Synthesis of 1-Methoxy-9-mercaptophenoxathiin and the Resolved 1-((*N*-(Benzyloxycarbonyl)-L-alanyl)oxy)-9-((methoxycarbonyl)dithio)phenoxathiin 10-Oxide Diastereomers. Comments on Improved Methods for Sulfone Reduction

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The syntheses of 1-methoxy-9-mercaptophenoxathiin (**5**) and the resolved diastereomeric Z-L-alanyl ester sulfoxides **13a** and **13b** are reported. The synthetic strategy employs the 10-sulfone functionality to direct substitution to the 1- and 9-positions by metalation with *n*-BuLi in THF at low temperature followed by hydroxylation with O_2/*n*-BuMgBr and sulfuration with S_8. In the subsequent reduction of sulfone **4**, unsatisfactory yields of thioether **5** were obtained by conventional methods, but remarkable selectivity is demonstrated using DIBAH in refluxing dioxane. Oxidation of the Z-L-alanyl ester **12** to the diastereomeric sulfoxides **13a** and **13b** with MCPBA is made selective for the 10-sulfur by (methoxycarbonyl)sulfenyl (Scm) protection of the 9-mercapto group. Complete separation of the diastereomers is obtained by preparative HPLC.

Introduction

Previous reports have described the basic features of the thiol capture strategy for amide formation between preformed medium-sized peptides bearing N-terminal cysteine residues.[1] A central feature of this strategy is the availability of a difunctionalized template molecule across which efficient intramolecular *O,N*-acyl transfer can occur. The principles of template design have been reported, along with the finding that for a series of rigid *o,o'*-bridged diphenyl ether derivatives, a 4,6-substituted dibenzofuran is structurally the most efficient, with an effective molarity for intramolecular acyl transfer of 5–10 M.[2] Molecular mechanics calculations[2] for the dibenzofuran case suggest that the acyl-transfer transition state for this reaction is in fact sterically strained, largely owing to van der Waals repulsion between the Cys α-CH and the aromatic template, as noted in Figure 1. The possibility therefore exists that other, more efficient template molecules can be developed with similar configurations to the bridged dibenzofuran but lacking its destabilizing features.

An attractive target series is the difunctionalized phenoxathiin structure **5**, which coincidentally shows parameters of fit similar to those of dibenzofuran, as noted in Table I, but whose puckered conformation allows less crowding of the transition state, which would increase the efficiency of acyl transfer. The change in size of the ring sulfur with oxidation to the sulfoxide offers the possibility of a refined tuning of template dimensions, and the presence of sulfoxide chirality in the template region may permit enantioselective acyl transfer with L-cysteine. The results of kinetic studies of intramolecular acyl transfer with these systems will be reported subsequently. In this paper we report the synthesis of **5**, a suitably functionalized precursor of the desired phenoxathiin template, as well as the separated diastereomeric sulfoxides **13a** and **13b**.

Important discoveries concerning the selective reduction of sulfones have been uncovered by the successful synthesis of **5**, which may find application in other contexts.

Results and Discussion

It is well-established that sulfur and oxygen heterocycles can undergo metalation and subsequent substitution ortho to the ring heteroatom. In the case of phenoxathiin, Gilman demonstrated that metalation occurs selectively ortho to the ring oxygen.[3] This observation was previously employed by us in the synthesis of 4-hydroxy-6-mercaptophenoxathiin[4] where the hydroxyl and mercapto substituents were introduced in a two-step synthesis by addition of first O_2/*n*-BuMgBr and then S_8 to the (aryllithio)phenoxathiin substrate.

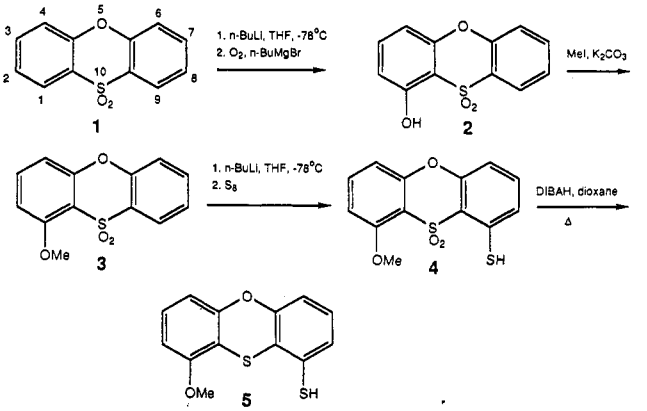
Gilman also demonstrated that in contrast to phenoxathiin, phenoxathiin 10,10-dioxide (**1**) selectively undergoes metalation ortho to the sulfone to produce 1- and 9-substituted derivatives.[5] We now report the application of these observations along with an efficient method for

Table I. Interatomic Parameters for Template Fit

	4-methoxy-6-mercaptodibenzofuran[a]	**5**[b]
$O–S_2$	5.44 Å	5.44 Å
$C_2–C_1$	4.82 Å	5.08 Å
$<O–C_1–C_2$	104°	96°
$<S_2–C_2–C_1$	98°	96°

[a] From crystal data.[2] [b] From crystal data of phenoxathiin[20] and the following assumed bond lengths: $C_2–S$ = 1.78 Å, $C_1–O$ = 1.37 Å.

Scheme I



(1) Kemp, D. S. *Biopolymers* **1981**, *20*, 1793. Galakatos, N. G. *J. Org. Chem.* **1986**, *51*, 1821.
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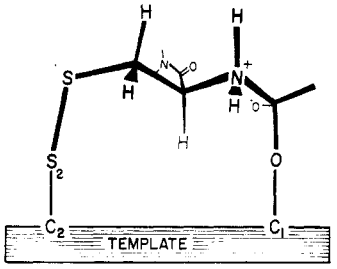


Figure 1. Molecular geometry used to model the transition state for intramolecular acyl transfer from a pheonolic oxygen (C_1–O) to a cysteine amine. The distances O–S_2 and C_1–C_2 are defined by the geometry of a molecular template that is complementary to a stable conformation of the transition state. Significant van der Waals interactions arise between the Cys α-CH and the atoms (not shown) of the template.

the selective reduction of the sulfone to thioether for the synthesis of a new template for acyl-transfer studies, 1-methoxy-9-mercaptophenoxathiin (**5**), as shown in Scheme I.

In the previously reported synthesis of 4-hydroxy-6-mercaptophenoxathiin,[4] confirmation of substitution pattern was established by ^{1}H NMR analysis of deuterio-substituted derivatives. In the present case, the deshielding effect exerted on the 1- and 9-protons in the sulfone derivatives makes characterization of substitution position by ^{1}H NMR spectroscopy more straightforward, since disappearance of the distinct doublets at ca. δ 8.0 indicates whether successful substitutions have occurred.

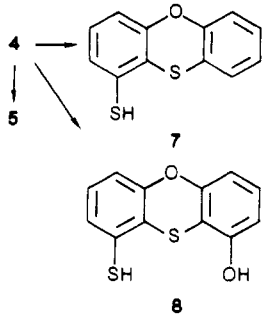
The starting material phenoxathiin 10,10-dioxide (**1**) is obtained in two steps via literature procedures. The reaction of diphenyl ether with elemental sulfur in the presence of $AlCl_3$ affords phenoxathiin in 78% yield,[6] and oxidation with H_2O_2/HOAc generates the sulfone **1** in 95% yield.[7]

The phenol **2** is obtained in 49% yield via the general oxygenation procedure of Gilman[8] when **1** is metalated with *n*-BuLi in THF at −78 °C followed by hydroxylation with O_2/*n*-BuMgBr. During the optimization of experimental conditions for this reaction sequence, several small-scale detonations of the reactive peroxide intermediate occurred. These are avoided when one full equivalent of the Grignard is first added to the aryllithium substrate followed by a carefully monitored, slow bubbling of nitrogen-diluted oxygen into the reaction mixture (see the Experimental Section).

Methylation of the phenol **2** generates the methyl ether **3** in 92% yield. Introduction of the thiol based on the general sulfuration procedure of Janczewski[9] proceeds by metalation of **3** with *n*-BuLi in THF at −78 °C followed by addition of elemental sulfur to generate the thiol **4** in 73% yield. In the presence of excess S_8 symmetrical disulfides are fomed as byproducts, but inclusion of a gentle reduction step ($LiAlH_4$, room temperature, 10 min) before workup assures good yields of the desired thiol.

The final step to the target requires reduction of the unreactive sulfone function to the thioether **5**. As outlined below, standard methods for sulfone reduction proved inefficient at best for this transformation. Strikingly, a selective and efficient reduction system for our substrate was discovered when the solvent dioxane was used with

Table II. Reaction Products from DIBAH[a]

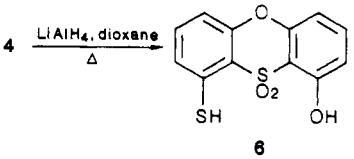


solvent	molar excess DIBAH	product distribution, % 7	8	5
toluene[b]	9:1	18	23	12
mesitylene[c]	3.5:1	27		9
mesitylene[d]	9:1	32	5	12

[a] General procedure: DIBAH in reaction solvent was added to substrate at 0.1 M. After reflux for the indicated time, the mixture was quenched with 0.5 N HCl, the organic phase was separated and dried, and the residue was subjected to Chromatotron silica chromatography. Workup was started when TLC indicated complete consumption of starting material. [b] t = 2 h. [c] t = 4 h. [d] t = 0.5 h.

DIBAH under nonstandard conditions.

The most widely used reagents for sulfone reduction[10] are $LiAlH_4$[11] and DIBAH.[12] Bordwell and McKellin showed that a series of alkyl and aryl sulfones could be reduced to the corresponding thioethers with $LiAlH_4$ at reflux in diethyl or ethyl *tert*-butyl ether.[11] For example, dibenzothiophene sulfone, the closest structural analogue to phenoxathiin sulfone that was included in their study, was reduced in 74% yield. However, none of these examples included methoxy or mercapto functions, which could prove sensitive to reaction conditions. Disappointingly under similar conditions in our hands the 1-methoxy-9-mercaptophenoxathiin sulfone **4** gave only the ether cleavage product **6**.



Alternatively, Gardner described the use of DIBAH in refluxing toluene for the efficient reduction of a series of dialkyl and diphenyl sulfones.[12] In our case the reaction of **4** with DIBAH at the reflux temperature of both toluene and mesitylene gave multiple products in poor overall yields with unsatisfactory reproducibility. For purposes of comparison a series of runs were subjected to the same workup procedures, and Table II lists the isolated products and yields from these reactions. Interestingly, a major product observed in each case was the thiol **7** which represents C–O bond cleavage at the aryl carbon bond, a cleavage pattern for which no literature precedent was found. The identity of **7** was confirmed by methylation and characterization by ^{1}H NMR and mass spectrometry of the purified methyl thioether. As indicated in Table II, under these conditions the desired thioethers were in-

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(11) Bordwell, F. G.; McKellin, W. H. *J. Am. Chem. Soc.* **1951**, *73*, 2251.
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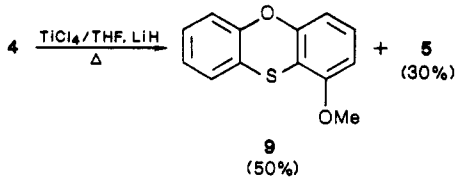
cluded among the products; however, the low overall yields, wide distribution of products, and poor reproducibility made this method inefficient.

In search for an improved method it was further found that the interesting method of Dzhemilev[13] for the reduction of simple dialkyl and alkyl aryl sulfones to thioethers showed limited use. The reducing agent is a low-valent titanium complex, which is generated by the addition of a $TiCl_4$/THF complex to 4 equiv of LiH in THF. No reaction was observed with **4** at 25 °C, but both reduction and cleavage reactions occurred at the temperature of reflux. Product distribution was clearly altered by varying stoichiometry, but satisfactory reproducibility was difficult to achieve, given the reactive nature of the reagents employed, which created uncertainty in determining the exact molar ratios of each experiment. Under the best conditions of approximately a 6:1 molar ratio of titanium to **4**, a 30% yield of the desired sulfide **5** was accompanied by a 50% yield of **9**, which resulted from C–S cleavage at the 9-mercapto substituent. Literature examples were



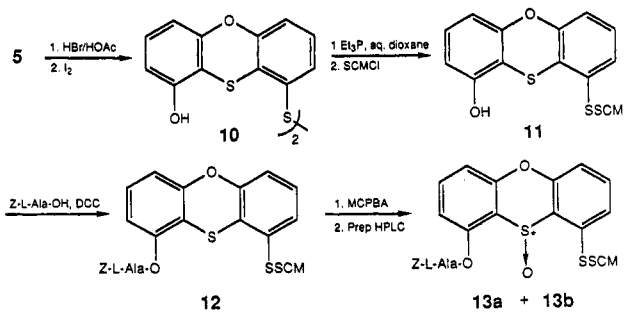
found for analogous but mechanistically more facile examples of C–S cleavage by low-valent titanium in the transformation of thioketals to hydrocarbons.[14]

In addition to the above methods, other examples of reduction of sulfones to thioethers include Zn/HCl/HOAc,[15] molten S_8,[16] and S_8 in KOH(aq).[17] In trial attempts with these reagents no reaction was observed, and starting material was reisolated in each case.

After the preceding studies were completed an efficient alternative for sulfone reduction was discovered in a reexamination of the DIBAH system. Although ethereal solvents are generally not used at elevated temperatures because of possible ether cleavage,[18] DIBAH in refluxing dioxane constitutes a uniquely effective combination for our system. Thus, under optimized reaction conditions of a 9:1 ratio of DIBAH to sulfone **4** in dioxane at reflux for 22 h, a 78% yield of crystalline product **5** is obtained. This method was found to be convenient, highly reproducible, and was used to generate gram quantities of the desired sulfide. If competing ether cleavage of solvent occurred, this side product did not complicate effective workup of the reaction mixture. After the fact one can rationalize that the ethereal solvent provides a medium that disfavors unusually reactive forms of DIBAH which could otherwise effect C–O cleavage, as was observed when the nonethereal solvents toluene and mesitylene were used. Nonetheless, the chelated form of DIBAH which must exist in dioxane is sufficiently active to effect the desired sulfone reduction.

With these optimized methods for sulfone reduction, the five-step transformation from unsubstituted phenoxathiin

Scheme II



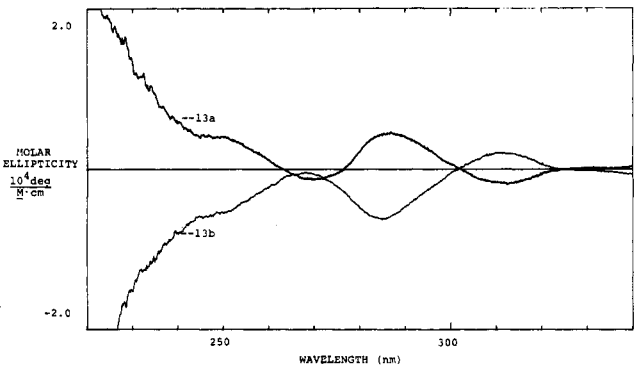


Figure 2. Circular dichroism spectra of **13a** and **13b** at 9.5×10^{-5} M in MeCN at 25 °C.

to the desired difunctionalized derivative **5** was achieved in 24% overall yield, including the low yield (49%) seen for introduction of the hydroxyl early in the synthesis. Although further work is required to establish the generality of this method, the interesting dependence on solvent for effective sulfone reduction discovered in this study may allow this often intractible functional group to be employed more routinely.

With an efficient synthesis of the desired template in hand, we next focused on the introduction of chirality at the ring sulfur by oxidation to the sulfoxide and separation of the enantiomeric sulfoxides as outlined in Scheme II. Cleavage of the methyl ether **5** to the phenol with HBr in acetic acid is followed by in situ oxidation with iodine in methanol to form in an overall 89% yield the symmetrical disulfide **10**, which is more easily purified than the free thiol. Reduction of the disulfide with 1 equiv of Et_3P is followed without purification of the thiol by reaction with (methoxycarbonyl)sulfenyl chloride (Scm-Cl)[19] to afford the sulfur-protected phenol **11** in 75% yield, and DCC coupling of Z-L-alanine with **11** affords the ester **12** in 89% yield. MCPBA oxidation of **12** occurs quantitatively (HPLC) and is selective for the ring sulfur with Scm protection of the 9-mercapto group. The diastereomeric sulfoxides **13a** and **13b** were successfully separated by preparative HPLC (retention times = 9.70 min vs 11.72 min with 70% MeOH, 30% 0.1% TFA eluent).

The Z-L-alanyl esters were exactly the desired materials for kinetic studies of *O,N*-acyl transfer, and we have therefore not studied further derivatives. However, circular dichroism spectra of the diastereomeric pair recorded in a spectral region where no absorbance was attributed to the chiral Z-L-alanine portion of the ester exhibited reciprocal traces (λ_{max} at 286 and 312 nm, Figure 2), consistent with HPLC and NMR data which confirm complete

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separation of pure diastereomers in two successive chromatographic separations.

Experimental Section

Melting points were determined on a Thomas-Hoover unimelt apparatus. High-resolution ^1H NMR spectra were obtained on either a Bruker WM-250 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 electron impact mass spectra were recorded on a Varian Mat 8200 spectrometer. Circular dichroism spectra were obtained from a JASCO J-500 C spectrophotometer using Version 1.21 I-500/XT software (Japan Spectroscopic Co., Ltd., Tokyo, Japan) and a step resolution of 0.2 nm. Microanalyses were performed by Multichem Laborabories, Lowell, MA.

Preparative silica chromatography was performed on a Harrison Research Model 7924T Chromatotron using 2-mm plates with silica gel 60 PF_{254} from EM Science. Analytical TLC was performed on aluminum-backed 0.2-mm silica gel 60 F_{254} plates. Analytical HPLC was performed on a Waters Associates system consisting of two Model 6000-A pumps, a Model 660 automated gradient controller, a Model U6-K injector, a Model 440 dual-channel UV detector (280, 254 nm), a Model 730 data module, and a VYDAC 218TP54 C_{18} reverse-phase column. Preparative HPLC was performed on a system including a Waters Associates Model 590 pump fitted with preparative heads, a Rheodyne injector, a prepump solvent mixer, a Waters Model 490 variable-wavelength detector, and a VYDAC 218TP1022 reverse-phase, C_{18} column. Sep Pac C_{18} cartridges for rapid sample separation were from Waters Associates.

THF and dioxane were distilled from sodium benzophenone ketyl. Petroleum ether was 30–60 °C boiling range. CH_3CN, toluene, mesitylene, and dichloromethane were stored at least 24 h over activated 4-Å sieves. *n*-BuLi was obtained as hexane solutions from Alfa. Solutions of DIBAH were made directly from neat DIBAH (obtained from Aldrich in Sure Seal cannisters) and the reaction solvent. $LiAlH_4$ was used as Et_2O or diglyme solutions obtained from Aldrich. Et_3P was obtained from Aldrich and used without further purification. Nitrogen and oxygen were passed through a $CaSO_4$ drying tower before use. For the metalation reactions glassware was oven-dried overnight, assembled hot, and cooled under a nitrogen atmosphere.

1-Hydroxyphenoxathiin 10,10-Dioxide (2). Caution: in optimizing reaction conditions several small-scale detonations occurred. Observing two practices were found to be crucial in avoiding explosive decomposition of the reactive peroxide: (1) the entire amount of Grignard is added before bubbling of O_2 is commenced, and (2) initial O_2 bubbling is maintained at a rate no greater than 2 bubbles/s.

The reaction vessel was a 1-L, three-necked round-bottom flask equipped with a magnetic stirring bar, equilibrated dropping funnel, septum, and stopcock adapter fitted to positive N_2 pressure. Phenoxathiin 10,10-dioxide (1)[7] (18.5 g, 79.7 mmol) was dissolved in 460 mL of THF and chilled in a dry ice/acetone bath (−78 °C). A solution of 3.1 M *n*-BuLi in hexane (23 mL, 71 mmol) was transferred via cannula to the equilibrated dropping funnel and added dropwise to the reaction mixture over 20 min. The deep red solution was stirred at −78 °C for 1.5 h, and then 55 mL (88 mmol) of a 1.6 M solution of *n*-BuMgBr in Et_2O was added dropwise under N_2 over 20 min to the reaction mixture at −78 °C. The dropping funnel was replaced with a glass stopper, the adapter was connected to the exit bubbler, and the septum was pierced with two wide-gauge syringe needles, which were attached to sources of N_2 and O_2. The N_2 flow rate was adjusted to 3 bubbles/s at the exit bubbler; then the O_2 influx rate (monitored by a separate bubbler between the O_2 tank and reaction vessel) was adjusted to no greater than 2 bubbles/s, and the O_2 needle tip was lowered and bubbled below the surface of the stirring reaction mixture. No more dry ice was added to the cold bath; after 2.5 h the cold bath was removed, and O_2 bubbling was continued an additional 2 h. O_2 bubbling was stopped, and N_2 was bubbled through the reaction mixture for 5 min before workup.

The reaction was carefully quenched with 12 mL of H_2O, causing precipitation of a white solid. Acidification with 30 mL of concentrated HCl yielded a clear, faint yellow solution. The volume of the reaction mixture was reduced on rotary evaporator by ca. 250 mL, EtOAc was added (100 mL), and the organic phase was washed with H_2O (3 × 125 mL) and brine. The organic phase was extracted with $LiOH_2$(aq) (2 × 100 mL of 1 N, 3 × 125 mL of 0.7 N), giving a deep green aqueous phase. Acidification with ca. 60 mL of concentrated HCl yielded a white precipitate, which was extracted with EtOAc (1 × 200 mL, 2 × 100 mL). The organic layer was washed with H_2O and brine and dried ($MgSo_4$). The volume was reduced, causing the product to crystallize as a white solid. The solid was filtered, and dilution of the filtrate with petroleum ether (30–60 °C) gave additional product. The total crude yield of **2** was 9.56 g, 49%, mp 170–175 °C, which was used directly in the next step. Crystallization from 5:1 AcOH–H_2O gave a pure sample: mp 183–184 °C; TLC R_f = 0.61 (1:1 EtOAc–petroleum ether, 1% HOAc); ^1H NMR (250 MHz, $CDCl_3$) δ 8.00 (1 H, d, J = 8 Hz, C-9 H), 7.67 (1 H, t, J = 8 Hz, C-7 H), 7.49 (1 H, t, J = 8 Hz), 7.42 (1 H, t, J = 8 Hz, C-8 H), 7.40 (1 H, *d*, J = 8 Hz), 6.95 (1 H, d, J = 8 Hz, C-4 H), 6.89 (1 H, d, J = 8 Hz, C-2 H); mass spectrum (70 eV), m/e (rel intensity) 248 (M^+, 61), 203 (16), 197 (11), 184 (21), 86 (62), 84 (100).

1-Methoxyphenoxathiin 10,10-Dioxide (3). 1-Hydroxyphenoxathiin 10,10-dioxide (**2**) (11.8 g, 47.5 mmol) was dissolved in 80 mL of acetone along with 30 mL (475 mmol) of MeI and 12.5 g (95 mmol) of K_2CO_3. The mixture was heated at reflux under N_2 for 14 h. Solvents were evaporated, and the residue was redissolved in 200 mL of CH_2Cl_2 and 200 mL of H_2O. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (1 × 50 mL). The combined organic fractions were washed with 0.5 N LiOH (2×), H_2O (2×), and brine (1×) and dried ($MgSO_4$). Solvent was evaporated until a white solid appeared. The mixture was reheated to afford a clear solution, and colorless prisms of **4** formed upon cooling. Collection of crystals and subsequent precipitation of additional product from the filtrate by addition of petroleum ether gave 11.5 g (92%): mp 167–168 °C; TLC R_f = 0.50 (1:1 EtOAc–petroleum ether); ^1H NMR (250 MHz, $CDCl_3$) δ 8.06 (1 H, d, J = 8 Hz), 7.61 (1 H, t, J = 8 Hz), 7.53 (1 H, t, J = 8 Hz), 7.37 (1 H, t, J = 8 Hz), 7.31 (1 H, d, J = 8 Hz), 6.94 (1 H, d, J = 8 Hz), 6.83 (1 H, t, J = 8 Hz), 4.07 (3 H, s, OMe); mass spectrum (70 eV), m/e (rel intensity) 262 (M^+, 99.5), 245 (100), 228 (60.4), 96 (32.4).

1-Methoxy-9-mercaptophenoxathiin 10,10-Dioxide (4). The reaction vessel was a three-necked, 1000-mL round-bottom flask equipped with an overhead stirrer, equilibrated dropping funnel, and adapter fitted to positive N_2 pressure. The vessel was charged with 500 mL of THF and 11.3 g (43.1 mmol) of 1-methoxyphenoxathiin 10,10-dioxide, which was dissolved with vigorous stirring. The equilibrated dropping funnel was charged with 20 mL (50 mmol) of a 2.5 M solution of *n*-BuLi in hexane via cannula under N_2. The reaction mixture was chilled on a dry ice/acetone bath (−78 °C), and the *n*-BuLi solution was added dropwise over 15 min, giving a chocolate-brown solution, which was stirred at −78 °C for 1 h. To the cold reaction mixture was added in one portion 2.77 g (86.3 mmol) of finely divided S_8. Vigorous stirring was continued, the mixture paled from brown to orange within one minute, and a finely divided, white precipitate appeared. The mixture was stirred for 1 h, the cold bath was removed, and the mixture was stirred an additional 1.75 h. To the heterogeneous mixture being stirred at 25 °C was added 10 mL (10 mmol) of a 1 M solution of $LiAlH_4$ in Et_2O. Gentle warming for 1–2 min on the steam bath yielded a clear brown solution, which was cooled to room temperature and diluted with 300 mL of CH_2Cl_2, and then 200 mL of 1 N HCl was carefully added. The organic phase was separated, 200 mL of H_2O was added to the aqueous phase, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL of CH_2Cl_2). The combined organic phases were washed with 0.1 N HCl (2×), H_2O (2×), and brine and dried ($MgSO_4$). The volume was reduced on rotary evaporator until appearance of a solid; the product was then allowed to crystallize overnight. A first crop gave 8.00 g (63%) of **4**: mp 246–248 °C; TLC R_f = 0.88 (1:1 EtOAc–petroleum ether, 1% HOAc). A second crop from the filtrate yielded an additional 1.20 g (9.5%): mp 236–245 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 7.50 (1 H, t, J = 8 Hz), 7.43 (1 H, t, J = 8 Hz), 7.22 (1 H, d, J = 8 Hz), 7.17 (1 H, d, J = 8 Hz), 6.91 (1 H, d, J = 8 Hz), 6.88 (1 H, d, J = 8 Hz), 4.08 (3 H, OMe); mass spectrum (70 eV), m/e (rel intensity) 249 (M^+, 100), 246 (13.5),

229 (12.5), 218 (20), 212 (39), 171 (14).

1-Methoxy-9-mercaptophenoxathiin (5). 1-Methoxy-9-mercaptophenoxathiin 10,10-dioxide (2.50 g, 8.49 mmol) was suspended in 130 mL of dioxane. To the stirring reaction mixture under N_2 was added via cannula a solution of 13.6 mL (76.4 mmol) of DIBAH in 30 mL of dioxane. As the hydride was added gas was evolved, and any undissolved sulfone went into solution. The mixture was heated to reflux (bath temperature = 120 °C) for 22 h. The reaction mixture was cooled and diluted with Et_2O (100 mL), cautiously with 2 N HCl (100 mL), and finally with EtOAc (100 mL). Gentle warming of the mixture yielded two clear phases. The organic layer was washed with 0.5 N HCl (2×), H_2O (1×), and brine (1×) and then dried ($MgSO_4$). Evaporation of the solvents left a yellow solid, which was recrystallized from MeOH, diluted with ca. 10% (v/v) H_2O. Yellow needles of **5** were collected: 1.74 g (78%); mp 155–156.5 °C; TLC R_f = 0.44 (1:4 EtOAc–petroleum ether); ^1H NMR (250 MHz, $CDCl_3$) δ 7.06 (1 H, t, J = 8 Hz), 7.04 (1 H, d, J = 6 Hz), 6.95 (1 H, t, J = 8 Hz), 6.77 (1 H, dd, J = 8 Hz, 1 Hz), 6.60 (1 H, dd, J = 5 Hz, 1 Hz), 6.57 (1 H, dd, J = 5 Hz, 1 Hz), 3.89 (3 H, s, OMe), 3.65 (1 H, s, SH). Anal. Calcd for $C_{13}H_{10}O_2S_2 \cdot {}^1/_8H_2O$: C, 59.01; H, 3.90; S, 24.23. Found: C, 58.90; H, 3.96; S, 23.62.

1-Hydroxy-9-phenoxathiin Disulfide (10). 1-Methoxy-9-mercaptophenoxathiin (**9**) (1.30 g, 4.96 mmol) was dissolved in 90 mL of HOAc to which 16 mL of 48% HBr(aq) was added. The heterogeneous mixture was heated to reflux (bath temperature = 125 °C) causing dissolution of all solid, and heating was continued for 22 h. The reaction mixture was reduced in volume by ca. 50% on rotary evaporator; the yellow solution was then diluted with EtOAc (100 mL) and Et_2O (50 mL). The organic layer was washed with H_2O (2 × 100 mL), and the combined aqueous fractions were back-extracted with EtOAc (2 × 50 mL). The combined organic fractions were washed with H_2O (1×) and brine (1×) and dried with ($MgSO_4$).

The solvents were evaporated, and the yellow residue was dissolved in 30 mL of MeOH. To the solution was added dropwise a solution of I_2 (ca. 5 mL of a 0.5 M solution in CH_2Cl_2) until the characteristic violet I_2 color persisted, indicating complete oxidation of available thiol. The solvents were evaporated; the yellow residue was redissolved in Et_2O, washed with 5% aqueous ascorbic acid (2×), H_2O (1×), and brine (1×), and dried ($MgSO_4$). The solvents were evaporated, and the yellow solid was recrystallized from MeOH/H_2O and washed with ice-cold MeOH to afford a microcrystalline, yellow solid, which was dried under vacuum, yielding 1.02 g (83%) of **10**: mp 215–217 °C; TLC R_f = 0.61 (1:1 EtOAc–petroleum ether); ^1H NMR (250 MHz, $CDCl_3$) δ 5.33 (1 H, s, ArOH), 6.61 (2 H, d, J = 8.1 Hz), 6.92–7.08 (m, 3 H), 7.22 (1 H, d, J = 8.0 Hz); mass spectrum (70 eV) (rel intensity) m/e 494 (M^+, 2.6), 493 (7.6), 274.5 (10), 246.5 (8.5), 218.6 (8.6), 186.7 (8.2), 43.7 (100).

1-Hydroxy-9-((methoxycarbonyl)dithio)phenoxathiin (11). The disulfide **10** (209 mg, 0.423 mmol) was dissolved in 8 mL of dioxane with gentle warming; 2 mL of H_2O was added, and the solution was cooled to 25 °C. To the solution was added in one portion Et_3P (66 μL, 0.44 mmol) in 2 mL of dioxane. After 10 min the solvents were evaporated, and the residue was redissolved directly in 8 mL of 1:1 MeOH–CH_2Cl_2 to which was added a solution of ScmCl[19] (81 μL, 0.89 mmol) in 3 mL of the same solvent. After 5 min the solvents were evaporated, and the residue was subjected to flash chromatography (eluent = 2:1 petroleum ether (bp 30–60 °C) –EtOAc), yielding 475 mg (75%) of **11** as a yellow solid: mp 147–156 °C; TLC R_f = 0.22 (1:4 EtOAc–petroleum ether); ^1H NMR (250 MHz, $CDCl_3$) δ 7.42 (1 H, d, J = 7.9 Hz), 6.97–7.15 (5 H, m), 5.27 (1 H, s, ArOH), 3.89 (3 H, s, OMe); mass spectrum (70 eV) (rel intensity) m/e 338 (M^+, 6.9), 279 (4.8), 248 (3.3), 247 (3.2), 219 (5.9), 215 (5.6), 187 (4.8), 6.91 (11.5), 57.2 (25), 43.8 (100).

1-((*N*-(Benzyloxycarbonyl)-L-alanyl)oxy)-9-((methoxycarbonyl)dithio)phenoxathiin (12). The phenol **11** (185 mg, 0.55 mmol) was dissolved in 1 mL of EtOAc with gentle warming and then diluted 10 mL of CH_2Cl_2. After the mixture was cooled to 25 °C, Z-L-alanine (197 mg, 0.88 mmol) was added as a solution in 3 mL of CH_2Cl_2. A nitrogen atmosphere was maintained, and the mixture was chilled to 0 °C. A solution of dicyclohexylcarbodiimide (153 mg, 0.74 mmol in 3 mL of CH_2Cl_2) was added, and the mixure was stirred at 0 °C for 2 h and then 12 h at 25 °C. The dicyclohexylurea that precipitated was removed by filtration, and the organic phase was washed with 5% $NaHCO_3$ (3×), H_2O, brine and dried ($MgSO_4$). Solvents were evaporated, the residue was resuspended in 4 mL of CH_2Cl_2, and the insoluble DCU was filtered and washed with 1 mL of CH_2Cl_2. The filtrate was diluted with petroleum ether, and **12** formed as a yellow solid, yielding 272 mg (89%): petroleum ether, and **12** formed as a yellow solid, yielding 272 mg (89%): mp 155–156 °C; TLC R_f = 0.24 (1:4 EtOAc–petroleum ether); ^1H NMR (250 MHz, $CDCl_3$) δ 7.44 (1 H, dd, J = 7.8, 2.6 Hz), 7.35 (5 H, m, Z-Ar), 7.09 (3 H, m, J = 8.1 Hz), 6.96 (2 H, dd, J = 8.4, 2.5 Hz), 6.88 (2 H, d, J = 8.31 Hz), 5.43 (1 H, d, J = 3.4 Hz, N-H), 5.23 (2 H, broad s, Z-CH_2), 4.74 (1 H, m, α-CH), 3.87 (3 H, s, OMe), 1.73 (3 H, d, J = 6.2 Hz, Ala-Me). Anal. Calcd for $C_{25}H_{21}NO_7S_3$: C, 55.24; H, 3.89; N, 2.58; S, 17.69. Found: C, 55.06; H, 4.02; N, 2.58; S, 17.20.

1-((*N*-(Benzyloxycarbonyl)-L-alanyl)oxy)-9-((methoxycarbonyl)dithio)phenoxathiin 10-Oxide (13a and 13b). To a solution of **12** (84.5 mg, 0.155 mmol) in 3 mL of dry CH_2Cl_2 at 0 °C was added a solution of MCPBA in dry CH_2Cl_2 at 0 °C (1.6 mL, max = 0.18 mmol. Note: the apparent small molar excesses of the the MCPBA solution required for complete oxidation of starting material was attributed to partial decomposition of the solid MCPBA used in making the solutions. The impurity of the MCPBA appeared to pose no problems in the reaction). Within 2 min the faint yellow color characteristic of the starting material in solution faded to colorless. Analytical HPLC at 3 min (70% MeOH, 30% 0.1% TFA) indicated clean formation of the diastereomer pair (retention times = 6.67 and 7.45 min). The solvents were evaporated, and the residue was redissolved in methanol and filtered through a Sep Pac prewetted with methanol. The residue was dried, redissolved in CH_2Cl_2, and washed with ice-cold 5% $NaHCO_3$ (3×) and brine (1×), and solvents were evaporated. The residue was brought up in ca. 200 μL MeOH, and one drop of 0.1 N HCl was added to inhibit basic cleavage of the active ester. The solution was subjected to preparative HPLC (65% MeOH, 35% 0.1% TFA) with 7 × 40 μL injections.

The faster moving diastereomer **13a** was collected (27.5 mg, 32%) free of contamination of the slower isomer, while the pooled fractions of **13b** (34.2 mg, 39%) retained 7% (analytical HPLC) of **13a**. The impure **13b** sample was resubjected to preparative HPLC, yielding a 72% recovery of pure **13b** (total combined yield for the pure diastereomers = 60%).

Diastereomer 1 (13a): HPLC t_R = 6.42 min (65% MeOH, 35% 0.1% TFA in H_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (1 H, dd, J = 7.5, 2.7 Hz), 7.62 (m, 2 H), 7.48 (1 H, dd, J = 8.2, 1.8 Hz), 7.38 (6 H, m), 7.24 (1 H, d, J = 8.4 Hz), 5.63 (1 H, d, J = 7 Hz, NH), 5.17 (2 H, d, J = 9 Hz, Z-CH_2), 4.86 (1 H, m, α-CH), 3.85 (3 H, s, OMe), 1.84 (3 H, d, J = 7.3 Hz, Ala-Me); molar ellipticity (see Figure 2 for complete molar ellipticity data) −2.0 × 10^3 deg M^{-1} cm^{-1} (312 nm).

Diastereomer 2 (13b): HPLC: t_R = 7.30 min (65% MeOH, 35% 0.1% TFA in H_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (1 H, dd, J = 7.5, 2.6 Hz), 7.62 (2 H, m), 7.49 (1 H, dd, J = 8.30, 1.9 Hz), 7.38 (6 H, m), 7.20 (2 H, d, J = 7.8 Hz), 5.57 (1 H, d, J = 7 Hz, N-H), 5.18 (2 H, d, J = 3.7 Hz, Z-CH_2), 4.82 (1 H, m, α-CH), 3.87 (3 H, s, OMe), 1.78 (3 H, d, J = 6.6 Hz, Ala-Me); molar ellipticity (see Figure 2 for complete molar ellipticity data) 2.1 × 10^3 deg M^{-1} cm^{-1} (312 nm).

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