b**, 2.6×10^{-4}; **29c**, 2.0×10^{-4}; **30c**, 7.0×10^{-4}; **31c**, 2.8×10^{-3}; **32c**, 2.8×10^{-2}.

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Demonstration of the Intramolecular Character of the O,N-Acyl Transfer Reaction of 1 → 2. Solutions of 1 (X = H) in dimethyl sulfoxide-d_6 were prepared at concentrations of 0.029 M and 0.21 M. The acetyl hydrogens and the aromatic 3-hydrogen were monitored to obtain rate constants of 0.35 h^{-1} and 0.43 h^{-1}, respectively, establishing that within the error limits of the measurements, the rate constant is concentration-independent.

Estimation of Atomic Distances in the Transition-State Model. The following bond lengths were obtained from diffraction data for LL-cystine:[12] S–S, 2.038; C–S, 1.816; C–C, 1.525; N–C, 1.484. The N–C and C–O bond lengths to the acyl carbon of the transition state were assumed to be 1.49 and 1.43 Å, respectively. Bond angles were obtained from the LL-cystine structure[12] as shown in **13.** A simple recursive distance-calculating program without energy minimization was written and used to obtain the O–S$_2$ distance for **17.** The O–S distance for **3** was calculated from X-ray data for dibenzofuran.[25]

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Phenonium Ion in [3.*n*]Paracyclophanes. Effects of Neighboring Groups, Steric Size of Substituents, and Strain on Solvolysis Reactions

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Received August 27, 1985

The effects of steric hindrance, of strain on the structure of the phenonium ion, and of the neighboring group have been studied in the solvolyses of some [3.*n*]paracyclophanylmethyl tosylates. The reaction path was affected considerably by the steric hindrance of a methyl group attached to the cyclophane skeleton. The effect of strain on the structure of the phenonium ion was clearly demonstrated in the acetolyses of secondary tosylates. A strong anchimeric assistance to the ionization step by the [3.3]paracyclophanyl group was shown. The acetolysis rate constants of [3.*n*]paracyclophanylmethyl tosylates decreased with increasing methylene chain length. The rate enhancement is attributed to the π–π transannular interaction of the two overlapping benzene nuclei.

Studies of the phenonium ion include reports on substituent effects,[1] solvent effects,[2] strain effects,[3] steric hindrance,[4,5] direct observation by NMR spectroscopy,[6] and through-space participation of one benzene nucleus.[7] We have been interested in how the solvolysis (dynamic) path and rate might be influenced by the through-space interaction of two or more benzene nuclei oriented face-to-face, as in the cyclophanes.

The static interactions of the two benzene nuclei of [2.2]paracyclophane and other cyclophanes have been reported in studies of the acidity of cyclophanecarboxylic acid[8] and donor–acceptor complex formation.[9] Sheehan and Cram[9b] showed that [2.2]paracyclophane, which has the shortest spacing between the benzene nuclei and the deformed benzene rings,[10] is less electron donating than [3.3]paracyclophane. Furthermore, UV spectroscopy[9a] indicates that the nature of [*n.n*]paracyclophanes should approach that of the corresponding α,ω-diarylalkanes as *n* increases. Accordingly, [3.3]paracyclophane, which shows the strongest static transannular π–π interaction, should also show strong "π–π through space" effects in solvolysis reactions.

Hedaya and Kyle have studied phenonium ion incorporated in the [2.2]paracyclophane ring system.[11] They

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