Novel 1,2-Dithiins: Synthesis, Molecular Modeling Studies, and Antifungal Activity

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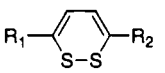
The first structure–activity study involving the 1,2-dithiin class of compounds (1,2-dithiacyclohexadienes) is herein reported. A series of 3,6-disubstituted 1,2-dithiins was synthesized from dithiins **1d** and **1e** and evaluated as antifungal agents. A new and versatile synthesis of dithiins **1d** and **1e** is reported which is amenable to scale-up at the kilogram level. The novelty of the process derives from the use of β-mercaptopropionitrile as the thiophile, relying on a β-elimination strategy and subsequent oxidation to create the 1,2-dithiin ring. Optimal geometries of dithiins **1d**, **18i**, and **45** and model dithiin **61** were determined by molecular mechanics and Hartree–Fock molecular orbital calculations. Two possible mechanisms of action are presented for the 1,2-dithiin class of compounds to explain their observed antifungal activities against *Candida albicans*, *Cryptococcus neoformans*, and *Aspergillus fumigatus*.

Introduction

1,2-Dithiins (1,2-dithiacyclohexadienes) are six-membered heterocycles characterized by a disulfide linkage in the place of two contiguous CH groups of benzene. Photosensitive and deeply colored, 1,2-dithiins have long been the subject of intense theoretical interest primarily due to their 8π electron antiaromatic[1-4] ring system. Naturally occurring 1,2-dithiins (thiarubrines) were first identified in the mid-1960s[5,6] in plants of the family Compositae (Asteraceae).[7,8] They have been used by indigenous peoples of Africa[8-10] to treat skin infections, intestinal parasites, and abdominal pains and by native North Americans[11] to treat infections from sores or wounds and as a snakebite remedy.[12]

All of the naturally occurring 1,2-dithiins discovered thus far[13-22] contain acetylene or polyacetylene side chains in the C-3 and C-6 positions. Isolation of the thiarubrines has been complicated by the fact that they are easily degraded by light and to a lesser extent by heat whereupon they extrude sulfur to form the corresponding thiophenes.[22] Among these, thiarubrine A, **1a**, (Figure 1), and thiarubrine B, **1b**, were shown to exhibit potent antifungal,[21,23] antibacterial,[21,23,24] antiviral,[25,26] antitumor,[22],and nematocidal activity[22] in both the light and the dark. In addition, thiarubrines A and B have shown good light-mediated activity against human immunodeficiency virus (HIV-1).[27] Although the thiarubrines are known as a class of natural products for 30 years, the first total syntheses of naturally occurring 1,2-dithiins were only recently achieved.[28,29]

Despite broad ethnomedical use of plants containing thairubrines, naturally occurring thiarubrine A, isolated from the roots of *Ambrosia chamissonis* (Asteraceae) collected in Marin County, CA, was found to be highly toxic, with an LD_{50} intraperitoneal dose of 0.6 mg/kg in a systemic toxicological study involving ICR mice.[30] Thiarubrine A was also shown to exhibit pronounced topical toxicity in a dermal irritation test.[30] In vitro, thiarubrine A was extremely potent against *Candida albicans* with an MIC of 0.15 μg/mL.[30] It was postulated that the novel 1,2-dithiin ring system was the pharmacophoric element responsible for the activity of the thiarubrines, thus suggesting that analogues without the polyacetylene moieties might still display pronounced antifungal activity.



1 a R_1= CH_2=CHC≡C–C≡C–, R_2 = CH_3C≡C– Thiarubrine A
b R_1= CH_2=CHC≡C–, R_2 = CH_3C≡C–C≡C– Thiarubrine B
c $R_1 = R_2$ =H
d $R_1 = R_2 = CH_2OH$
e $R_1 = CH_2OH$, $R_2 = CH_2OSitBuMe_2$

Figure 1. Structures of thiarubrine A, thiarubrine B, and representative 1,2-dithiins.

We report a new and versatile methodology for synthesizing dithiins **1d** and **1e** which is amenable to scale-up at the kilogram level. The novelty of the process derives from the use of β-mercaptopropionitrile as the thiophile, relying on a β-elimination strategy and subsequent oxidation to create the 1,2-dithiin ring. We report the synthesis of novel symmetrical and unsymmetrical 3,6-disubstituted 1,2-dithiins, their evaluation as antifungal agents, and the first structure–activity study involving the 1,2-dithiin class of compounds. Optimized geometries for representative 1,2-dithiins were determined using Hartree–Fock molecular orbital methods. A divergence in structure–activity relationships (SAR) is reported between the series of 1,2-dithiins containing electron-withdrawing groups and the 1,2-dithiin series that contains leaving groups. Finally, SARs and modeling were used to postulate discrete modes of action for each series and a single consensus model which is consistent with a single biological target.

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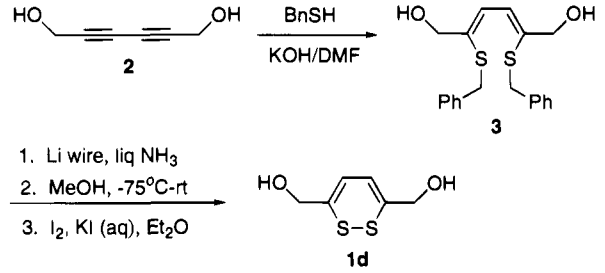
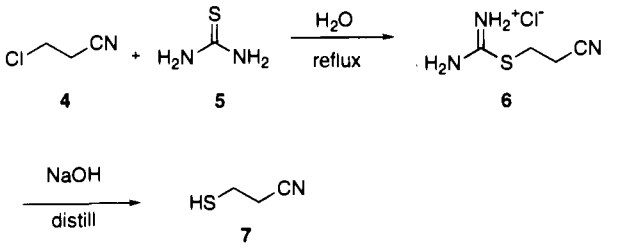
Scheme 1



Scheme 2



Chemistry

I. Synthesis of the 1,2-Dithiin Ring System. Schroth and co-workers[31-33] reported the first preparation of the parent 1,2-dithiin **1c** and 3,6-disubstituted analogues in the 1960s. Their methodology was highly effective in the cases where the 3,6-substituents were aromatic but largely ineffective for the synthesis of 1,2-dithiins bearing nonaromatic substituents at the C-3 and C-6 positions. Through a collaborative approach, an effort was initiated to develop synthetic methodology designed to prepare 1,2-dithiins with nonaromatic substituents, and the results of this work were recently published by Koreeda and Yang[34] (Scheme 1).

We required multigram quantities of dithiin **1d** and were discouraged by our initial attempts at scale-up of this reaction. While the yields approximated those of the literature report[34] on a 1–2 g scale (of **3**) and were reproducible, larger scale reactions gave much lower yields of **1d** and were complicated by emulsions. This one-pot process gave yields of **1d** which ranged from 20% to 45%, with the highest yield being unreproducible.[35] Other process considerations deserved attention. The large reduction in molecular weight in the transformation of **3** to **1d** was a concern; typically, the 30 g runs gave about 4 g of **1d**. In addition, the use of dissolving metal conditions in a large-scale process environment is hazardous and undesirable. These factors led us to pursue an alternative strategy to synthesize the 1,2-dithiin ring system which would allow for the preparation of multigram quantities of **1d** and **1e**.

Our approach involved a β-elimination strategy, whereby the sulfur atoms could be introduced to the diyne using a β-substituted mercaptan. Removal of the protecting groups followed by oxidative ring closure would then afford the desired 3,6-disubstituted 1,2-dithiin. We chose to use β-mercaptopropionitrile[36-38] as the thiophile, relying on previous β-elimination protecting group experience for its removal.[39] The requisite 2,4-hexadiyne-1,6-diol **2** could be purchased commercially, but was conveniently prepared on kilogram scale by Glaser coupling of propargyl alcohol in 60% yield.[40] The β-mercaptopropionitrile was prepared in two steps (Scheme 2). 2-Chloropropionitrile **4** was condensed with thiourea **5** in refluxing water to provide 78–88% yields of thiouronium hydrochloride salt **6**. The reaction is exothermic at around 80 °C and had to be monitored carefully to prevent a lower yield. On a multikilogram scale, the thiouronium salt **6** was reproducibly prepared in 78% yield. Hydrolysis of the thiouronium salt with sodium hydroxide followed by acidic workup and vacuum distillation gave the desired 2-mercaptopropionitrile **7** in 55% yield.

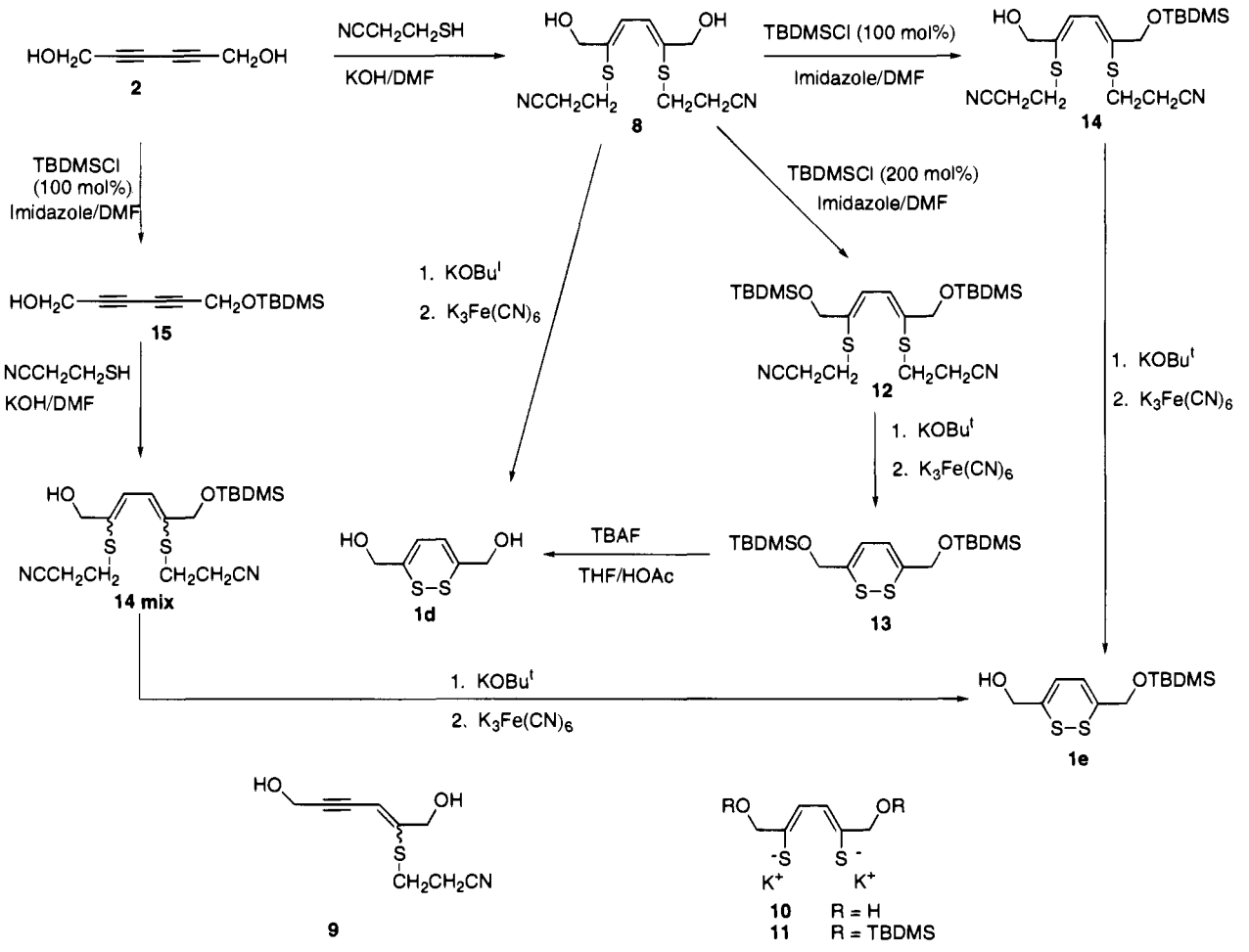
Bis-addition of the β-mercaptopropionitrile to 2,4-hexadiyne-1,6-diol **2** was carried out in a manner similar to that reported for benzyl mercaptan[30,34] except that excess mercaptan (4 equiv) was routinely used (Scheme 3). Yields for this transformation were 60–70%, and the reaction was successfully scaled to the 100–200 g range without a reduction in yield. As with earlier reported examples,[34] this bis-adduct **8** was obtained in a highly trans-selective and regioselective manner. On occasion (when less mercaptan was used), small amounts of the monothioadducts **9** were observed. Removal of the propionitrile protecting groups was accomplished by using KOBu^t to afford the postulated dipotassium dithioenolate **10**. Oxidation of **10** using potassium ferricyanide gave a 33% yield of dithiin **1d**.

While dithiin **1d** could be produced in multigram quantities using the above procedure, further scale-up of this reaction gave variable results. A better overall process involved the use of bissilylated bisthioadduct **12**. Deprotection of **12** with KOBu^t followed by oxidation with potassium ferricyanide gave dithiin **13** in 65% yield. Removal of the TBDMS protecting groups using a buffered tetrabutylammonium fluoride (TBAF) solution provided dithiin **1d** in 58% yield.

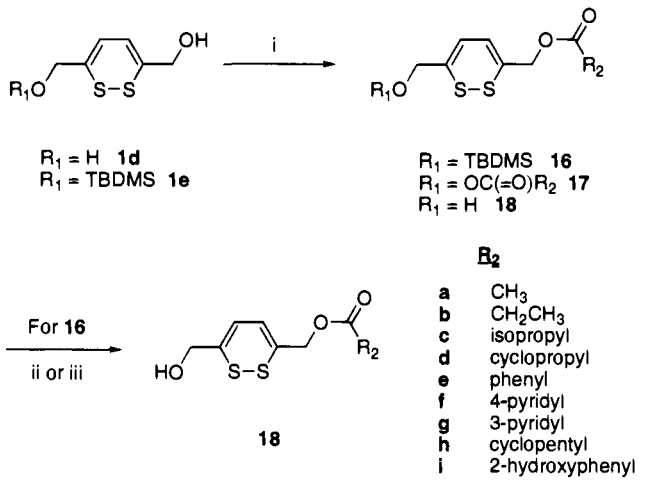
To prepare monofunctional dithiin derivatives, dithiin **1e** was required. We explored two approaches to dithiin **1e**. The first involved monosilylation of 2,4-hexadiyne-1,6-diol **2** to **15**, which was accomplished in 45% yield. Treatment of **15** with β-mercaptopropionitrile in the presence of KOH gave a mixture of bisthioadducts, **14mix**. This stereoisomeric mixture was not separated, but was subjected to the KOBu^t deprotection/potassium ferricyanide oxidation sequence to afford the monoprotected dithiin **1e** in 30–40% yield. The second approach, which turned out to be far superior, involved monosilylation of bisthioadduct **8**. Treatment of **8** with 1 equiv of TBDMSCl (imidazole/DMF) gave a 50% yield of **14**, along with 25% yields each of the bissilylated bisthioadduct **12** and unreacted **8**. Deprotection of **14** with KOBu^t, followed by oxidation with potassium ferricyanide, gave the desired dithiin **1e** in 76% yield. Monosilylated bisthioadduct **14** turned out to be a convenient intermediate to stockpile, and thus large-scale reactions involving dithiin formation were not carried out. However, the dithiin ring closure reaction from **14** to **1e** was successful on a 10 g scale without a reduction in yield.

II. Chemistry of 3,6-(Hydroxymethyl)-1,2-dithiin (1d) and 3-(Hydroxymethyl)-6-[[(*tert*-butyldimethylsilyl)oxy]methyl]-1,2-dithiin (1e). With a synthetic route to prepare appreciable amounts of dithiins **1d** and **1e** in place, we set out to explore the chemistry of these novel compounds. Use of dithiin **1d** would allow us to pursue symmetrically substituted dithiin analogues, while use of dithiin **1e** would allow for asymmetric analogues. We initially explored the formation of ester derivatives, and later expanded our scope to include amide, urea, carbonate and ether functionalities. We

Scheme 3



Scheme 4



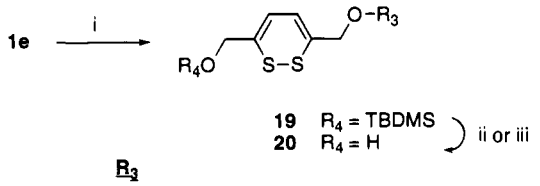
[a] Conditions: (i) acid chloride, acid anhydride, or DCC; (ii) TBAF/HOAc; (iii) HF(aq)/CH_3CN.

were also interested in preparing functionalized methylenedithiin derivatives, conceivably available by nucleophilic displacement of an activated hydroxyl substitutent. Finally, we investigated the synthesis of dithiin aldehyde, olefin, and oxime derivatives.

(A) Esters. Esters of dithiins **1d** and **1e** were readily prepared by reaction with the appropriate anhydride or acid chloride reagents in the presence of base (Scheme 4). Use of 2 equiv or more of the acid chloride or the acid anhydride gave diesters **17a–h**. If 1 equiv of reagent was used, both the mono- and diesters, **18a–h** and **17a–h**, respectively, were obtained. In principle, it would be possible to obtain monoesters **16** from dithiin **1e** by a similar approach. For the salicylic acid adducts **17i** or **18i**, DCC coupling conditions were employed. Treatment of **1d** with 1 equiv each of DCC and salicylic acid in 4/1 CH_2Cl_2/EtOAc gave monoester **18i** in 28% yield. When 2 equiv each of DCC and salicylic acid were used, diester **17i** was obtained (14%). In both experiments, the bulk of the recovered mass balance was unreacted dithiin **1d**. The coupling could also be effected by carbonyldiimidazole (CDI); thus, use of 1 equiv each of CDI, salicylic acid, and dithiin **1d** gave an 18% yield of **18i** along with unreacted starting material.

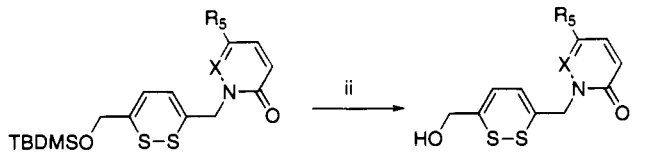
(B) Ethers and Thioethers. Aromatic ether derivatives were prepared via the Mitsunobu reaction of dithiin **1e** with the appropriate phenol (Scheme 5). The reaction was generally performed using Ph_3P, the appropriate phenol, and diethyl azodicarboxylate (DEAD) in THF at 0 °C. Yields of ether **19** were substrate dependent, ranging from 11% to 71%. In most reactions, small amounts of the corresponding thiophene derivative were formed. In some instances, this impurity could be separated by column chromatography. In cases where separation was difficult, purification to remove the thiophene impurity was done in the next step. Mono(*tert*-butyldimethylsilyl)catechol was used to obtain the 2-hydroxyphenyl dithiin derivative **19a** (62% yield). Mitsunobu reaction of **1e** with the 2-hydroxypyridine derivatives were generally low-yielding and gave two products, the desired 2-hydroxypyridines, **19d**

Scheme 5



R3

- **a** 2-hydroxyphenyl
- **b** phenyl
- **c** methyl benzoate-2-yl
- **d** 2-pyridyl
- **e** 3-pyridyl
- **f** 3-dimethylaminophenyl
- **g** 3-hydroxyphenyl
- **h** 3-hydroxy-1,2-pyridazine-6-yl
- **i** 2-(trifluoromethyl)phenyl
- **j** 5-nitropyridine-2-yl
- **k** 2-fluorophenyl
- **l** 3-ethynylphenyl
- **m** methyl benzoate-3-yl
- **n** 2-chloro-5-(trifluoromethyl)phenyl
- **o** methyl benzoate-4-yl
- **p** 4-(N-imidazolyl)phenyl
- **q** 4-hydroxypyridine

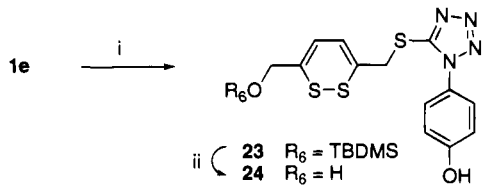


21d X = C-H; R_5 = H
21h X = N; R_5 = OH
21j X = C-H; R_5 = NO_2

22d X = C-H; R_5 = H
22h X = N; R_5 = OH
22j X = C-H; R_5 = NO_2

[a] Conditions: (i) Ph_3P, DEAD, R_3OH; (ii) TBAF/HOAc; (iii) HF(aq)/CH_3CN.

Scheme 6

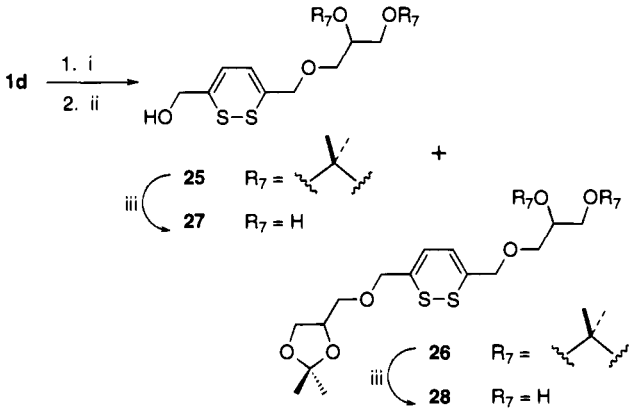


[a] Conditions: (i) Ph_3P, DEAD, 4-(4-hydroxyphenyl)-1*H*-tetrazole-5-thiol; (ii) TBAF/HOAc.

and **19j**, and the respective pyridone adducts, **21d** and **21j**, which were the major products. 3-Hydroxypyridine gave only the 3-hydroxypyridyl ether **19e**, but in low yield (18%). Attempted preparation of the 4-hydroxypyridine derivative **19q** gave only the corresponding pyridone adduct. Mitsunobu coupling of **1e** with 1,2-pyridazine-3,6-diol proceeded in a similar manner, yielding both the hydroxypyridazine derivative **19h** (11%) and the pyridazone derivative **21h** (25%). Desilylation of the Mitsunobu adducts **19** and **21** was best accomplished by using a buffered TBAF solution (TBAF/HOAc) or aqueous HF in acetonitrile to afford dithiins **20** and **22**, respectively. Use of TBAF in THF without acetic acid led to extensive decomposition of the dithiins **19**.

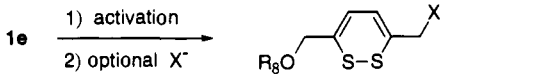
Mitsunobu reaction of 1-(4-hydroxyphenyl)-1*H*-tetrazole-5-thiol with dithiin **1e** gave thioester **23** in 51% yield (Scheme 6). Subsequent desilylation with TBAF/HOAc in THF gave dithiin **24** in 80% yield. To resolve the question of the site of alkylation in **24**, the structure was determined by the following NMR and IR experiments. The ^1H NMR spectrum of **24** in DMSO-d_6 shows a singlet at 10.26 ppm, corresponding to a phenol OH.

Scheme 7



[a] Conditions: (i) NaH; (ii) TfO  ; (iii) 60% HOAc, rt

Scheme 8



- **a** X = OTs
- **b** X = N_3
- **c** X = Cl
- **d** X = OTf
- **e** X = I
- **f** X = NH_2

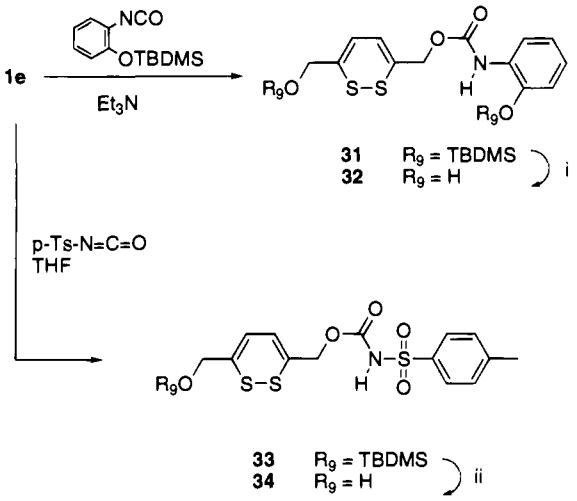
[a] Conditions: (i) HF(aq)/CH_3CN.

The ^{13}C NMR spectrum of **24** shows the two dithiin methylene carbons at 64.67 and 40.01 ppm; the latter indicates a thioether carbon. All previous dithiins have this methylene carbon for ($-CH_2O-$) at 60–72 ppm. The IR spectrum of **24** shows two OH streching frequencies at 3378 and 3135 cm^{-1}, and an absence of a C=S stretch. The ^1H NOESY spectrum shows interactions between the aromatic protons and the dithiin ring protons. Such interactions would be unlikely in other possible structures. Further confirmation of the structure was provided by HMBC data, where a long-range correlation was observed between the CH_2 protons at 4.30 ppm and the C-5 tetrazole carbon at 154.90 ppm. All the data is consistent with the thioether structure of **24**.

The synthesis of dithiin alkyl ethers was also investigated (Scheme 7). The disodium salt of dithiin **1d** was first prepared *in situ* by use of 2 equiv of NaH in THF at room temperature. Subsequent treatment with freshly prepared 1-[(trifluoromethyl)sulfonyl]-2,3-*O*-isopropylideneglycerol gave monoether **25** (29%) and bisether **26** (36%). When 100 mol % of NaH was used in the above experiment, the yields of monoether and bisether were 20% and 3%, respectively, along with unreacted starting dithiin (33%). The isopropylidene protecting groups were removed from each by treatment with 60% HOAc at room temperature, affording dithiins **27** (43%) and **28** (21%), respectively.

(C) Functionalized Methylene Derivatives. We were interested in preparing dithiin derivatives in which the free hydroxyl group of dithiin **1e** could be replaced with alternative functionality (Scheme 8). This in general would require activation of the hydroxyl group before displacement by an appropriate nucleophile. Only two of the desired analogues were obtained,

Scheme 9



[a] Conditions: (i) TBAF/HOAc; (ii) HF(aq)/CH_3CN.

presumably due to the inherent reactivity of the dithiin ring system. Attempted activation of the hydroxyl group of **1e** as the triflate, **29d** (Tf_2O), failed. The tosylate derivative, **29a**, was also inherently unstable. It could be prepared *in situ* using *p*-toluenesulfonic anhydride, but could not be isolated. Attempts to prepare **29a** using *p*-toluenesulfonyl chloride in the presence of pyridine and DMAP, or in refluxing benzene, gave chloride derivative **29c**. Attempted preparation of amino dithiin **29f** from the chloro derivative **29c** using ammonia led only to dithiin decomposition. Attempted Finkelstein reaction of chlorodithiin **29c** (KI, acetone) led only to decomposition of the dithiin ring. Initial attempts to prepare the azide dithiin **29b** from the tosyldithiin **29a** or the chlorodithiin **29c** using NaN_3 or $Bu_4N^+N_3^-$ led only to decomposition products. However, azide **29b** was successfully prepared from **1e** using diphenyl phosphorazidate[41] and DBU in toluene (75% yield). Dithiin **29b** was then desilylated (HF/CH_3CN) to provide dithiin **30b** in 62% yield.

(D) Amides, Ureas, and Carbamate Dithiins. The general instability of ester functionality *in vivo* led us to pursue the synthesis of amide, urea, and carbamate derivatives. Carbamate derivative **31** was prepared in 87% yield from 2-[(*tert*-butyldimethylsilyl)oxy]phenyl isocyanate, which was prepared from 2-aminophenol in two steps by silylation of the hydroxyl substituent (TBDMSCl, Et_3N) followed by treatment with phosgene in toluene (Scheme 9). Desilylation using TBAF/HOAc provided carbamate **32** in 75% yield. Similarly, sulfonylcarbamate **33** could be prepared in 66% yield by treatment of dithiin **1e** with *p*-toluenesulfonyl isocyanate. Desilylation with aqueous HF in acetonitrile provided the deprotected sulfonylcarbamate **34**.

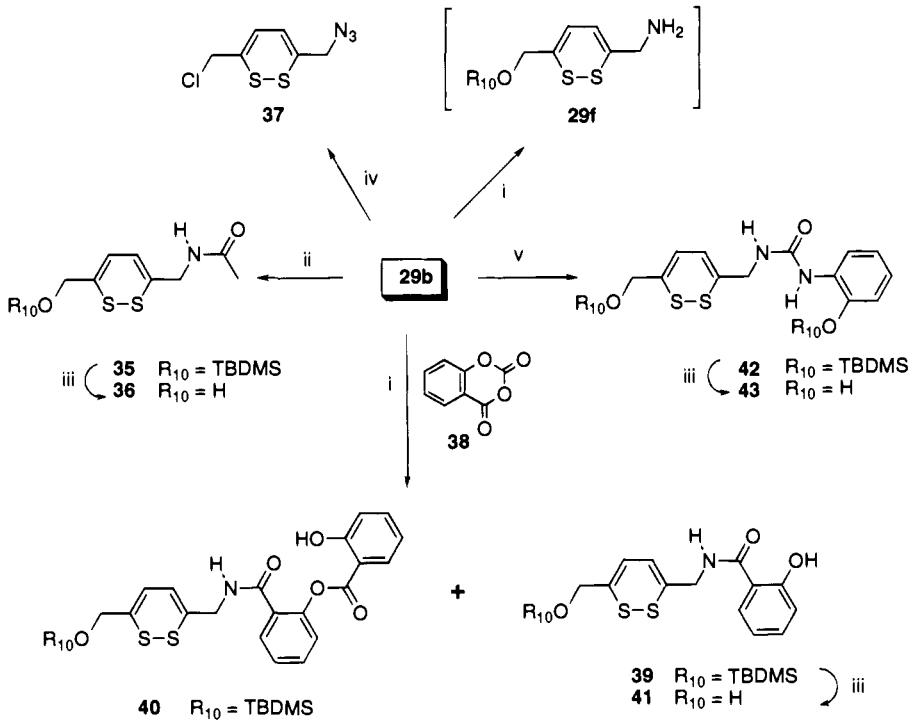
The successful synthesis of azide **29b** allowed us to pursue the synthesis of amide and urea derivatives (Scheme 10). Attempts to reduce azide **29b** to the amine dithiin **29f** using $NaBH_4$, propanedithiol,[42] or sodium disulfide/Et_3N failed, leading only to decomposition products as determined by TLC. The azide functionality could be reduced using Ph_3P/H_2O/THF[43] conditions, but the desired amine **29f** could not be isolated. Amine **29f** could be trapped by carrying out the reduction in the presence of acetic anhydride, providing acetamide derivative **35** in 35% yield after chromatography. Desilylation of **35** using aqueous HF in acetonitrile gave dithiin **36** in 71% yield. An attempt to trap amine **29f** as its isocyanate using triphosgene (Ph_3P/H_2O/THF) led to the unexpected isolation of chloroazide **37** in 40% yield. Salicylic acid amide **39** was prepared by trapping *in situ*-generated **29f** (Ph_3P/H_2O/THF conditions) with anhydride **38**[44] (26% yield). Also isolated in 20% yield was diadduct **40**. Subsequent desilylation of **39** using aqueous HF in acetonitrile gave the desired amide **41** in 82% yield. Dithiin urea **42** was prepared by trapping *in situ*-generated **29f** (Ph_3P/H_2O/THF conditions) with 2-[(*tert*-butyldimethylsilyl)oxy]phenyl isocyanate. Subsequent desilylation using aqueous HF in acetonitrile gave the desired dithiin urea **43**.

(E) Dithiin Aldehydes and Their Analogues. Koreeda and co-workers have reported the synthesis of dialdehyde dithiin **44**,[30,34] prepared from dithiin diol **1d** by oxidation using the Dess–Martin reagent[45] (Scheme 11). We wished to use this precursor to synthesize various aldehyde derivatives; two such derivatives are reported here. In our hands, dialdehyde **44** was best prepared when the Dess–Martin reagent was recently prepared using the Ireland procedure.[46] Yields of dialdehyde 44 were reproducibly above 80% in multigram quantities utilizing these conditions. Treatment of dialdehyde **44** with hydroxylamine hydrochloride in pyridine provided bisoxime **45** in 44% yield after chromatography. The stereochemistry of this oxime product has not been definitively established as bis-*E* or bis-*Z*, but NMR data excludes a *Z*/*E* mixed product based on symmetry considerations. The bis-*E* stereoisomer is presumed to be the preferred one. Comparison of molecular models for the bis-*E* and bis-*Z* stereoisomers indicated severe steric and electronic contacts between the oxygen atoms and the 1,2-dithiin ring in the bis-*Z* stereoisomer case that were not present for the bis-*E* stereoisomer. The calculated energy difference between the bis-*E* and the bis-*Z* stereoisomers of **45** was 25.85 kcal/mol (Hartree–Fock, 3-21G* basis set), favoring the bis-*E* stereoisomer.

During isolation of **45**, considerable loss of material occurred upon chromatography, yet the reaction was generally clean by TLC and the product was pure by NMR. The chromatographic step proved unneccessary as workup alone produced pure bisoxime **45** in 90% yield. Likewise, bisoxime **46** was prepared in 48% yield following chromatography by treatment of dialdehyde **44** with methoxylamine hydrochloride in pyridine. As before, a symmetrical bisoxime was obtained, and its stereochemistry is presumed to be bis-*E*.

We were also interested in the synthesis of unsymmetrical olefinic dithiin derivatives, which required dithiin monoaldehyde **47**. Aldehyde **47** was prepared from dithiin **1e** using the Dess–Martin periodinane reagent. Yields for this transformation were consistently above 80% on multigram scale. Once again, the reaction worked best when the reagent was prepared using the Ireland procedure.[46] Desilylation of **47** using a mixture of TBAF and acetic acid gave the deprotected aldehyde **48** in 83% yield. Monooxime **49** was prepared from aldehyde **47** by treatment with hydroxylamine hydrochloride in pyridine at room temperature in 65% yield as an *E*/*Z* mixture. The corresponding thiophene was also formed, and could be isolated in yields up to 18%. Desilylation of **49** using TBAF/acetic acid conditions gave the deprotected oxime **50** in 87% yield. Attempted preparation of the *O*-methyloxime **51** using

Scheme 10



[a] Conditions: (i) Ph_3P, THF–H_2O; (ii) Ac_2O, Ph_3P, THF–H_2O; (iii) HF/(aq)/CH_3CN; (iv) $(Cl_3CO)_2CO$, Ph_3P, THF–H_2O; (v) Ph_3P, THF–H_2O, 2-[(*tert*-butyldimethylsilyl)oxy]phenyl isocyanate.

literature conditions (refluxing pyridine) failed.[47] Oxime **51** was successfully prepared by treatment of dithiin aldehyde **47** with methoxylamine hydrochloride in the presence of pyridine and *N*-methylmorpholine in glyme at room temperature in 50% yield. Desilylation of **51** using TBAF/acetic acid conditions afforded the desired oxime **52** in 90% yield.

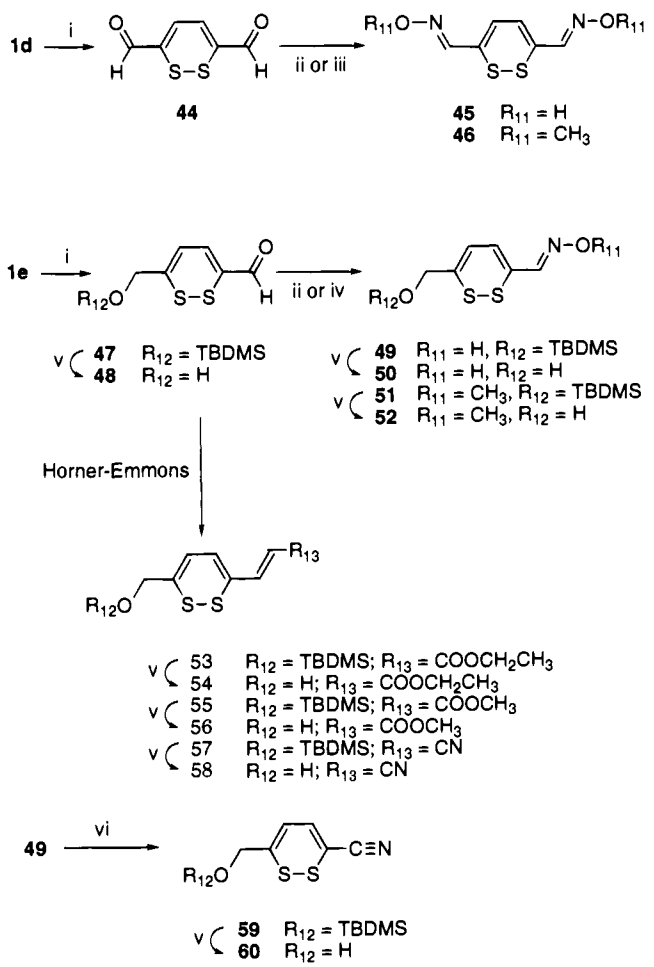
Olefinic derivatives of the dithiin aldehyde **47** were pursued via Wittig chemistry. On the basis of our previous experience with Mitsunobu chemistry yielding small amounts of thiophene impurities, we felt that standard Wittig chemistry would fail but that the less thiophilic phosphonate reagents might be successful. Olefinic ethyl ester **54** was successfully prepared from aldehyde **47** in two steps. Treatment of aldehyde **47** with a preformed mixture of triethyl phosphonoacetate/*n*-BuLi at low temperature gave the intermediate olefin **53** in 52% yield. Desilylation using TBAF/acetic acid in THF gave the desired deprotected olefin **54** in 80% yield. The olefinic methyl ester **56** was prepared in a similar manner, using a preformed mixture of trimethyl phosphonoacetate and *n*-BuLi at low temperature to obtain the silylated olefin **55**. Removal of the silicon protecting group (TBAF/acetic acid/THF) gave the desired olefin **56** in 87% yield. For preparation of the olefinic nitrile **58**, the conditions using a preformed solution of diethyl (cyanomethyl)phosphonate and *n*-BuLi did not work, presumably due to reaction of the cyano funtionality with the butyllithium. Use of sodium amide as base was successful, providing the silylated nitrile **57** in 55% yield. Deprotection using TBAF and acetic acid in THF afforded the desired nitrile **58** in 84% yield.

Nitrile **60** was envisioned to come from oxime **49** by dehydration, followed by desilylation. Dehydration of **49** using dicyclohexylcarbodiimide appeared to work; however, the desired product **59** could not be purified from the byproduct dicyclohexylurea. This purification problem was circumvented with the use of the newly developed carbodiimide reagent, bis[[4-(2,2-dimethyl-1,3-dioxolyl)]methyl]carbodiimide (BDDC),[48] in which the urea byproduct is water soluble. Thus, treatment of oxime **49** with BDDC and copper(I) chloride in dichloromethane at room temperature gave the protected nitrile **59** in 68% yield, free of any carbodiimide byproduct. Desilylation using TBAF/acetic acid in THF afforded the desired nitrile analogue **60** in 90% yield.

Biological Results

The synthesized dithiins were routinely tested in an antifungal susceptibility test using a 96-well microplate broth assay[49,50] against three pathogenic fungi: *Candida albicans* (ATCC 10259), *Cryptococcus neoformans* (ATCC 36556), and *Aspergillus fumigatus* (ATCC 13073); the results are shown in Table 1. Dithiindiol **1d** exhibited moderate activity against *C. albicans* (CA) and *C. neoformans* (CN) but showed good activity against *A. fumigatus* (AF). Among the diesters **17**, the size of the substituent seemed to be important. Diacetate **17a** exhibited good activity against all three fungi. Dipropionate **17b** was 10-fold less active, and the diisopropyl ester **17c** was inactive against CA, but retained activity against the other two fungi. Interestingly, the dicyclopropyl ester **17d** was active against CA (6.3 μg/mL) and was 4-fold more active than diisopropyl ester **17c** against CN and AF, whereas the bulkier dicyclopentyl ester was inactive against all three fungi. Among the aromatic diesters **17**, only the dipyridyl esters were active (**17f** and **17g**). In those examples where mono- and diesters were both prepared (e.g., **18** and **17**, respectively), the monoesters **18** were more active than their diester counterparts. The exceptions to this trend were monoacetate **18a** and monopyridyl ester **18f**, which both were of comparable activity to their respective diester counterparts. Notably, the monosalicylic acid ester **18i** was very active (0.2 μg/mL) against all three

Scheme 11



[a] Conditions: (i) Dess–Martin; (ii) $H_2NOH{\cdot}HCl$, pyridine, glyme, room temperature; (iii) $H_2NOCH_3{\cdot}HCl$, pyridine, glyme, room temperature; (iv) $H_2NOCH_3{\cdot}HCl$, pyridine, glyme, *N*-methylmorpholine, room temperature; (v) TBAF/HOAc; (vi) BDDC, Cu^ICl, CH_2Cl_2.

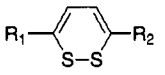
fungi. On the basis of the active monosalicylic acid analogue, we pursued the synthesis of a more stable linkage, keeping the 2-hydroxyphenyl substituent constant. Thus, we synthesized ether **20a**, carbamate **32**, amide **41**, and urea **43**. The amide, urea, and carbamate analogues were inactive or only marginally active, while the ether analogue was active (6.3, 25, and 12.5 μg/mL, respectively, against CA, CN, and AF). This result led us to pursue the ether series more thoroughly. Phenyl ether **20b** was less active than the 2-hydroxy derivative **20a**, while the 2-pyridyl and 3-pyridyl ethers, **20d** and **20e**, respectively, were more active than phenyl ether **20b**. Electron-withdrawing substituents on the aromatic ring tended to increase the activity of the dithiin ether analogue (**20c, 20i**, **20k**, **20l**, **20m**, **20n**, and **20o**). The same trend was observed with the pyridyl ethers, as the 5-nitro-2-pyridyl ether **20j** was very active against all three fungi (0.2, 0.1, and 0.4 μg/mL, respectively, against CA, CN, and AF). In the one example where all three ortho, meta, and para analogues were prepared (**20c**, **20m**, and **20o**, respectively), the position of the electron-withdrawing substituent had little effect (± one dilution factor) in activity enhancement. Electron-donating substituents on the aromatic ring (dithiins **20f** and **20g**) resulted in dithiin analogues which were less active than the phenyl ether, with the same trend being observed in the heteroaromatic example as well (pyridazine dithiin **20h**). The notable exception was the previously discussed 2-hydroxyphenyl ether **20a**. The alkyl ether derivatives (**25**, **26**, **27**, and **28**) were inactive, while thioether **24** showed marginal activity.

One possible factor contributing to the activity of the dithiin analogue in the antifungal screening assay is the ability of the methylene functionality to act as a leaving group. Most of the phenyl or pyridyl ethers with electron-withdrawing substituents enhance the ability of the aromatic moiety to act as a leaving group. Corroborating this postulate is that alkyl ethers **25**–**28** were inactive. Among the salicylic acid analogues (e.g., ester **18i**, ether **20a**, carbamate **32**, amide **41**, and urea **43**), ester **18i** was much more active than its counterparts and in fact was the most active ester analogue prepared. It is conceivable that the ability of the salicylic acid moiety to act as a leaving group enhances the activity of the dithiin ring system in the assay. Furthermore, azide **30b** was very active against all three fungi as well. Chloro azide **37**, with the second hydroxymethyl substituent of dithiin **1d** replaced, was 25–100-fold less active than azide **30b**. While the ability of a substituent in the 3- or 6-position of the dithiin ring to act as a leaving group may result in enhanced activity of the dithiin analogue, it undoubtedly is not the only factor. The role of hydrogen bonding to side chain functionality at either the 3- or 6-positions may also be important to activity (e.g., CH_2OH functionality, pyridyl substituent in **17f**, **17g**, and chloro azide **37** vs hydroxymethyl azide **30b**).

Another additional factor may be the inductive effect that the substituent imparts on the dithiin ring system. This was further explored by the synthesis and testing of the dithiin aldehydes (**48** and **44**), olefins (**54**, **56**, and **58**), oximes (**45, 46, 50**, and **52**), and nitrile **60**. Bisaldehyde 44 was active (1.6 μg/mL) against CA and CN and against AF (6.3 μg/mL), while monoaldehyde **48** was 4–8 times less active. Methyl acrylate analogue **56** was equipotent against all three fungi (6.3 μg/mL). The ethyl acrylate derivative **54** was less active than **56** against CA and AF, while the acrylonitrile analogue **58** was one dilution less active against CA than **56,** one dilution more active against CN, and equipotent with **56** against AF. Removal of any steric constraint, as in nitrile **60**, resulted in increased activity against all three fungi. In comparing the oxime derivatives, bisoximes **45** and **46** were more active than their respective monooxime counterparts, **50** and **52**. In both examples, the *O*-methyloximes **46** and **52** were 4–8-fold less active against all three fungi than the respective hydroxyloximes **45** and **50** were. Even in this series, the presence of side chain functionality able to participate in hydrogen bonding was important for activity.

A sampling of dithiin analogues were tested similarly against other strains and types of fungi:[49,50] *Candida albicans* A-26, *Candida albicans* B-311, *Candida krusei* GK7831, *Candida parapsilosis* CP18, *Candida tropicalis* 1525, *Cryptococcus neoformans* MI-106, *Aspergillus fumigatus* WM-1, *Trichophyton rubrum* ATCC18762; the results are summarized in Table 2. Dithiin esters **18a** and **18d** showed good activity against *Candida parapsilosis* (CP), *Candida tropicalis* (CT), *Candida krusei* (CK), and *Trichophyton rubrum* (TR). Monooxime **50** was less active against most of strains and fungi tested than was bisoxime **45**. Monooxime **50** and

Table 1. Structure and Antifungal Activity of New 1,2-Dithiins



compd no.	R_1	R_2	MIC (μg/mL) CA	CN	AF
1d	CH_2OH	CH_2OH	16	31	2
17a	CH_2OCOCH_3	CH_2OCOCH_3	1.25	0.63	0.63
17b	$CH_2OCOCH_2CH_3$	$CH_2OCOCH_2CH_3$	12.5	6.3	3.1
17c	$CH_2OCOCH(CH_3)CH_3$	$CH_2OCOCH(CH_3)CH_3$	>100	12.5	6.3
17d	CH_2OCO-cyclopropyl	CH_2OCO-cyclopropyl	6.3	3.1	1.6
17e	$CH_2OCOC_6H_5$	$CH_2OCOC_6H_5$	>100	>100	>100
17f	CH_2OCO-4-pyridyl	CH_2OCO-4-pyridyl	2	NT[a]	2
17g	CH_2OCO-3-pyridyl	CH_2OCO-3-pyridyl	2	NT[a]	2
17h	CH_2OCO-cyclopentyl	CH_2OCO-cyclopentyl	>250	NT[a]	>250
17i	CH_2OCO-*o*-hydroxyphenyl	CH_2OCO-*o*-hydroxyphenyl	>250	NT[a]	>250
18a	CH_2OH	CH_2OCOCH_3	3.1	0.2	0.4
18d	CH_2OH	CH_2OCO-cyclopropyl	3.1	1.6	0.4
18e	CH_2OH	$CH_2OCOC_6H_5$	6.3	3.1	3.1
18f	CH_2OH	CH_2OCO-4-pyridyl	3.1	NT[a]	1.6
18h	CH_2OH	CH_2OCO-cyclopentyl	6.3	NT[a]	3.1
18i	CH_2OH	CH_2OCO-*o*-hydroxyphenyl	0.2	0.2	0.2
20a	CH_2OH	CH_2O-*o*-hydroxyphenyl	6.3	25	12.5
20b	CH_2OH	$CH_2OC_6H_5$	25	12.5	25
20c	CH_2OH	CH_2O-2-carbomethoxylphenyl	6.3	6.3	12.5
20d	CH_2OH	CH_2O-2-pyridyl	3.1	3.1	3.1
20e	CH_2OH	CH_2O-3-pyridyl	3.1	1.6	3.1
20f	CH_2OH	CH_2O-3-(dimethylamino)phenyl	>50	50	100
20g	CH_2OH	CH_2O-3-hydroxyphenyl	50	100	>100
20h	CH_2OH	CH_2O-3-hydroxy-1,2-pyridazin-6-yl	>100	>100	>100
20i	CH_2OH	CH_2O-2-(trifluoromethyl)phenyl	25	6.3	50
20j	CH_2OH	CH_2O-5-nitropyridin-2-yl	0.2	0.1	0.4
20k	CH_2OH	CH_2O-2-fluorophenyl	3.1	1.6	3.1
20l	CH_2OH	CH_2O-3-ethynylphenyl	1.6	1.6	6.3
20m	CH_2OH	CH_2O-3-carbomethoxylphenyl	3.1	6.3	25
20n	CH_2OH	CH_2O-2-chloro-5-(trifluoromethyl)phenyl	1.6	1.6	6.3
20o	CH_2OH	CH_2O-4-carbomethoxylphenyl	3.1	3.1	12.5
20p	CH_2OH	CH_2O-4-(*N*-imidazolyl)phenyl	12.5	100	100
22d	CH_2OH	CH_2-2-oxopyrid-1-yl	>100	12.5	>100
22h	CH_2OH	CH_2-3-hydroxy-6-oxopyridazin-1-yl	>100	>100	>100
22j	CH_2OH	CH_2-5-nitro-2-oxopyrid-1-yl	>100	100	>100
24	CH_2OH	CH_2S-1-(4-hydroxyphenyl)tetrazol-5-yl	25	6.3	12.5
25	CH_2OH	CH_2O-2,3-isopropylideneglycerol	>100	>100	>100
26	CH_2O-2,3-isopropylideneglycerol	CH_2O-2,3-isopropylideneglycerol	>100	>100	>100
27	CH_2OH	CH_2O-2,3-dihydroxyprop-1-yl	>100	>100	>100
28	CH_2O-2,3-isopropylideneglycerol	CH_2O-2,3-dihydroxyprop-1-yl	>100	>100	>100
30b	CH_2OH	CH_2N_3	0.25	0.25	0.25
32	CH_2OH	CH_2OCONH-*o*-hydroxyphenyl	100	50	50
34	CH_2OH	CH_2OCONH-tosyl	100	50	100
36	CH_2OH	$CH_2NHCOCH_3$	>100	100	>100
37	CH_2Cl	CH_2N_3	25	6.3	50
41	CH_2OH	CH_2NHCO-*o*-hydroxyphenyl	>100	100	>100
43	CH_2OH	$CH_2NHCONH$-*o*-hydroxyphenyl	>100	>100	>100
44	CHO	CHO	1.6	1.6	6.3
45	CH=NOH	CH=NOH	0.1	0.8	0.4
46	$CH=NOCH_3$	$CH=NOCH_3$	0.8	1.6	6.3
50	CH_2OH	CH=NOH	1.6	1.6	1.6
52	CH_2OH	$CH=NOCH_3$	6.3	6.3	6.3
54	CH_2OH	$CH=CHCOOCH_2CH_3$	12.5	6.3	25
56	CH_2OH	$CH=CHCOOCH_3$	6.3	6.3	6.3
58	CH_2OH	CH=CHCN	12.5	3.1	6.3
60	CH_2OH	CN	0.8	0.8	1.6

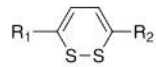
[a] Not tested.

bisoxime **45** were equipotent against the MI-106 strain of CN and against the resistant strain, *C. krusei*, where the MIC activity was 6.3 μg/mL. Potent activity was observed for bisoxime **50** against the two *C. albicans* strains, *A. fumigatus* WM-1, *C. parapsilosis*, and *T. rubrum*.

Molecular Models. The apparent differences in SAR between the leaving group and electron-withdrawing group series stimulated further questions: What is the optimal geometry and electronic structure of the novel 1,2-dithiin structure, do differences in ring electronics account for activity differences between the series, and do the resulting molecular models implicate one or more biological targets?

Optimal geometries were determined for **1d**, **18i**, and **45** using Hartree–Fock molecular orbital techniques (SPARTAN, 3-21G* and 6-31G* basis sets).[51,52] The global minimum conformations for the flexible **1d** and **18i** were first determined using molecular-mechanics-based Monte Carlo conformational search techniques (MacroModel, AMBER force field parameter set, water GB/SA solvation parameter set). The optimized geometries (Figure 2) exhibit a half-chairlike conformation with a disulfide linkage ($C_6-S_1-S_2-C_3$) dihedral angle

Table 2. Further Antifungal Activities of Selected New 1,2-Dithiins



compd no.	R_1	R_2	MIC (μg/mL) A-26[a]	B311[b]	CK[c]	CP[d]	CT[e]	MI-106[f]	WM-1[g]	TR[h]
18a	CH_2OH	CH_2OCOCH_3	NT[i]	NT[i]	1.25	1.25	1.25	NT[i]	NT[i]	0.31
18d	CH_2OH	CH_2OCO-cyclopropyl	NT[i]	NT[i]	1.25	2.50	1.25	NT[i]	NT[i]	0.31
45	CH=NOH	CH=NOH	0.2	0.1	6.3	0.2	1.6	1.6	0.2	0.05
50	CH_2OH	CH=NOH	1.6	1.6	6.3	3.1	6.3	1.6	1.6	0.8

[a] *Candida albicans* A-26. [b] *Candida albicans* B-311. [c] *Candida krusei* GK7831. [d] *Candida parapsilosis* CP18. [e] *Candida tropicalis* 1525. [f] *Cryptococcus neoformans* MI-106. [g] *Aspergillus fumigatus* WM-1. [h] *Trichophyton rubrum* ATCC18762. [i] Not tested.

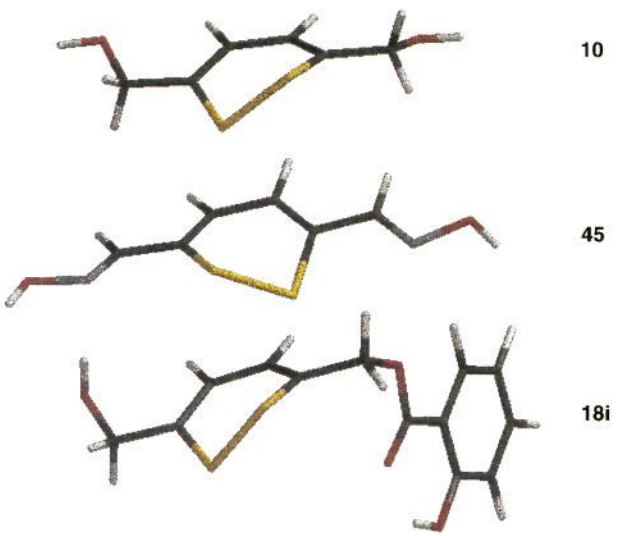


Figure 2. Optimized geometries of **10**, **18i**, and **45** in an edge-on-view.

of 51° (48–61°). The dihedral angle through C_3–C_4–C_5–C_6 was far flatter at 24°, preserving diene conjugation in the ring and with extended π system functionality at positions 3 and 6.

The first dihedral angle of side chains attached at the 3- and 6-positions were influenced by steric and electronic factors. Sulfur–oxygen electrostatic repulsion resulted in a transoid S–C–C–O geometry for **1d**. Substituted derivatives such as **18i** exhibited the same preference for the first dihedral as **1d**. In contrast, **45** preferred a cisoid S–C–C–N geometry, the result of steric hindrance between the lone pair on the oxime nitrogen and the hydrogen at C-4.

The transition state geometry and energy barrier for ring inversion was calculated at 35.42 kcal/mol for the simplified model 3,6-dimethyl-1,2-dithiin **61** using a molecular orbital transition state optimization. The transition state geometry exhibited an S–S bond length of 2.59 Å and a significantly flattened overall ring geometry (Figure 3). The magnitude of the barrier suggests that ring inversion would be slow and the ring system could possibly exist as enantiomers. Also, in the transition state, S_2–C_3–C_4–C_5–C_6 is roughly planar and the C–C bonds exhibit calculated lengths, suggestive of an aromatic character in the transition state.

Proposed Mechanism of Action. The observed chemical lability of the 1,2-dithiin under basic conditions as well as its structural novelty suggested that the ring was the focus of biological activity possibly through a nucleophilic attack mechanism. Because the SAR patterns differed between the series containing leaving groups and the electron-withdrawing groups, it was

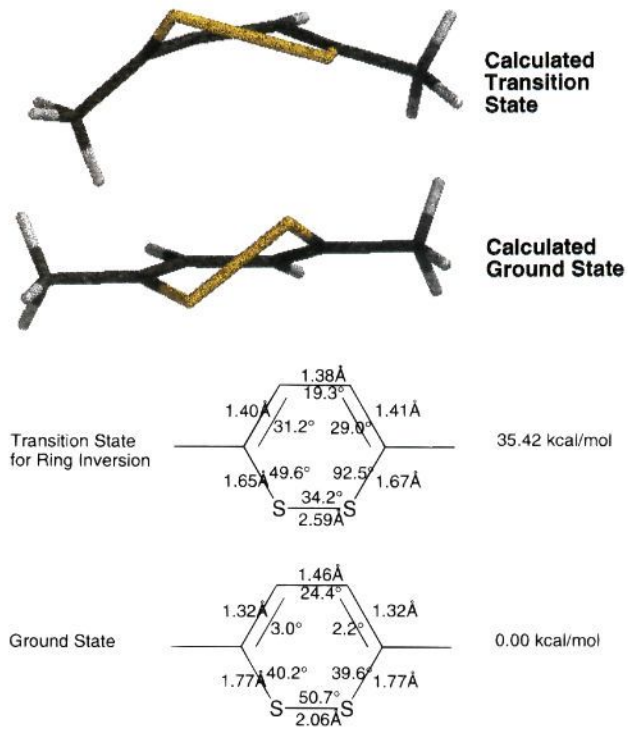


Figure 3. Comparison of transition state and ground state geometries for 3,6-dimethyl-1,2-dithiin **61**.

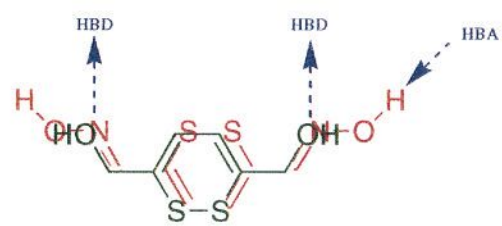
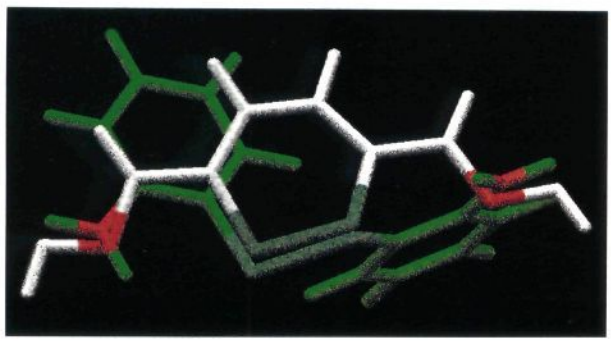
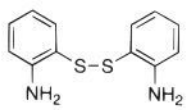


Figure 4. Pharmacophoric model (HBD = H-bond donor; HBA = H-bond acceptor).

initally thought that they worked through two separate mechanisms possibly on separate biological targets.

A simple overlap model derived from the observed structure–activity patterns showed that the 1,2-dithiin ring and the proximal heteroatoms on the side chains could be satisfactorily overlapped but required **45** to be either in a conformer 4.24 kcal/mol higher than the global minimum or with the 1,2-dithiin ring flipped (Figure 4). The side chain heteroatom overlap suggested the probability of interactions with H-bond acceptors in the active site. No other structural or feature matches could be obtained to generate a rational model. The known antifungal agent bis(2-aminophenyl) disulfide[53] **62** (activity = 6.3, 6.3, and 6.3 μg/mL, respectively, against CA, CN, and AF) could be mapped





62

Figure 5. Alignment of disulfide **62** (green) to the pharmacophoric model represented by **45** (white). Side chain heteroatom overlaps colored red. Disulfide overlaps colored blue-green.

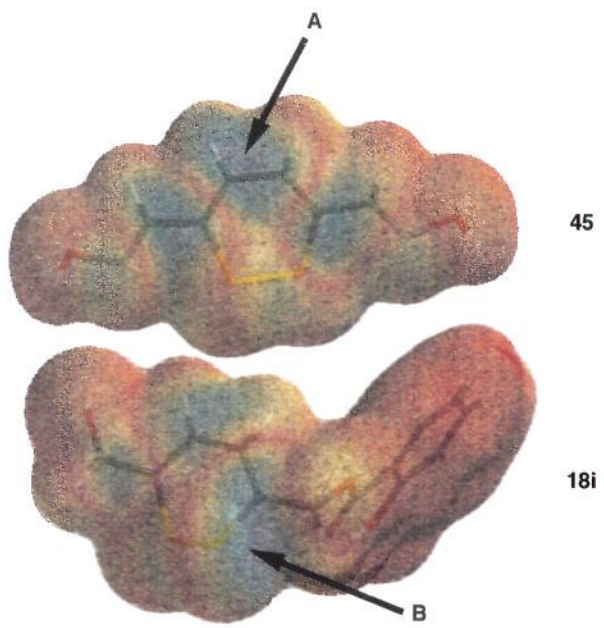


Figure 6. Comparison of LUMO projected on electronic surface for **18i** and **45**. Nucleophilic attack pathway is indicated by arrows A and B for **45** and **18i**, respectively.

to this simple pharmacophore with an energy cost of 4.36 kcal/mol but with the implication that the 1,2-dithiin was not an absolute requirement for activity (Figure 5). Disulfide **62** was found during database searching (ISIS with the ACD database) using flexible search techniques and a query derived from the spacing of the heteroatoms.

The most likely sites for nucleophilic attack on **18i** and **45** were visualized using LUMO isoorbital surfaces (Figure 6). These surfaces locate the positions and magnitudes of the LUMO where it is available outside the normal steric volume of the molecule for interaction with the HOMO of an approaching nucleophile. The LUMO orbital lobe that is attacked is color-coded blue. The location, size, and intensity of the blue patches can be used for intermolecular reactivity and selectivity assessments.[54] The largest and darkest blue patches are the more likely sites for nucleophilic attack.

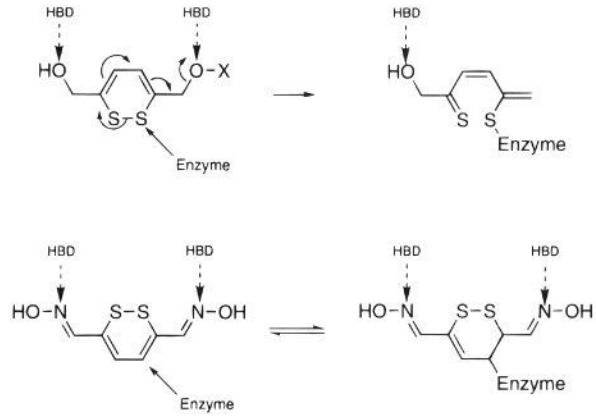


Figure 7. Proposed mechanisms of action for each series (HBD = H-bond donor).

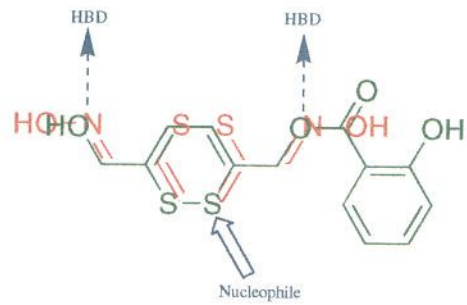


Figure 8. Consensus model.

Examination of the LUMO isoorbital surfaces revealed sharply different LUMO surface patterns between **18i** and **45**, suggestive of a mechanism change for nucleophilic attack between the two series. The isosurface model predicted that nucleophilic attack on **18i** would proceed through the single blue patch located coaxially with the disulfide bond and proximal to the salicylate leaving group presumably leading to disulfide ring opening and covalent attachment. The model predicted that the sulfurs of the disulfide are not equivalent and that attack would be expected to be stereospecific. The isoorbital model for **45** predicted that nucleophilic attack would most likely occur between C-4 and C-5, consistent with a reversible conjugate addition. The location of the patch in the **45** series suggested no preference in conjugate addition to either C-4 or C-5.

The proposed mechanisms of action for both series is shown in Figure 7. Although the biological target for either series is unknown, the target protein active site may have an appropriate nucleophilic functionality or a water molecule capable of attacking the 1,2-dithiin ring when bound. If the nucleophilic functionality were a sulfhydryl as found in cysteine proteases, then pathway 1 amounts to a strain-relief-driven disulfide exchange resulting in covalent attachment and irreversible inhibition.

Figure 8 shows a model for bioactivity that reconciles both proposed mechanisms into a single binding mode consistent with a single biological target. Alignment of the global minimum conformations of **18i** and **45** using the H-bond acceptor side chain interactions and the most likely sites for nucleophilic attack from the isoorbital models results in a qualitative model in which all important interactions can be satisfied. The resulting overlap of the 1,2-dithiin moiety in each series was isosteric in a region of the active site in which large

steric deviations would probably not be tolerated. The model suggested that the target protein may be a protease.

Conclusion

We have presented a novel synthesis of the 1,2-dithiin ring system, specifically dithiins **1d** and **1e**, which is amenable to scale-up at the kilogram level. The process demonstrates the utility of the 2-cyanoethyl functionality as a sulfur protecting group via a β-eliminative approach. Using dithiins **1d** and **1e**, we have presented syntheses of novel 1,2-dithiin ester, ether, thioether, azide, amide, urea, carbamate, aldehyde, oxime, olefin, and nitrile analogues and presented the first structure–activity study involving the 1,2-dithiin class of compounds. We proposed separate SAR and modes of action for the electron-withdrawing group and the leaving group containing 1,2-dithiins. This was consistent with an initial nucleophilic attack on the 1,2-dithiin ring. The location of attack was influenced by changes in the ring electronics depending on the substitutent in positions 3 and 6. The separate models could be combined into a consensus model in which a single active-site nucleophile in the protein target active site needs to be invoked in the proposed mechanisms for each series.

Experimental Section

Tetrahydrofuran (THF) was distilled from potassium/benzophenone; benzene, triethylamine, and methylene chloride were distilled from calcium hydride. Anhydrous dimethylformamide (DMF), anhydrous dimethoxyethane (glyme), and anhydrous pyridine were obtained from Aldrich. *All reactions involving dithiins were done under red light (darkroom!) conditions only.* All moisture-sensitive reactions were done under a nitrogen atmosphere, using dry solvents, and all reactions were monitored by TLC. Reaction mixtures following workup were dried over Na_2SO_4 or $MgSO_4$ and then filtered before rotary evaporation. Evaporation of solvents was done at room temperature unless otherwise noted. The Dess–Martin periodinane reagent was prepared according to the recent procedure reported by Ireland.[46] Bis[[4-(2,2-dimethyl-1,3-dioxolyl)]methyl]carbodiimide (BDDC) was prepared by the procedure of Rapoport.[48] All other reagents were used as received. Flash column chromatography was performed on E. Merck 60 silica gel (230–400 mesh) using nitrogen pressure. TLC was performed on E. Merck Kieselgel 60 F_{254} aluminum plates, and the developed plates were visualized by UV or visible light. ^1H and ^{13}C NMR were recorded on a Varian Unity Plus 400 MHz or a Varian Unity 400 MHz spectrometer with chloroform as an internal reference unless otherwise noted. NMR shifts were expressed in ppm downfield from internal tetramethylsilane, and NMR coupling constants are reported in hertz. NMR assignments were determined on the basis of COSY, NOESY, HMQC, HMBC, and DEPT experiments performed on selected intermediates. Multiplicities for carbons in DEPT experiments are reported in parentheses following the chemical shift value acccording to the following format: quaternary (0), methine (1), methylene (2), and methyl (3). Low-resolution mass spectra were recorded on a Kratos MS50 or a Kratos Profile spectrometer. High-resolution mass spectra were recorded at Shaman Pharmaceuticals on a Kratos MS50 spectrometer or were performed by the Analytical Services Department at the University of California, Berkeley. GCMS analysis was performed on a Hewlett-Packard 5890 Series II gas chromatograph equipped with a 5972 series mass selective detector and an HP-5 30m × 0.25 mm × 0.25 μm column under the following conditions: oven temperature 50 °C, ramp 15 °C/min, final temperature 200 °C, helium gas flow 1.0 mL/min. Elemental analyses were performed by the Analytical Services Department at the University of California, Berkeley. Analytical samples of most 1,2-dithiins were purified by reverse-phase HPLC. Preparative HPLC was performed using a Rainin HPLC equipped with two SD-1 pumps and UV-1 detector, with detection at 254 nm, and using a Hamilton PRP-1 reverse-phase column with an acetonitrile–water solvent gradient. Analytical HPLC was performed on a Rainin HPLC equipped with two SD-1 pumps, a PDA-1 diode array detector, and a Sedex 55 light scattering detector, using a Hamilton PRP-1 reverse-phase column with an acetonitrile–water solvent gradient. Melting points were determined using a Buchi model 535 melting point apparatus and are uncorrected. Molecular modeling was performed in the Molecular Design Studio at BioData, Inc., San Mateo, CA.

2,4-Hexadiyne-1,6-diol (2). To a solution of propargyl alcohol (124.2 g, 2.22 mol) and pyridine (70 mL) in methanol (220 mL) was added CuCl (10.97 g, 0.111 mol). The solution was flushed with O_2 and stirred under positive pressure of O_2 (balloon) for 48 h. The dark green solution was acidified with concentrated HCl (120 mL), diluted with brine (220 mL), and extracted with EtOAc (5 × 600 mL). The organic extracts were washed with water (300 mL) and brine (2 × 250 mL) and dried. After evaporation, the dark brown residue was suspended in a solution of EtOAc–hexane (1:3, 600 mL), filtered, and washed (300 mL) to give 85.49 g (70%) of **2** as a tan solid: mp 111.5–112.5 °C (lit.[55] mp 111–112 °C); ^1H NMR (CD_3OD) δ 4.24 (s, 4H); ^{13}C NMR (CD_3OD) δ 78.87, 69.50, 51.02. Anal. ($C_6H_6O_2$) C, H.

(2-Cyanoethyl)Thiouronium Hydrochloride (6). A heterogeneous suspension of 3-chloropropionitrile (500 g, 5.58 mol) and thiourea (575 g, 7.57 mol) in water (380 mL) was refluxed for 2 h. (The reaction became exothermic at 65 °C when the solution became homogenous.) The mixture was cooled to below 0 °C, and the resultant solid was broken up and washed with cold acetone (7 L) and ether (2 L). The filter cake was dried *in vacuo* to yield 817 g (88%) of salt **6** as white crystals: mp 161.2–162.0 °C; ^1H NMR (D_2O) δ 3.29 (t, J = 6.2, 2H), 2.84 (t, J = 6.2, 2H); ^{13}C NMR (D_2O) δ 169.60, 118.70, 26.14, 17.91. Anal. ($C_4H_8N_3SCl$) C, H, N.

2-Cyanoethyl Mercaptan (7). To a solution of salt **6** (783 g, 4.73 mol) in water (1.2 L) was added NaOH (580 mL, 14.6 M aqueous solution, 6.53 mol). The solution was heated to 45 °C for 45 min, rapidly cooled to 20 °C, and neutralized to pH 6 with cold 6 N H_2SO_4. The mixture was extracted with ether (5 × 1 L), and the combined ether extracts were dried and evaporated. Vacuum distillation [44–56 °C, 0.18 Torr (lit.[36] 57–59 °C, 6 Torr)] afforded 155 g (38%) of **7** as a clear oil which was stored under nitrogen at −78 °C until use: ^1H NMR ($CDCl_3$) δ 2.8–2.7 (m, 2H), 2.67 (t, J = 6.8, 2H), 1.79 (t, J = 8.8, 1H); ^{13}C NMR ($CDCl_3$) δ 118.02, 22.78, 20.51; GCMS (m/z) 87 (M^+); t_R 5.32 min. Anal. (C_3H_5NS) C, H, N.

2,5-Bis[(2-Cyanoethyl)thio]-2,4-hexadiene-1,6-diol (8). To a solution of KOH (16.2 g, 0.289 mol) in water (50 mL) and DMF (600 mL) was added mercaptan **7** (218 g, 2.50 mol). After 15 min, diol **2** (63.7 g, 0.579 mol) was added. The internal temperature was allowed to rise to 45 °C, and then the solution was cooled and stirred at 22 °C for 16 h. Water (1 L) and brine (600 mL) were added, and the mixture was extracted with EtOAc (4 × 1.5 L). The combined organic extracts were dried and evaporated. Chromatography, eluting with EtOAc–hexane (1:1), and then EtOAc, gave 65.2 g of diol **8**. Recrystallization of mixed fractions (residue was dissolved in a minimum of EtOAc at 22 °C and chilled to −25 °C, and hexane was added dropwise) afforded an additional 42.0 g. Total yield of the white solid **8** was 107.2 g (65%): mp 73.9–74.3 °C; ^1H NMR (CD_3OD) δ 7.20 (s, 2H), 4.28 (s, 4H), 3.05 (t, J = 6.8, 4H), 2.73 (t, J = 6.8, 4H); ^{13}C NMR (CD_3OD) δ 138.63, 130.33, 119.77, 66.56 28.56, 19.49. Anal. ($C_{12}H_{16}N_2O_2S_2$) C, H, N.

1-[(*tert*-Butyldimethylsilyl)oxy]-2,5-bis[(2-cyanoethyl)-thio]-2,4-hexadien-6-ol (14). To a solution of diol **8** (30.0 g, 0.106 mol) and imidazole (14.4 g, 0.211 mol) stirring in DMF (500 mL) was added dropwise a solution of *tert*-butyldimethylchlorosilane (17.5 g, 0.83 M solution in DMF, 0.116 mol), and the mixture was stirred for16 h at room temperature. The mixture was diluted with water (500 mL) and brine (1.2 L) and extracted with EtOAc (5 × 600 mL). The combined organic extracts were washed twice with an equivolume amount of water, dried, and concentrated. Purification by flash chromatography, eluting with EtOAc–hexanes (1:1), and then EtOAc, afforded 20.74 g (49.3%) of 14 as a yellow oil: ^1H NMR ($CDCl_3$) δ 7.22 (s, 2H), 4.34 (br s, 4H), 3.05–2.95 (m,

4H), 2.70–2.60 (m, 4H), 2.3 (bt, 1H), 0.94 (s, 9H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 136.64, 136.60, 130.41, 130.27, 118.28, 117.97, 67.25, 66.46, 28.22, 27.58, 25.84, 19.17, 18.92, 18.29, −5.31. Anal. ($C_{18}H_{30}N_2O_2S_2Si$) H, N; C: calcd, 54.2; found, 53.5.

3-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-6-(hydroxymethyl)-1,2-dithiin (1e). To a vigorously stirred solution of compound **14** (11.5 g, 28.9 mmol) in ether (300 mL) was rapidly added potassium *tert*-butoxide (35.4 g, 289 mmol). After 11 min, water (230 mL) and K_3FeCN_6 (182 mL, 0.35 M aqueous solution, 63.6 mmol) were added, and the mixture was stirred for 12 min. Ether (140 mL) was added, and after stirring for 4 min, the mixture was transferred to a separatory funnel where the dark brown aqueous layer was allowed to fully separate from the tan ethereal emulsion. The brown aqueous portion was extracted with ether (2 × 150 mL). The emulsion was patiently extracted with ether (7 × 250 mL) using a sonication bath as necessary to resolve the partition. The total ether extracts were combined, washed with brine, dried, and evaporated. Chromatography, eluting with EtOAc–hexane (7:50), gave 6.41 g (76%) of **1e** as a red oil: ^{1}H NMR ($CDCl_3$) δ 6.34–6.40 (AB q, J = 6.4, 2H), 4.30 (s, 2H), 4.27 (d, J = 6, 2H), 1.97 (t, J = 6, 1H), 0.92 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 135.38, 133.94, 125.31, 123.67, 64.89, 64.68, 25.78, 18.33, −5.38. Anal. ($C_{12}H_{22}O_2SiS_2$) C, H.

1,6-Bis[(*tert*-butyldimethylsilyl)oxy]-2,5-bis[(2-cyanoethyl)thio]-2,4-hexadiene (12). Isolated in 20–25% yield along with hexadiene **14** during monosilylation experiments, or from disilylation of hexadiene **8** using *tert*-butyldimethylsilyl chloride (220 mol %) and imidazole (300 mol %) in DMF: yield 80%; ^{1}H NMR ($CDCl_3$) δ 4.40 (s, 4H), 3.09 (t, J = 8.0, 4H), 2.71 (t, J = 7.6, 4H), 1.01 (s, 18H), 0.21 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 136.33, 129.68, 117.92, 67.22, 28.10, 25.83, 19.04, 18.28, −5.31; MS (EI, m/z) 512.0 (M^+).

3,6-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1,2-dithiin (13). To a solution of diene **12** (14.4 g, 28.13 mmol) in ether (300 mL) was added potassium *tert*-butoxide (19.93 g, 168.75 mmol) as fast as possible, and the heterogeneous mixture was stirred mechanically for 10 min, followed by addition of ice-cold H_2O (230 mL). To this suspension was added $K_3Fe(CN)_6$ (21.29 g, 64.68 mmol), and stirring was continued for 11 min. The mixture was then diluted with ether (140 mL), stirred for another 4 min, and transferred to a separatory funnel. The mixture was allowed to sit for 5 min before the layers were separated, the emulsion part being taken into the organic layer. The aqueous layer was back-extracted with ether (1×). To crack the emulsion, an ultrasonic bath was used. The combined organics were washed with H_2O and brine, dried, and evaporated. Chromatography, eluting with hexane–CH_2Cl_2 (2:1), gave 6.88 g (60%) of dithiin **13** as a light-yellow oil, which solidified at −10 °C; R_f 0.40 hexane–CH_2Cl_2 (2:1); ^{1}H NMR ($CDCl_3$) δ 6.36 (s, 2H), 4.29 (s, 4H), 0.92 (s, 18H), 0.11 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 134.2, 123.7, 64.9, 25.7, 18.3, −5.4; MS (EI, m/z) 404 (M^+), 315 (100).

3,6-Bis(hydroxymethyl)-1,2-dithiin (1d). Procedure A. To a solution of dithiin **13** (620 mg, 1.53 mmol) in THF (40 mL) at 0 °C was added a previously prepared mixture of tetrabutylammonium fluoride (TBAF, 10.46 mL, 10.46 mmol; 1 M in THF) and acetic acid (6.01 mL) at 0 °C via syringe. The mixture was stirred at 0 °C for 1 h and then at room temperature for 3 h. Upon completion (TLC), the mixture was concentrated to a small volume (5 mL) and then partitioned between H_2O (20 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organics were washed with $NaHCO_3$ (3% solution) and brine, dried, and evaporated. Chromatography, eluting with hexane–EtOAc (1:1), gave 156 mg (58%) of dithiin **1d** as a light-yellow powder: mp 70.1–71.1 °C (lit.[30,34] mp 64–66 °C); R_f 0.13 hexane–EtOAc (1:1); ^{1}H NMR (DMSO-d_6) δ 6.36 (s, 2H), 5.36 (t, J = 6.0, 2H), 4.07 (d, J = 6.0, 4H); MS (EI, m/z) 176 (M^+), 144 ($M - S^+$), 113 ($M - S - CH_2OH^+$). **Procedure B.** To a stirred solution of **8** (1.00 g, 3.52 mmol) in 100 mL of dry ether was added 3.95 g (35.2 mmol) of solid potassium *tert*-butoxide. The resulting suspension was stirred for 5 min, and then water (70 mL) was added. The reaction mixture was treated with a solution of K_3FeCN_6 (2.55 g; 7.74 mmol) in 30 mL of water. The reaction mixture was extracted with ether (5 × 100 mL), dried, and concentrated. Purification by chromatography using EtOAc–hexane (1:1) gave 204 mg (33%) of dithiin **1d**: ^{1}H NMR ($CDCl_3$) δ 6.41 (s, 2H), 4.30 (d, J = 6.0, 4H), 1.79 (t, J = 6.0, 2H); ^{13}C NMR ($CDCl_3$) δ 134.89 (0), 125.15 (1), 64.61 (2). Anal. ($C_6H_8O_2S_2$) C, H.

3,6-Bis[(acetyloxy)methyl]-1,2-dithiin (17a). To a stirred solution of dithiin **1d** (600 mg, 3.40 mmol) in pyridine (15 mL) was added dropwise acetic anhydride (2.0 mL, 1000 mol %). After stirring overnight the mixture was diluted with ether (200 mL) and partitioned between ether (50 mL) and 3.0 M H_3PO_4 (200 mL). The ether layer was washed with 3.0 M H_3PO_4 (200 mL) and saturated $NaHCO_3$ (200 mL), dried, and then concentrated. Purification by chromatography, eluting with ether–hexane (1:3), afforded 870 mg (97%) of dithiin **17a** as a red oil: ^{1}H NMR ($CDCl_3$) δ 6.38 (s, 2H), 4.70 (s, 4H), 2.10 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 170.37, 130.48, 127.75, 65.19, 20.77; MS (EI, m/z) 260.0 (M^+); HRMS (EI) calcd for $C_{10}H_{12}O_4S_2$ 260.0177, found 260.0176. Anal. ($C_{10}H_{12}O_4S_2$) C, H.

3,6-Bis[(propionyloxy)methyl]-1,2-dithiin (17b). To a stirred solution of dithiin **1d** (20 mg, 0.113 mmol) and triethylamine (0.30 mL, 2.15 mmol, 1900 mol %) in THF (2.0 mL) was added dropwise excess propionyl chloride dropwise until a heavy precipitate formed. To this mixture was added 1.0 M H_3PO_4 (20 mL), and the mixture was extracted with ether (2 × 20 mL). The combined ether extracts were washed with saturated $NaHCO_3$ (100 mL), dried, and then concentrated. Purification by chromatography, eluting with ether–hexane (1:3), afforded 22.2 mg (68%) of dithiin **17b** as a red oil: ^{1}H NMR ($CDCl_3$) δ 6.38 (s, 2H), 4.72 (s, 4H), 2.39 (q, J = 7.2, 4H), 1.16 (t, J = 7.2, 6H); ^{13}C NMR ($CDCl_3$) δ 173.80, 130.64, 127.61, 65.07, 27.38, 9.00; MS (EI, m/z) 288.0 (M^+); HRMS calcd for $C_{12}H_{16}O_4S_2$ 288.0490, found 288.0485. Anal. ($C_{12}H_{16}O_4S_2$) C, H.

3,6-Bis[(isobutyryloxy)methyl]-1,2-dithiin (17c). To a stirred solution of isobutyric anhydride (0.2 mL, 1000 mol %) in pyridine (2.0 mL) was added in one portion solid dithiin **1d** (20 mg, 0.113 mmol). After stirring at room temperature overnight, the mixture was partitioned between 3.0 M H_3PO_4 (80 mL) and ether (30 mL). The separated ether layer was washed with saturated $NaHCO_3$ (100 mL), dried, and then concentrated. Purification by chromatography, eluting with ether–hexane (1:3), gave 32 mg (89.5%) of dithiin **17c** as a red oil; ^{1}H NMR ($CDCl_3$) δ 6.37 (s, 2H), 4.71 (s, 4H), 2.60 (m, 2H), 1.19 (d, J = 6.8, 6H); ^{13}C NMR ($CDCl_3$) δ 176.39 (0), 130.72 (0), 127.45 (1), 65.00 (2), 33.91 (1), 18.87 (3); MS (EI, m/z) 316.1 (M^+); HRMS (EI) calcd for $C_{14}H_{20}O_4S_2$ 316.0803, found 316.0816. Anal. ($C_{14}H_{20}O_4S_2$) C, H.

3,6-Bis[[(cyclopropylcarbonyl)oxy]methyl]-1,2-dithiin (17d). To a stirred solution of triethylamine (0.30 mL, 2.15 mmol, 1900 mol %) in THF (2.0 mL) at 0 °C was added dropwise cyclopropanecarbonyl chloride (0.10 mL, 1.10 mmol, 975 mol %), followed by the addition of a solution of dithiin **1d** (20 mg, 0.113 mmol) in THF (1.0 mL). After stirring at room temperature overnight the mixture was diluted with ether (20 mL) and partitioned between 1.0 M H_3PO_4 (80 mL) and ether (30 mL). The ether layer was washed with saturated $NaHCO_3$ (100 mL), dried, and then concentrated. Purification by chromatography, eluting with ether–hexane (1:3), afforded 31.5 mg (89.2%) of dithiin **17d** as a reddish-orange oil: ^{1}H NMR ($CDCl_3$) δ 6.40 (s, 2H), 4.72 (s, 4H), 1.70–1.62 (m, 2H), 1.05–1.01 (m, 4H), 0.94–0.88 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 174.28, 130.59, 127.57, 65.20, 12.76, 8.84; MS (EI, m/z) 312.1 (M^+); HRMS (EI) calcd for $C_{14}H_{16}O_4S_2$ 312.0490, found 312.0499. Anal. ($C_{14}H_{16}O_4S_2$) C, H.

3,6-Bis[(benzoyloxy)methyl]-1,2-dithiin (17e). To a stirred solution of dithiin **1d** (20 mg, 0.113 mmol) in pyridine (1.0 mL) was added in one portion benzoyl chloride (0.13 mL, 991 mol %). After stirring at room temperature overnight the mixture was diluted with ether (10 mL) and partitioned between 1.0 M H_3PO_4 (20 mL) and ether (5 mL). The ether layer was washed with saturated $NaHCO_3$ (20 mL), dried, and then concentrated. Purification by chromatography, eluting with ether–hexane (1:3), afforded 40.1 mg (89.2%) of dithiin **17e** as a red oil: ^{1}H NMR ($CDCl_3$) δ 8.07 (d, J = 7.6, 4H), 7.59 (t, J = 7.2, 2H), 7.46 (t, J = 7.6, 4H), 6.50 (s, 2H), 4.98 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 165.91 (0), 133.37, 130.63 (0), 129.78, 129.42 (0), 128.55, 127.70, 65.65; MS (EI, m/z) (M^+).

3,6-Bis[[(4-pyridylcarbonyl)oxy]methyl]-1,2-dithiin (17f). To a heterogeneous mixture of isonicotinoyl chloride hydrochloride (202 mg, 1.13 mmol) in THF (5 mL) was added triethylamine (500 μL, 363 mg, 3.59 mmol) and then 20 mg (0.113 mmol) of dithiin **1d**. After 8 h, the reaction mixture was partitioned between 1 M aqueous H_3PO_4 (50 mL) and CH_2Cl_2 (80 mL). The layers were separated, and the organic phase was washed with a 10% aqueous solution of $NaHCO_3$ and water, then dried, and concentrated. Purification by chromatography, eluting with ether, gave 27 mg (62.8%) of the bis(isonicotinyl) ester **17f**: ^1H NMR ($CDCl_3$) δ 8.82 (d, J = 4.8, 4H), 7.88 (d, J = 4.4, 4H), 6.52 (s, 2H), 5.02 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 164.53, 150.75, 136.1, 130.33, 128.34, 122.89, 66.25; MS (EI, m/z) 386 (M^+); HRMS (EI) calcd for $C_{18}H_{14}N_2O_4S_2$ 386.0395, found 386.0393.

3,6-Bis[[(3-pyridylcarbonyl)oxy]methyl]-1,2-dithiin (17g). To a heterogeneous mixture of nicotinoyl chloride hydrochloride (303 mg, 1.70 mmol) in THF (7.5 mL) at −35 °C was injected 750 μL (0.545 mg, 5.38 mmol) of Et_3N to give a cloudy solution. Next, dithiin **1d** (30 mg, 0.17 mmol) was added. The bath temperature was kept at −35 °C to −40 °C with a dry ice−CH_3CN bath, and the reaction mixture was stirred for 3 h, after which time TLC showed that the starting material had been consumed. The reaction mixture was partitioned between CH_2Cl_2 (80 mL) and 1 M aqueous H_3PO_4 (80 mL). The water layer was extracted with CH_2Cl_2 (2 × 40 mL), and the combined CH_2Cl_2 extracts were washed sequentially with $NaHCO_3$ (10% aqueous solution) and water (40 mL). The organic phase was dried, concentrated, then purified by chromatography, eluting with EtOAc−hexane (1:1), and then EtOAc, to give 30 mg (38%) of diester **17g**: ^1H NMR ($CDCl_3$) δ 9.26 (s, 2H), 8.81 (dd, J = 5.2, 2.0, 2H), 8.32 (d, J = 7.6, 2H), 7.42 (dd, J = 7.6, 4.8, 2H), 6.52 (s, 2H), 5.01 (s, 4H); MS (EI, m/z) 386.0 (M^+).

3,6-Bis[[(cyclopentylcarbonyl)oxy]methyl]-1,2-dithiin (17h). To a stirred solution of triethylamine (700 μL, 502 mg, 5.02 mmol) in THF (5 mL) at 0 °C was added cyclopentanecarbonyl chloride (250 μL, 272 mg, 2.06 mmol) followed by addition of dithiin **1d** (32 mg, 0.18 mmol). After 5 min, TLC showed the reaction to be complete. The reaction mixture was partitioned between 1 M aqueous H_3PO_4 (50 mL) and ether (80 mL). The organic phase was washed sequentially with a 10% aqueous solution of $NaHCO_3$ and water and then dried. The organic phase was concentrated and the residue was purified on silica gel, eluting with ether−hexane (1:3), to give 43 mg (64.3%) of dithiin diester **17h**: ^1H NMR ($CDCl_3$) δ 6.37 (s, 2H), 4.71 (s, 4H), 2.78 (m, 2H), 1.89−1.58 (m, 16H); ^{13}C NMR ($CDCl_3$) δ 176.07, 130.71, 127.45, 65.03, 43.60, 29.95, 25.77; MS (EI, m/z) 367.2 (M − H); HRMS (EI) calcd for $C_{18}H_{24}O_4S_2$ 368.1116, found 368.1106.

3,6-Bis[[(2-hydroxybenzoyl)oxy]methyl]-1,2-dithiin (17i) and 3-[[(2-hydroxybenzoyl)oxy]methyl]-6-(hydroxymethyl)-1,2-dithiin (18i). To a stirred solution of dithiin **1d** (3.5 g, 20 mmol) in CH_2Cl_2 (200 mL) and ethyl acetate (50 mL) were added salicylic acid (2.74 g, 19.8 mmol) and 4.50 g (21.8 mmol) of dicyclohexylcarbodiimide (DCC). The reaction mixture was stirred at room temperature for 14 h. TLC showed two new products, along with starting material. The TLC did not change after an additional 10 h of reaction time. The reaction mixture was evaporated to a small volume and purified by chromatography, eluting with EtOAc−hexane (1:3), to give 40 mg (10.6%) of diester **17i**: ^1H NMR ($CDCl_3$) δ 7.88 (d, J = 6.8, 2H), 7.49 (t, J = 7.2, 2H), 7.00 (d, J = 8.4, 2H), 6.91 (t, J = 7.6, 2H), 6.52 (s, 2H), 5.00 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 169.35, 161.82, 136.12, 130.35, 129.95, 128.07, 119.31, 117.69, 111.86, 65.60; MS (EI, m/z) 416 (M^+). Continued elution afforded 1.68 g (28.4%) of the monosalicylate ester **18i**: mp 56−58 °C; ^1H NMR ($CDCl_3$) δ 10.57 (s, 1H), 7.88 (d, J = 8.0, 1H), 7.49 (t, J = 8.8, 1H), 6.99 (d, J = 8.8, 1H), 6.91 (t, J = 7.6, 1H), 6.49 (d, J = 5.6, 1H), 6.42 (d, J = 5.6, 1H), 4.99 (s, 2H), 4.30 (s, 2H), 2.08 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 169.47, 161.72, 136.76, 136.13, 130.01, 128.58, 128.39, 124.75, 119.36, 117.65, 111.90, 65.91, 64.41; MS (LSIMS, m/z) 296.0 (M^+). Finally, continued elution afforded unreacted dithiin **1d** (2.0 g, 57.1%). The yield of diester could be improved to 14.1% when 220 mol % salicylic acid and 220 mol % CDI were used, with stirring at room temperature for 3 d. The use of 110 mol % of carbonyldiimidazole (CDI) instead of DCC above gave an 18.6% yield of **18i**. Anal. for **18i** ($C_{13}H_{12}O_4S_2$) C, H, S.

3-[(Acetyloxy)methyl]-6-(hydroxymethyl)-1,2-dithiin (18a). To a solution of acetic anhydride (150 μL, 160 mg, 110 mol %) and anhydrous pyridine (20 mL), cooled to 0 °C, was added dithiin **1d** (250 mg,1.42 mmol). The reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was warmed to 10 °C for 2 h then stored in a cold room (5 °C) overnight. The reaction mixture was poured into a mixture of ice-cold 1 M aqueous H_3PO_4 (200 mL) and Et_2O (200 mL). The organic layer was washed with saturated $NaHCO_3$ (250 mL), washed with H_2O (100 mL), dried, and evaporated to an orange oil which was purified by chromatography, eluting with EtOAc−hexane (1:3), to give 74 mg (24%) of the monoacetate **18a**; ^1H NMR ($CDCl_3$) δ 6.40 (s, 2H), 4.71 (s, 2H), 4.29 (d, J = 4.8, 2H), 2.12 (s, 3H), 1.85 (bt, 1H); ^{13}C NMR ($CDCl_3$) δ 170.48, 136.21, 129.18, 128.11, 124.82, 65.40, 64.49, 20.80; MS (EI, m/z) 218 (M^+). Also isolated were diacetate dithiin **17a** (66 mg, 21.3%) and unreacted dithiin **1d** (50 mg, 16%).

3,6-Bis[[(cyclopropylcarbonyl)oxy]methyl]-1,2-dithiin (17d) and 3-[(cyclopropylcarbonyl)oxy]methyl]-6-(hydroxymethyl)-1,2-dithiin (18d). To a stirred solution of dithiin **1d** (2.02 g, 11.5 mmol) in dry THF (100 mL), at −7 °C was added triethylamine (2.0 mL, 1.45 g, 14.3 mmol), followed by 1.0 mL (1.15 g, 11.0 mmol) of cyclopropanecarbonyl chloride. The reaction mixture was allowed to warm to room temperature overnight and then poured into a vigorously stirred, cold mixture of ether (100 mL) and 1 M aqueous H_3PO_4 (50 mL). The layers were separated, and the aqueous phase was extracted with ether (2 × 100 mL). The combined ether phases were washed with 10% aqueous Na_2CO_3 (100 mL) and brine (2 × 50 mL), dried, and then concentrated, yielding 2.85 g of a red-orange oil. Purification by chromatography, eluting with EtOAc−hexane (1:3) and then EtOAc−hexane (1:1), afforded 1.17 g (33%) of diester **17d** as a reddish-yellow oil: ^1H NMR ($CDCl_3$) δ 6.38 (s, 2H), 4.72 (s, 4H), 1.70−1.62 (m, 2H), 1.05−1.01 (m, 4H), 0.94−0.88 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 174.27, 130.57, 127.58, 65.21, 12.77, 8.86. Anal. for **17d** ($C_{14}H_{16}O_4S_2$) C, H. Continued elution afforded 1.16 g (41%) of the monocyclopropyl ester **18d** as a reddish-orange solid: ^1H NMR ($CDCl_3$) δ 6.39 (s, 2H), 4.72 (s, 2H) 4.28 (d, J = 6, 2H), 1.98 (t, J = 6, 1H) 1.69−1.63 (m, 1H), 1.06−1.02 (m, 2H), 0.93−0.88 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 174.41, 136.11, 129.34, 127.92, 124.84, 65.40, 64.50, 12.80, 8.86; HRMS (EI) calcd for $C_{10}H_{12}O_3S_2$ 244.0228, found 244.0219. Further elution afforded unreacted dithiin **1d** (358 mg, 18%).

3-[(Benzoyloxy)methyl]-6-(hydroxymethyl)-1,2-dithiin (18e). A solution of triethylamine (2.0 mL, 14.3 mmol) in THF (5 mL) was cooled to −10 °C, and benzoyl chloride (0.10 g, 0.71 mmol) was added. Diol **1e** (200 mg, 0.69 mmol) was introduced in one portion, and the mixture was stirred at −10 to −5 °C for 1 h. The reaction mixture was partitioned between ether and cold 1 M H_3PO_4. The separated organic layer was washed with water, dried, and concentrated. Purification by chromatography, eluting with EtOAc−hexane (1:3), gave 0.25 g (92.5%) of dithiin **17e** as an oil. Desilylation of dithiin **17e** (250 mg, 0.63 mmol) according to procedure B gave 94 mg (53.4%) of dithiin **18e** as an orange-yellow oil: ^1H NMR ($CDCl_3$) δ 8.08−8.05 (m, 2H), 7.57 (dd, J = 7.2, 8.0, 1H), 7.48−7.39 (m, 2H), 6.47 (d, J = 6.0, 1H), 6.40 (d, J = 6.0, 1H), 4.96 (s, 2H), 4.28 (s, 2H), 2.2 (bs, 1H); MS (EI) 280.0 (M^+).

3-[[(4-Pyridylcarbonyl)oxy]methyl]-6-(hydroxymethyl)-1,2-dithiin (18f). To a mixture of isonicotinyl chloride hydrochloride (202 mg, 1.13 mmol) in THF (5 mL) was added triethylamine (0.5 mL), and the mixture was cooled to −45 °C. Diol **1d** (20 mg, 0.113 mmol) was added at −45 °C, and the mixture was stirred for 7 h. The reaction mixture diluted with 1 M H_3PO_4 (50 mL), extracted with CH_2Cl_2 (3 × 50 mL), washed with 5% $NaHCO_3$ (50 mL) and water (50 mL), then dried, and concentrated. Purification by chromatography, eluting with ether−hexane (1:3), gave 13 mg (29.6%) of diester **17f**: ^1H NMR ($CDCl_3$) δ 8.82 (d, J = 4.8, 4H), 7.88 (d, J = 4.4, 4H), 6.52 (s, 2H), 5.02 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 164.53, 150.75, 136.1, 130.33, 128.34, 122.89, 66.25; MS (EI, m/z) 386 (M^+). Further elution gave 6 mg (18.8%) of monoester **18f**: ^1H NMR ($CDCl_3$) δ 8.80 (d, J = 5.2, 2H), 7.87 (d, J = 5.2, 2H),

6.50 (d, J = 6.0, 1H), 6.43 (d, J = 6.0, 1H), 5.00 (s, 2H), 4.31 (s, 2H); ^{13}C NMR ($CDCl_3$; one quaternary carbon missing) δ 164.57, 150.68, 134.61, 128.85, 128.28, 124.68, 122.91, 66.55, 64.44; MS (EI) 281 (M^+).

3-[[(Cyclopentylcarbonyl)oxy]methyl]-6-(hydroxymethyl)-1,2-dithiin (18h). To a stirred solution of triethylamine (0.35 mL, 500 mol %) in 5 mL of THF, cooled to −45 °C, was added cyclopentanecarbonyl chloride (25 μL, 120 mol %), followed by the addition of dithiin **1d** (30 mg, 0.17 mmol). After 5 min, the reaction mixture was partitioned between 1 M aqueous H_3PO_4 (50 mL) and ether (80 mL). The layers were separated, and the organic phase was washed with 10% aqueous $NaHCO_3$ and water, dried, and concentrated. Purification by chromatography, eluting with ether−hexane (1:3), gave 25 mg (39.9%) of diester **17h**. Continued elution afforded 10 mg (21.6%) of the monoester dithiin **18h**: ^{1}H NMR ($CDCl_3$) δ 6.40 (s, 2H), 4.73 (s, 2H), 4.30 (d, J = 4.4, 2H), 2.80 (m, 1H), 1.89−1.61 (m, 8H); ^{13}C NMR ($CDCl_3$) (9 of 10 expected signals observed) δ 136.03, 129.61, 127.79, 124.88, 65.20, 64.53, 43.64, 29.97, 25.79; MS (EI, m/z) 272.0 (M^+); HRMS (EI) calcd for $C_{12}H_{16}O_3S_2$ 272.0509, found 272.0532.

General Procedure for the Preparation of Protected Aromatic Dithiin Ethers (19). General Procedure A. To a stirred solution of dithiin **1e** (100 mol %) in dry THF (0.34−0.8 M) was added a solution of the appropriate phenol (150 mol %) in THF (0.4−1.2 M), followed by the addition of triphenylphosphine (122 mol %). The solution was cooled to 0 °C, and then diethyl azodicarboxylate (DEAD, 125−130 mol %) was added. The reaction mixture was kept at 0 °C for n hours or warmed up to room temperature. After disappearance of dithiin **1e** by TLC, the reaction mixture was directly applied to a silica gel column and purified using an EtOAc−hexane eluent to provide dithiin ether **19**.

General Procedure for Desilylation of TBDMS-Protected Aromatic Dithiin Ethers (19). General Procedure B. A stirred solution of dithiin **19** (100 mol %) in THF (0.2−0.3 M) was treated with a premixed solution of tetrabutylammonium fluoride (TBAF, 800−1250 mol % of a 1 M solution in THF) and acetic acid (1.75−2:1, v/v, 1 M TBAF/HOAc) at room temperature. The mixture was stirred until dithiin **19** was consumed by TLC (1−4 h). The solvent was concentrated, and the residue was partitioned between water (40 mL) and EtOAc (60 mL). The organic phase was washed with dilute aqueous $NaHCO_3$ (50 mL) and water (50 mL), dried (Na_2SO_4), and concentrated to a small volume. Purification was done by chromatography, eluting with an EtOAc−hexane eluent to give dithiin **20**.

Desilylation of TBDMS-Protected Aromatic Dithiin Ethers (19). General Procedure C. Dithiin **19** (0.5−1 mmol, 100 mol %) was dissolved in acetonitrile (0.2−0.3 M) and cooled to 0 °C. A premixed solution of aqueous HF (1 mL) and acetonitrile (3 mL) was added, and the solution was stirred for 45−60 min in an ice bath. The reaction mixture was neutralized with aqueous 10% K_2CO_3 until evolution of CO_2 ceased (ca. 25 mL). This solution was diluted with saturated NaCl (25 mL) and extracted with EtOAc (2 × 50 mL). The combined EtOAc layers were washed with saturated aqueous NaCl (2 × 50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification of the residue by chromatography using an EtOAc−hexane eluent gave dithiin **20**.

1-[(*tert*-Butyldimethylsilyl)oxy]-2-hydroxybenzene. To a stirred solution of catechol (5.5 g, 50 mmol) in DMF (20 mL) was added imidazole (7.14 g, 105 mmol) and *tert*-butyldimethylsilyl chloride (7.53 g, 50 mmol). The reaction mixture was stirred for 3 h. The reaction mixture was applied directly onto silica gel, eluting with EtOAc−hexane (1:20), to give 7.4 g (66%) of the monosilyl catechol: ^{1}H NMR ($CDCl_3$) δ 6.96 (dd, J = 8.0, 1.6, 1H), 6.89 (dt, J = 8.0, 2.0, 1H), 6.85 (dd, J = 8.0, 1.6, 1H), 6.77 (dt, J = 7.6, 1.6, 1H), 5.52 (s, 1H), 0.99 (s, 9H), 0.252 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 1 47.25, 142.55, 122.14, 119.99, 117.83, 114.87, 25.73, 18.19, −4.32; MS (EI, m/z) 224.1 (M^+).

3-(Hydroxymethyl)-6-[[(2-hydroxyphenyl)oxy]methyl]-1,2-dithiin (20a). Treatment of dithiin **1e** (200 mg, 0.688 mmol) with 1-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxybenzene (310 mg, 1.38 mmol), triphenylphosphine (220 mg, 0.839 mmol), and DEAD (140 μL, 0.89 mmol) at 5 °C (3 h) according to procedure A gave 213 mg (62.3%) of dithiin **19a**, eluent EtOAc−hexane (1:6): ^{1}H NMR ($CDCl_3$) δ 6.86−6.82 (m, 4H), 6.41 (d, J = 6.4, 1H), 6.32 (d, J = 5.6, 1H), 4.61 (s, 2H), 4.26 (s, 2H), 0.98 (s, 9H), 0.89 (s, 9H), 0.15 (s, 6H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 149.51, 145.63, 135.94, 129.38, 127.09, 123.50, 122.13, 121.69, 121.28, 115.25, 70.76, 64.83, 25.78, 25.75, 18.32, −4.51, −5.39; MS (LSIMS, m/z) 496.4 (M^+), 273.2 (100). Desilylation of dithiin **19a** (150 mg, 0.302 mmol) according to procedure B gave 50 mg (62%) dithiin **20a**, mp 89.7−91 °C, eluent EtOAc−hexane (1:3): ^{1}H NMR ($CDCl_3$) δ 6.99−6.82 (m, 4H), 6.43 (AB q, J = 6.4, 2H), 5.67 (s, 1H), 4.78 (s, 2H), 4.31 (d, J = 4.8, 2H), 1.80 (bt, J = 6.0, 1H); ^{13}C NMR ($CDCl_3$) δ 146.14, 144.99, 136.27, 129.77, 127.61, 124.81, 122.73, 120.21, 115.22, 113.09, 70.89, 64.52; MS (LSIMS, m/z) 268.0 (M^+); HRMS (EI) calcd for $C_{12}H_{12}O_3S_2$ 268.0228, found 268.0219. Anal. ($C_{12}H_{12}O_3S_2$) C, H.

3-(Hydroxymethyl)-6-[(phenyloxy)methyl]-1,2-dithiin (20b). Treatment of dithiin **1e** (200 mg, 0.688 mmol) with phenol (150 mg, 1.59 mmol), triphenylphosphine (220 mg, 0.839 mmol), and DEAD (144 mg, 0.827 mmol) at 5 °C (3.5 h) according to procedure A gave 250 mg of dithiin **19b**, eluent EtOAc−hexane (1:7). Desilylation according to procedure C gave dithiin 44.2 mg (25.4%) of **20b** as an orange oil, eluent EtOAc−hexane (1:2): ^{1}H NMR (CD_3OD) δ 7.26 (dd, J = 7.60, 7.60, 3H), 6.93 (dd, J = 7.60, 0.80, 2H), 6.47 (d, J = 6.40, 1H), 6.38 (d, J = 6.40, 1H), 4.68 (s, 2H), 4.18 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 159.61, 137.75, 131.16, 130.53, 128.41, 125.53, 122.48, 116.17, 70.87, 64.78; MS (LSIMS, m/z) 252.0 (M^+); HRMS (EI) calcd for $C_{12}H_{12}O_2S_2$ 252.0278, found 252.0277.

3-(Hydroxymethyl)-6-[[(2-carbomethoxyphenyl)oxy]methyl]-1,2-dithiin (20c). Treatment of dithiin **1e** (216 mg, 0.744 mmol) with methyl salicylate (200 μL, 235 mg, 1.54 mmol), triphenylphosphine (240 mg, 1.09 mmol), and DEAD (144 mg, 0.827 mmol) at 5 °C to room temperature (5.5 h) according to procedure A gave 265 mg of dithiin **19c**, eluent EtOAc−hexane (1:7). Desilylation of **19c** (265 mg) according to procedure C gave 64.3 mg (28%) of **20c** as an orange oil: ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J = 7.6, 1H), 7.48 (t, J = 7.6, 1H), 7.08 (d, J = 8.8, 1H), 7.03 (t, J = 8.0, 1H), 6.56 (d, J = 5.6, 1H), 6.41 (d, J = 6.0, 1H), 4.76 (s, 2H), 4.19 (s, 2H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.59, 158.79, 138.02, 134.77, 132.53, 130.32, 128.52, 125.55, 122.25, 116.01, 115.54, 71.61, 64.81, 52.63; MS (LSIMS) 310 (M^+); HRMS (EI) calcd for $C_{14}H_{14}O_4S_2$ 310.0334, found 310.0355.

3-(Hydroxymethyl)-6-[(pyrid-2-yloxy)methyl]-1,2-dithiin (20d) and 3-(Hydroxymethyl)-6-[(2-oxopyrid-1-yl)methyl]-1,2-dithiin (22d). Treatment of dithiin **1e** (200 mg, 0.688 mmol) with 2-hydroxypyridine (132 mg, 1.38 mmol), triphenylphosphine (220 mg, 0.839), and DEAD (140 μL, 155 mg, 0.827 mmol) at 5 °C (2 h) according to procedure A gave 45 mg (17.8%) of dithiin **19d**, eluent EtOAc−hexane (1:6): ^{1}H NMR ($CDCl_3$) δ 8.14 (d, J = 3.6, 1H), 7.58 (t, J = 7.2, 1H), 6.89 (t, J = 6.0, 1H), 6.79 (d, J = 8.4, 1H), 6.48 (d, J = 5.6, 1H), 6.36 (d, J = 6.4, 1H), 4.98 (s, 2H), 4.29 (s, 2H), 0.91 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$; one quaternary carbon missing) δ 146.63, 138.73, 135.97, 130.18, 127.51, 123.54, 117.22, 111.17, 67.01, 64.82, 25.76, 18.30, −5.42; MS (LSIMS, m/z) 367.2 (M^+). Further elution with EtOAc−hexane (1:3) provided pyridone **21d** (137 mg, 72.2%): ^{1}H NMR ($CDCl_3$) δ 7.39 (d, J = 6.81, 1H), 7.34 (t, J = 7.6, 1H), 6.59 (d, J = 8.8, 1H), 6.34 (s, 2H), 6.21 (t, J = 6.4, 1H), 4.72 (s, 2H), 4.27 (s, 2H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 164.15, 139.68, 136.74, 136.37, 128.85, 128.53, 123.63, 121.13, 106.24, 64.75, 51.89, 25.74, 18.28, −5.44; MS (LSIMS, m/z) 367.2 (M^+). Both **19d** and **21d** were used separately for their subsequent desilylation reactions. Desilylation of dithiin **19d** (40 mg, 0.10 mmol) according to procedure B gave 20 mg (72%) of dithiin **20d**, eluent EtOAc−hexane (1:3): ^{1}H NMR (CD_3OD) δ 8.11 (d, J = 4.8, 1H), 7.69 (t, J = 6.8, 1H), 6.96 (t, J = 6.2, 1H), 6.83 (d, J = 8.4, 1H), 6.50 (d, J = 6.4, 1H), 6.39 (d, J = 5.6, 1H), 4.88 (s, 2H), 4.18 (s, 2H); ^{13}C NMR (CD_3OD) δ 164.36, 147.75, 140.51, 137.91, 131.53, 128.88, 125.57, 118.63, 112.08, 68.15, 64.79; MS (EI, m/z) 253.0 (M^+); IR ($CHCl_3$) 1598, 1570 cm^{-1}. HRMS (EI) calcd for $C_{11}H_{11}NO_2S_2$ 253.0231, found 253.0232. Desilylation of dithiin **21d** (130 mg, 0.35 mmol) according to procedure B gave 52 mg (58%) of dithiin **22d**, eluent EtOAc: ^{1}H NMR (CD_3OD) δ 7.68 (d, J = 6.8, 1H), 7.55

(dt, J = 7.2, 1.6, 1H), 6.56 (d, J = 8.9, 1H), 6.43–6.37 (m, 3H), 4.70 (s, 2H), 4.17 (s, 2H); ^{13}C NMR (CD_3OD) δ 164.67, 142.49, 139.41, 138.16, 130.49, 129.96, 125.64, 120.87, 108.74, 64.71, 53.04; MS (LSIMS, m/z) 254.0 (MH^+); IR ($CHCl_3$) 1654 (C=O), 1575, 1538 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{11}NO_2S_2$ 253.0231, found 253.0225.

3-(Hydroxymethyl)-6-[(pyrid-3-yloxy)methyl]-1,2-dithiin (20e). Treatment of dithiin **1e** (200 mg, 0.69 mmol) with 3-hydroxypyridine (132 mg, 1.376 mmol), triphenylphosphine (220 mg, 0.84 mmol), and DEAD (155 mg, 0.89 mmol) at 0–5 °C (2 h) according to procedure A gave 46 mg (18%) of dithiin **19e**, eluent EtOAc–hexane (1:3): ^{1}H NMR ($CDCl_3$) δ 8.36 (s, 1H), 8.26 (d, J = 2.0, 1H), 7.23 (d, J = 2.4, 2H), 6.45 (d, J = 4.8, 1H), 6.38 (d, J = 4.8, 1H), 4.72 (s, 2H), 4.30 (s, 2H), 0.92 (s, 9H), 0.10 (s, 6H); MS (LSIMS) 367.2 (M^+). Desilylation according to procedure B gave 21 mg (76%) of dithiin **20e** as yellow crystals, eluent EtOAc–hexane (1:2): mp 97–98 °C; ^{1}H NMR (CD_3OD) δ 8.28 (d, J = 2.4, 1H), 8.16 (dd, J = 6.0, 1.2, 1H), 7.49–7.46 (m, 1H), 7.38 (dd, J = 8.4, 8.8, 1H), 6.54 (d, J = 6.4, 1H), 6.41 (d, J = 6.4, 1H), 4.82 (s, 2H), 4.19 (s, 2H); ^{13}C NMR (CD_3OD) δ 168.40, 156.32, 142.96, 139.01, 138.56, 129.43, 125.77, 125.35, 124.08, 71.23, 64.68; MS (LSIMS, m/z) 253.1 (M^+); HRMS (EI) calcd for $C_{11}H_{11}NO_2S_2$ 253.0231, found 253.0239. Anal. ($C_{11}H_{11}NO_2S_2$) C, H.

3-(Hydroxymethyl)-6-[[(3-hydroxyphenyl)oxy]methyl]-1,2-dithiin (20g). Treatment of dithiin **1e** (200 mg, 0.688 mmol) with 3-[(*tert*-butyldimethylsilyl)oxy]phenol (164 mg, 0.732 mmol), triphenylphosphine (220 mg, 0.839 mmol), and DEAD (155 mg, 0.890 mmol) at 0–5 °C (3 h) according to procedure A gave 242 mg (71%) of dithiin **19g** as an orange oil, eluent EtOAc–hexane (1:6): ^{1}H NMR ($CDCl_3$) δ 7.07 (t, J = 8.0, 1H), 6.50 (dd, J = 8.0, 2.4, 1H), 6.47–6.38 (m, 3H), 6.32 (d, J = 6.4, 1H), 4.59 (s, 2H), 4.25 (s, 2H), 0.94 (s, 9H), 0.87 (s, 9H), 0.16 (s, 6H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 159.19, 156.82, 135.88, 129.74, 129.35, 126.78, 123.54, 113.42, 107.94, 107.46, 69.68, 64.84, 25.80, 25.68, 18.35, 18.20, −4.40, −5.37; MS (LSIMS) 496.3 (M^+). Desilylation according to procedure B gave 95 mg (85%) of dithiin **20g** as yellow crystals, eluent EtOAc–hexane (1:3): mp 116 °C; ^{1}H NMR (CD_3OD) δ 7.06 (t, J = 8.0, 1H), 6.48–6.38 (m, 5H), 4.64 (s, 2H), 4.18 (s, 2H); ^{13}C NMR (CD_3OD) δ 160.82, 159.69, 137.65, 131.22, 130.94, 128.26, 125.52, 109.64, 107.14, 103.51, 70.78, 64.75; MS (LSIMS, m/z) 268.0 (M^+); HRMS (EI) calcd for $C_{12}H_{12}O_3S_2$ 268.0228, found 268.0243. Anal. ($C_{12}H_{12}O_3S_2$) C, H.

3-(Hydroxymethyl)-6-[[[2-(trifluoromethyl)phenyl]oxy]methyl]-1,2-dithiin (20i). Treatment of dithiin **1e** (200 mg, 0.688 mmol) with 2-(trifluoromethyl)phenol (223 mg, 1.37 mmol), triphenylphosphine (234 mg, 0.89 mmol), and DEAD (140 μL,156 mg, 0.89 mmol) at 0–5 °C according to procedure A gave 110 mg (37%) of dithiin **19i**, eluent EtOAc–hexane (1:3): ^{1}H NMR ($CDCl_3$) δ 7.56 (d, J = 8.0, 1H), 7.45 (t, J = 8.0, 1H), 7.01 (m, 2H), 6.49 (d, J = 6.0, 1H), 6.37 (d, J = 6.0, 1H), 4.71 (s, 2H), 4.26 (s, 2H), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (quaternary carbons missing) 136.19, 133.24, 127.23, 123.57, 120.81, 113.15, 69.58, 64.85, 25.79, 18.34, −5.38; MS (LSIMS, m/z) 434.1 (M^+). Desilylation of **19i** (70 mg, 0.16 mmol) according to procedure B gave 30 mg (58%) of dithiin **20i**, eluent EtOAc–hexane (1:3): ^{1}H NMR ($CDCl_3$) δ 7.60 (dd, J = 8.0, 1.6 1H), 7.50 (t, J = 8.4, 1H), 7.08 (t, J = 8.0, 1H), 6.99 (d, J = 8.0, 1H), 6.54 (d, J = 6.0, 1H), 6.44 (d, 1H, J = 6.0), 4.76 (s, 2H), 4.30 (s, 2H), 1.93 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 161.14, 135.73, 133.26, 128.84, 127.31 (q, J = 5.4), 126.59, 125.06, 123.33, 120.90, 113.11, 69.45, 64.59; MS (EI, m/z) 320.62 (M^+).

3-(Hydroxymethyl)-6-[[(5-nitropyrid-2-yl)oxy]methyl]-1,2-dithiin (20j) and 3-(Hydroxymethyl)-6-[(5-nitro-2-oxopyrid-1-yl)methyl]-1,2-dithiin (22j). Treatment of dithiin **1e** (650 mg, 2.24 mmol) with 2-hydroxypyridine (470 mg, 3.36 mmol), triphenylphosphine (715 mg, 2.73 mmol), and DEAD (455 μL, 504 mg, 2.89 mmol) at 0–5 °C for 2 h according to procedure A gave 120 mg (13.0%) of dithiin **19j**, eluent EtOAc–hexane (1:20): ^{1}H NMR ($CDCl_3$) δ 9.07 (d, J = 2.8, 1H), 8.37 (d, J = 2.4, 1H), 7.52–7.43 (m, 1H), 6.49 (d, J = 6.4, 1H), 6.38 (d, J = 5.6, 1H), 5.09 (s, 2H), 4.23 (s, 2H), 0.92 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 160.22, 144.52, 137.10, 134.18, 132.18, 131.48, 123.33, 111.44, 68.48, 64.72, 25.74, 18.30, −5.31. Further elution with EtOAc–hexane (1:6) provided 373 mg (40.5%) of pyridone **21j**: ^{1}H NMR ($CDCl_3$) δ 8.82 (d, J = 2.8, 1H), 8.12 (dd, J = 2.8, 10.4, 1H), 6.60 (d, J = 10.4, 1H), 6.53 (d, J = 6.0, 1H), 6.41 (d, J = 6.0, 1H), 4.76 (s, 2H), 4.30 (s, 2H), 0.91 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (3 quaternary carbons missing) 138.45, 133.35, 131.45, 125.65, 123.38, 119.63, 64.61, 53.00, 25.73, 18.28, −5.45. Both products were used separately for their subsequent desilylation reactions. Desilylation of **19j** (165 mg, 0.55 mmol) according to procedure B gave 82 mg (69%) of dithiin **20j** as yellow crystals: mp 102–103 °C; ^{1}H NMR (CD_3OD) δ 9.06 (d, J = 3.2, 1H), 8.48 (dd, J = 2.8, 9.2, 1H), 7.00 (dd, J = 9.2, 0.40, 1H), 6.56 (d, J = 6.0, 1H), 6.41 (d, J = 6.0, 1H), 5.13 (s, 2H), 4.19 (s, 2H); ^{13}C NMR (CD_3OD) δ 167.67, 145.34, 138.69, 135.62, 130.17, 129.92, 125.83, 125.49, 112.53, 69.33, 64.70; MS (EI, m/z) 298.0 (M^+); IR ($CHCl_3$) 1603, 1579 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{10}N_2O_4S_2$ 298.0082, found 298.0084. Anal. ($C_{11}H_{10}N_2O_4S_2$) C, H. Desilylation of **21j** (100 mg, 0.24 mmol) according to procedure B gave 48 mg (66.4%) of pyridone **22j**, eluent EtOAc: ^{1}H NMR (CD_3OD) δ 9.08 (d, J = 3.2, 1H), 8.23 (dd, J = 10.4, 3.2, 1H), 6.59 (d, J = 10.0, 1H), 6.55 (d, J = 6.0, 1H), 6.42 (d, J = 6.0, 1H), 4.86 (overlap with HDO, s, 2H), 4.19 (s, 2H); ^{13}C NMR (CD_3OD) δ 163.48, 141.07, 139.11, 135.28, 132.73, 131.59, 128.77, 125.57, 119.87, 64.64, 53.75; MS (EI) 298.0 (M^+); IR (KBr) 1666.6 (C=O), 1608, 1562 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{10}N_2O_4S_2$ 298.0082, found 298.0055. Anal. ($C_{11}H_{10}N_2O_4S_2$) C, H.

3-(Hydroxymethyl)-6-[[(2-fluorophenyl)oxy]methyl]-1,2-dithiin (20k). Treatment of dithiin **1e** (350 mg, 1.20 mmol) with 2-fluorophenol (270 mg, 215 μL, 2.40 mmol), triphenylphosphine (385 mg, 1.47 mmol), and DEAD (245 μL, 271 mg, 1.55 mmol) at 0–5 °C for 30 min and then 2 d at room temperature according to procedure A gave 329 mg (71%) of dithiin **19k**, eluent EtOAc–hexane (1:3): ^{1}H NMR ($CDCl_3$) δ 7.7–6.83 (m, 4H), 6.47 (d, J = 6.0, 1H), 6.38 (d, J = 6.0, 1H), 4.8 (s, 2H), 4.26 (s, 2H), 0.92 (s, 9H), 0.10 (s, 6H). Desilylation of **19k** (250 mg, 0.65 mmol) according to procedure B gave 120 mg (68%) of dithiin **20k**, eluent EtOAc–hexane (1:3): ^{1}H NMR ($CDCl_3$) δ 7.12–6.9 (m, 4H), 6.47 (d, J = 6.0, 1H), 6.39 (d, J = 6.0, 1H), 4.74 (s, 2H), 4.28 (s, 2H); MS (EI, m/z) 270.1 (M^+).

3-(Hydroxymethyl)-6-[[(3-ethynylphenyl)oxy]methyl]-1,2-dithiin (20l). Treatment of dithiin **1e** (235 mg, 0.80 mmol) with 3-hydroxyphenylacetylene (142 mg, 1.20 mmol), triphenylphosphine (315 mg, 1.20 mmol), and DEAD (190 μL, 210 mg, 1.20 mmol) at 0–5 °C for 1.5 h according to procedure A gave 175 mg (56%) of dithiin **19l**, eluent EtOAc–hexane (1:20): ^{1}H NMR ($CDCl_3$) δ 7.23 (t, J = 8.0, 1H), 7.12 (d, J = 8.0, 1H), 7.05 (s, 1H), 6.93 (dd, J = 6.0, 2.4, 1H), 6.44 (d, J = 6.0, 1H), 6.37 (d, J = 6.0, 1H), 4.66 (s, 2H), 4.30 (s, 2H), 3.07 (bs, 1H), 0.92 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 157.79, 136.21, 132.54, 129.46, 128.74, 127.03, 125.43, 123.45, 118.29, 116.22, 83.28, 77.21, 69.73, 64.79, 25.76, 18.31, −5.41; MS (EI, m/z) 390.1 (M^+). Desilylation of **19l** (160 mg, 0.41 mmol) according to procedure B gave 35 mg (30.9%) of dithiin **20l** as yellow crystals: mp 70.5–71.5 °C; eluent EtOAc–hexane (1:3); ^{1}H NMR ($CDCl_3$) δ 7.46 (t, J = 8.4, 8.4, 1H), 7.35 (d, J = 7.6, 1H), 7.27 (s, 1H), 7.16 (d, J = 8.0, 1H), 6.67 (d, J = 6.4, 1H), 6.62 (d, J = 5.6, 1H), 4.98 (s, 2H), 4.51 (s, 2H), 3.29 (s, 1H), 2.10 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 157.71, 135.73, 129.90, 129.50, 126.88, 125.52, 124.91, 123.20, 118.27, 116.22, 83.25, 77.28, 69.62, 64.53; MS (EI, m/z) 276.0 (M^+); HRMS (EI) calcd for $C_{14}H_{12}O_2S_2$ 276.0278, found 276.0275. Anal. ($C_{14}H_{12}O_2S_2$) C, H.

3-(Hydroxymethyl)-6-[[(3-carbomethoxyphenyl)oxy]methyl]-1,2-dithiin (20m). Treatment of dithiin **1e** (235 mg, 0.80 mmol) with methyl 3-hydroxybenzoate (183 mg, 1.20 mmol), triphenylphosphine (315 mg, 1.20 mmol), and DEAD (190 μL, 210 mg, 1.20 mmol) at 0–5 °C for 3 h according to procedure A gave 205 mg (60.3%) of dithiin **19m**, eluent EtOAc–hexane (1:20): ^{1}H NMR ($CDCl_3$) δ 7.67 (d, J = 7.6, 1H), 7.59 (s, 1H), 7.36 (t, J = 8.0, 1H), 7.14 (d, J = 7.6, 1H), 6.47 (d, J = 6.4, 1H), 6.38 (d, J = 6.4, 1H), 4.72 (s, 2H), 4.30 (s, 2H), 3.92 (s, 3H), 0.92 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 166.74, 158.02, 136.34, 131.52, 129.50, 128.64, 127.23, 123.44, 122.76, 120.27, 115.35, 69.88, 64.79, 52.19, 25.77, 18.55, −5.40; MS (EI, m/z) 424.1 (M^+). Desilylation of **19m** (200 mg, 0.47 mmol) according to procedure B gave 100 mg (68.5%) of dithiin **20m**, eluent EtOAc–hexane (1:3): ^{1}H NMR

(CD_3OD) δ 7.62 (d, J = 7.6, 1H), 7.56 (s, 1H), 7.39 (t, J = 8.0, 1H), 7.20 (dd, J = 8.0, 2.0, 1H), 6.51 (d, J = 6.0, 1H), 6.40 (d, J = 6.0, 1H), 4.76 (s, 2H), 4.18 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (CD_3OD) δ 168.27, 159.65, 138.16, 132.76, 130.81, 130.58, 128.90, 125.49, 123.60, 121.32, 116.75, 71.10, 64.76, 52.76; MS (EI, m/z) 310.0 (M^+); HRMS (EI) calcd for $C_{14}H_{14}O_4S_2$ 310.0334, found 310.0369.

3-(Hydroxymethyl)-6-[[[2-chloro-5-(trifluoromethyl)-phenyl]oxy]methyl]-1,2-dithiin (20n). Treatment of dithiin **1e** (200 mg, 0.69 mmol) with 2-chloro-5-(trifluoromethyl)phenol (180 μL, 271 mg, 1.38 mmol), triphenylphosphine (220 mg, 0.83 mmol), and DEAD (140 μ L,155 mg, 0.89 mmol) at 0–5 °C for 30 min and then 17 h at room temperature according to procedure A gave 200 mg (62%) of dithiin **19n**, eluent: EtOAc–hexane (1:3): ^1H NMR ($CDCl_3$) δ 7.54 (d, J = 8, 1H), 7.23 (d, J = 8.4, 1H), 7.16 (s, 1H), 6.54 (d, J = 6.4, 1H), 6.42 (d, J = 6.4, 1H), 4.78 (s, 2H), 4.31 (s, 2H), 0.9 (s, 9H), 0.1 (s, 6H); MS (EI, m/z) 468.1. Desilylation of **19n** (290 mg, 0.62 mmol) according to procedure B gave 120 mg (57%) of dithiin **20n** as a yellow solid, mp 94.2–96 °C, eluent EtOAc–hexane (1:3): ^1H NMR ($CDCl_3$) δ 7.51 (d, J = 8.4, 1H), 7.22 (dd, J = 6.8, 2.0, 1H), 7.16 (d, J = 1.2, 1H), 6.55 (d, J = 6.0, 1H), 6.5 (d, J = 6.0, 1H), 4.79 (s, 2H), 4.31 (d, J = 5.6, 2H) 1.80 (t, J = 6.0, 1H); ^{13}C NMR ($CDCl_3$) δ 153.69, 136.86, 136.49, 130.98, 130.85, 128.30, 127.54, 124.77, 119.13, 118.28, 111.03, 70.73, 64.53; MS (EI, m/z) 354 (M^+). Anal. ($C_{13}H_{10}ClF_3O_2S_2$) C, H.

3-(Hydroxymethyl)-6-[[(4-carbomethoxyphenyl)oxy]-methyl]-1,2-dithiin (20o). Treatment of dithiin **1e** (200 mg, 0.688 mmol) with methyl 4-hydroxybenzoate (155 mg, 1.02 mmol), triphenylphosphine (268 mg, 1.02 mmol), and DEAD (161 μL, 178 mg, 1.02 mmol) at 0–5 °C for 3 h according to procedure A gave 70 mg (23.9%) of dithiin **19o**, eluent EtOAc–hexane (1:2): ^1H NMR ($CDCl_3$) δ 8.00 (d, J = 8.8, 2H), 6.95 (d, J = 8.8, 2H), 6.46 (d, J = 6.4, 1H), 6.39 (d, J = 6.4, 1H), 4.73 (s, 2H), 4.31 (s, 2H), 3.90 (s, 3H), 0.92 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 166.66, 161.72, 136.47, 132.28, 131.42, 128.53, 127.26, 123.37, 114.48, 69.54, 64.76, 51.87, 25.75, 18.30, −5.42; MS (EI, m/z) 424.1 (M^+). Desilylation of **19o** (70 mg, 0.16 mmol) according to procedure B gave 36 mg (70.5%) of dithiin **20o**, eluent EtOAc–hexane (1:1): ^1H NMR (CD_3OD) δ 7.95 (d, J = 6.8, 2H), 7.02 (d, J = 6.8, 2H), 6.52 (d, J = 6.0, 1H), 6.41 (d, J = 6.0, 1H), 4.78 (s, 2H), 4.19 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (CD_3OD) δ 168.28, 163.50, 138.28, 132.56, 130.17, 128.99, 125.41, 124.24, 115.78, 70.82, 64.70, 52.40; MS (EI, m/z) 310.0 (M^+); HRMS (EI) calcd for $C_{14}H_{14}O_4S_2$ 310.0334, found 310.0354.

3-(Hydroxymethyl)-6-[[(4-imidazol-1-ylphenyl)oxy]-methyl]-1,2-dithiin (20p). Treatment of dithiin **1e** (300 mg, 1.04 mmol) with 4-imidazol-1-ylphenol (250 mg, 1.56 mmol), triphenylphosphine (402 mg, 1.50 mmol), and DEAD (242 μL, 267 mg, 1.50 mmol) at 0–5 °C for 3 h according to procedure A gave 330 mg of dithiin **19p** as a yellow residue which was impure with triphenylphosphine oxide, eluent EtOAc–hexane (1:2). The crude residue was desilylated according to procedure B to give 66 mg (20.1%) of dithiin **20p** as yellow crystals: mp 122–124 °C; eluent EtOAc–hexane (1:2): ^1H NMR (CD_3OD) δ 8.02 (s, 1H), 7.48 (d, J = 3.6, 2H), 7.46 (s, 1H), 7.12 (d, J = 3.2, 2H), 7.10 (s, 1H), 6.53 (d, J = 6.4, 1H), 6.41 (d, J = 6.4, 1H), 4.78 (s, 2H), 4.19 (s, 2H); ^{13}C NMR (CD_3OD) δ 159.01, 138.18, 137.02, 132.45, 130.60, 129.93, 128.89, 125.41, 124.03, 120.14, 117.38, 71.19, 64.71.

3-(Hydroxymethyl)-6-[[[1-(4-hydroxyphenyl)tetrazol-5-yl]thio]methyl]-1,2-dithiin (24). Treatment of dithiin **1e** (600 mg, 2.07 mmol) with 4-(4-hydroxyphenyl)-1*H*-tetrazole-5-thiol (594 mg, 3.07 mmol), triphenylphosphine (804 mg, 3.07 mmol), and DEAD (483 μL, 534 mg, 3.07 mmol) at 0–5 °C for 1 h according to procedure A gave 480 mg (51.5%) of dithiin **23**, eluent EtOAc–hexane (1:3): ^1H NMR (CD_3OD) δ 7.36 (d, J = 8.0, 2H), 6.96 (d, J = 8.0, 2H), 6.46 (d, J = 6.0, 1H), 6.31 (d, J = 6.4, 1H), 4.28 (s, 2H), 4.24 (s, 2H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (CD_3OD) δ 160.97, 154.94, 137.65, 130.27, 129.53, 127.46, 126.15, 125.53, 117.33, 66.13, 40.11, 26.33, 19.22, −5.18: MS (FAB, m/z) 466.0 (M^+). Desilylation of **23** (440 mg, 0.94 mmol) according to procedure B gave 265 mg (79.8%) of dithiin **24** as yellow crystals, mp 130–131 °C, eluent EtOAc–hexane (1:3): ^1H NMR (CD_3OD) δ 7.36 (d, J = 9.2, 2H), 6.97 (d, J = 9.2, 2H), 6.47 (d, J = 6.0, 1H), 6.34 (d, J = 6.4, 1H), 4.24 (s, 2H), 4.15 (s, 2H); ^1H NMR (DMSO-d_6) δ 10.26 (s, 1H, phenol OH), 7.41 (d, J = 8.8, 2H), 6.97 (d, J = 8.8, 2H), 6.52 (d, J = 6.0, 1H), 6.35 (d, J = 6.0, 1H), 5.39 (t, J = 5.2, 1H), 4.30 (s, 2H), 4.06 (d, J = 5.2, 2H); ^{13}C NMR (CD_3OD) δ 160.99, 154.90, 138.09, 130.34, 129.49, 127.42, 126.05, 125.77, 117.29, 64.67, 40.01; ^1H NMR NOESY showed an interaction between aromatic and dithiin rings protons; HMBC (DMSO-d_6) showed a long range correlation between the protons at 4.30 ppm and the carbon at 154.90 ppm; MS (FAB, m/z) 353.5 (MH^+); IR (KBr) 3378.7 (OH), 3135 (OH) cm^{-1}. Anal. ($C_{13}H_{12}N_4O_2S_3$) C, H, N, S.

3-(Hydroxymethyl)-6-[[[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]oxy]methyl]-1,2-dithiin (25) and 3,6-Bis[[[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]oxy]methyl]-1,2-dithiin (26). To a stirred solution of dithiin **1d** (330 mg, 1.87 mmol) in 8 mL of THF was added in portions at room temperature NaH (160 mg, 4.00 mmol, 60% supension in oil). After 15 min a freshly prepared solution of 1-[(trifluoromethyl)sulfonyl]-2,3-*O*-isopropylideneglycerol[56] (1.8 g, 6.82 mmol) in 2 mL of THF was added dropwise. After 3 h at room temperature, the reaction mixture was quenched with 10 mL of methanol and concentrated to a small volume, and then the products were separated on a silica gel column, eluting with EtOAc–hexane (1:3), to give 247 mg (35.9%) of dithiin **26** as an orange oil: R_f 0.51 EtOAc–hexane (1:1); ^1H NMR ($CDCl_3$) δ 6.33 (s, 2H), 4.29 (p, J = 5.6, 6.0, 2H), 4.15 (dd, J = 13.2, 13.2, 4H), 4.07 (dd, J = 6.4, 6.4, 2H), 3.72 (dd, J = 6.4, 6.4, 2H), 3.47 (dddd, J = 5.6, 5.6, 5.2, 5.2, 4H), 1.39 (s, 6H), 1.32 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 132.34, 126.45, 109.42, 74.49, 72.88, 70.97, 66.59, 26.66, 25.28; MS (EI, m/z) 404.3 (M^+); HRMS (EI) calcd for $C_{18}H_{28}O_6S_2$ 404.1327, found 404.1303. Further elution with EtOAc–hexane (1:3) gave 144 mg (29.1%) of dithiin **25**: R_f 0.36 EtOAc–hexane (1:1); ^1H NMR ($CDCl_3$) δ 6.36 (dd, J = 6.4, 6.4, 2H), 4.32–4.23 (m, 3H), 4.20 (d, J = 5.2, 2H), 4.07 (dd, J = 6.4, 6.8, 1H), 3.77 (dd, J = 6.4, 6.4, 1H), 3.58–3.48 (m, 2H), 2.16 (bt, 1H), 1.43 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 135.35, 131.95, 126.75, 124.84, 109.49, 74.54, 72.97, 70.96, 66.63, 64.49, 26.70, 25.32; MS (EI, m/z) 290.2 (M^+); HRMS (EI) calcd for $C_{12}H_{18}O_4S_2$ 290.0647, found 290.0629. Further elution with EtOAc–hexane (1:3) gave 27 mg (8.2%) of unreacted dithiin **1d**.

3-(Hydroxymethyl)-6-[[(2,3-dihydroxyprop-1-yl)oxy]-methyl]-1,2-dithiin (27). A solution of dithiin **25** (105 mg, 0.36 mmol) in 60% AcOH (6 mL) was stirred for 4 h at room temperature and then was partitioned between 30 mL of water and 50 mL of EtOAc. The separated organic phase was washed with dilute aqueous $NaHCO_3$ and water, dried, and then concentrated to a small volume. The residue was purified by chromatography, eluting with EtOAc, to give 39.6 mg (43.7%) of dithiin **27** as an orange oil: R_f 0.27 EtOAc; ^1H NMR (CD_3OD) δ 6.39 (AB q, J = 6.4, 2H), 4.18 (s, 4H), 3.73 (p, 1H), 3.61–3.44 (m, 4H); ^{13}C NMR (CD_3OD) δ 137.21, 132.81, 128.11, 125.54, 73.89, 72.59, 72.20, 64.76, 64.48; MS (EI, m/z) 250.1 (M^+); HRMS (EI) calcd for $C_9H_{14}O_4S_2$ 250.0333, found: 250.0329.

3-[[[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]oxy]methyl]-6-[[(2,3-dihydroxyprop-1-yl)oxy]methyl]-1,2-dithiin (28). A solution of dithiin **26** (80 mg, 0.19 mmol) in 60% AcOH (5 mL) was stirred for 2 h at room temperature, and then it was partitioned between 30 mL of water and 50 mL of EtOAc. The organic phase was washed with dilute aqueous $NaHCO_3$ and water, dried, and then concentrated. The residue was purified by chromatography, eluting with EtOAc, to give 15 mg (20.8%) of dithiin **28** as an orange oil: R_f 0.32 EtOAc; ^1H NMR (CD_3OD) δ 6.41 (s, 2H), 4.26 (p, 1H), 4.19 (d, J = 4.4, 4H), 4.05 (t, J = 6.4, 1H), 3.79–3.72 (m, 2H), 3.61–3.44 (m, 6H), 1.38 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (CD_3OD) δ 134.01, 133.54, 128.16, 127.82, 110.61, 76.10, 73.90, 73.84, 72.71, 72.26, 71.96, 67.59, 64.51, 27.05, 25.66; MS (EI, m/z) 364.1 (M^+); HRMS (EI) calcd for $C_{15}H_{24}O_6S_2$ 364.1014, found 364.1027.

3-(Azidomethyl)-6-(hydroxymethyl)-1,2-dithiin (30b). To a stirred solution of dithiin **1e** (3.40 g, 11.7 mmol) in toluene (12 mL) was added a solution of diphenyl phosphorazidate (3.02 mL, 3.86 g, 14.0 mmol) in toluene (8 mL), and the solution was cooled to 0 °C. DBU (2.09 mL, 2.13 g, 14.0 mmol) was then added dropwise. After 2 h at 0 °C, the reaction mixture was allowed to warm to room temperature. After 14 h the reaction mixture was purified by chromatography, using

EtOAc–hexane (1:20) as eluent, to give 2.75 g (74.5%) of azide **29b**: ^{1}H NMR ($CDCl_3$) δ 6.38 (AB q, J = 6.4, 2H), 4.30 (s, 2H), 3.98 (s, 2H), 0.92 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 136.89 128.01, 127.59, 123.47, 64.73, 55.15, 25.85, 18.28, −5.44; MS (EI, m/z) 315.1 (M^+). Desilylation of dithiin azide **29b** (62 mg, 19.7 mmol) according to procedure C gave 24.4 mg (61.9%) of dithiin **30b**: ^{1}H NMR ($CDCl_3$) δ 6.37 (AB q, J = 6.4, 2H), 4.27 (d, J = 6.0, 2H), 3.96 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 136.43, 128.66, 127.95, 124.93, 64.47, 55.09; MS (LSIMS, m/z) 201.0 (M^+); IR ($CHCl_3$) 3344 (b, OH), 2102 (N_3) cm^{-1}; HRMS (EI) calcd for $C_6H_7N_3OS_2$ 210.0030, found 201.0016. Anal. ($C_6H_7N_3OS_2$) C, H, N.

2-[(*tert*-Butyldimethylsilyl)oxy]phenyl Isocyanate. To a stirred solution of 2-aminophenol (1.0 g, 9.16 mmol) in THF (10 mL) was added triethylamine (3.57 mL, 2.59 g, 25.6 mmol) and *tert*-butyldimethylsilyl chloride (3.46 g, 22.9 mmol). The reaction mixture was stirred for 15 h at room temperature, filtered, and concentrated *in vacuo*. The residue was dissolved in toluene (10 mL), and this solution was cooled to −15 °C. The solution was treated with 1.4 mL (1.02 g, 10.0 mmol) of triethylamine, followed by the dropwise addition of 4.75 mL (9.17 mmol) of a 1.93 M solution of phosgene in toluene. After the addition was complete, the reaction mixture was allowed to warm up to room temperature and stirred for 1 h. The mixture was filtered, and the filtrate was concentrated *in vacuo* to give the title isocyanate as a pink oil: ^{1}H NMR ($CDCl_3$) δ 7.1–7.0 (m, 1H), 6.93–6.85 (m, with d at 6.89, J = 7.6, 2H), 1.08 (s, 9H), 0.35 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 150.29, 126.01, 124.28, 121.34, 118.34, 25.70, 18.54, −4.15; IR ($CHCl_3$) 2251 (NCO) cm^{-1}; MS (EI, m/z) 249 (M^+).

3-(Hydroxymethyl)-6-[[[[(2-hydroxyphenyl)amino]carbonyl]oxy]methyl]-1,2-dithiin (32). To a stirred solution of 2-[(*tert*-butyldimethylsilyl)oxy]phenyl isocyanate (230 mg, 0.924 mmol) in THF (1 mL) was added 143 μL (104 mg, 1.03 mmol) of triethylamine followed by a solution of dithiin **1e** (230 mg, 0.792 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 15 h and then purified directly by chromatography, eluting with EtOAc–hexane (1:20), to give 375 mg (87%) of carbamate **31** as an orange oil: ^{1}H NMR ($CDCl_3$; spectrum shows amide bond rotamers) δ 8.03 (br s, 1H), 7.19 (br s, 1H), 6.99–6.89 (m, 3H), 6.81 (d, J = 7.2, 1H), 6.44 (d, J = 6.0, 1H), 6.38 (d, J = 6.0, 1H), 5.31 (s, 2H, minor rotamer), 4.85 (s, 2H minor rotamer), 4.82 (s, 2H major rotamer), 4.31 (s, 2H major rotamer), 1.10 (s, 9H), 0.94 (s, 9H), 0.26 (s, 6H), 0.12 (s, 6H); MS (LSIMS, m/z) 539.3 (M^+). Desilylation of carbamate **31** (58 mg, 0.109 mmol) according to procedure B gave, after chromatography with EtOAc–hexane (1:3), 25 mg (75%) of carbamate **32**: ^{1}H NMR (CD_3OD; spectrum shows amide bond rotamers) δ 7.68 (br s, 1H), 7.01 (d, J = 3.6, 1H), 6.96–6.85 (m, 2H), 6.85–6.79 (m, 2H), 6.52 (d, J = 6.0, 1H), 6.43 (d, J = 6.4, 1H), 5.39 (s, 2H, minor rotamer), 4.78 (s, 2H, major rotamer), 4.70 (s, 2H, minor rotamer), 4.19 (s, 2H, major rotamer); ^{13}C NMR (CD_3OD; spectrum shows amide bond rotamers) δ 147.83, 139.74, 138.15, 130.48, 129.18, 128.97, 125.71, 125.61, 125.42, 125.27, 120.68, 116.14, 66.78, 64.78, 62.35, 60.13; MS (LSIMS, m/z) 311.1 (M^+).

3-(Hydroxymethyl)-6-[[(4-methylbenzenesulfonamido)carbonyl]oxy]-1,2-dithiin (34). To a stirred solution of dithiin **1e** (100 mg, 0.344 mmol) in dry THF (2 mL) was added 4-methylbenzenesulfonyl isocyanate (408 mg, 2.07 mmol) in 500 μL of THF. After 5 min TLC analysis showed complete consumption of starting material. The reaction mixture was applied directly on silica gel, eluting with EtOAc–hexane (1:3), to give 110 mg (66.6%) of *N*-sulfonylcarbamate **33**: ^{1}H NMR ($CDCl_3$; spectrum shows amide bond rotamers) δ 7.93 (d, J = 8.0, 2H), 7.34 (d, J = 8.4, 2H), 6.32 (s, 2H), 5.17 (s, 2H, minor rotamer), 4.81 (s, 2H, minor rotamer), 4.67 (s, 2H, major rotamer), 4.27 (s, 2H, major rotamer), 2.44 (s, 3H), 0.91 (s, 9H), 0.09 (s, 6H); IR ($CHCl_3$) 2360, 1751 cm^{-1}. Desilylation of **33** (27 mg, 0.055 mmol) according to procedure C gave 5 mg of dithiin **34**, eluent EtOAc–hexane (1:1); ^{1}H NMR ($CDCl_3$; spectrum shows amide bond rotamers) δ 7.93 (d, J = 8.4, 2H), 7.35 (d, J = 8.0, 2H), 6.35 (AB q, J = 6.8, 2H), 5.19 (s, 2H, minor rotamer), 4.79 (s, 2H, minor rotamer), 4.69 (s, 2H, major rotamer), 4.28 (s, 2H, major rotamer), 2.45 (s, 3H).

3-(Hydroxymethyl)-6-(acetamidomethyl)-1,2-dithiin (36). To a stirred solution of dithiin azide **29b** (94 mg, 0.328 mmol) in anhydrous THF (1.8 mL) was added acetic anhydride (100 μL, 107 mg, 1.06 mmol), followed by the addition of 25 μL of water and triphenylphosphine (120 mg, 0.457 mmol). After 3 h, the reaction mixture was partitioned between water (25 mL) and EtOAc (40 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 × 40 mL). The combined organic phases were washed with brine (2 × 50 mL), dried, and then concentrated. Purification of the orange-brown oil by chromatography, eluting with EtOAc–hexane (5:2), gave 36 mg of a semisolid mixture. Continued elution afforded 58 mg of a yellow-brown oil which was contaminated with triphenylphosphine oxide. Repurification of this material on silica gel using EtOAc–hexane (5:2) afforded 38 mg (35%) of amide **35**: ^{1}H NMR ($CDCl_3$; spectrum shows amide bond rotamers) δ 6.79 (d, J = 3.2, 1H, minor rotamer), 6.74 (d, J = 3.6, 1H, minor rotamer), 6.31 (br t, J = 7.2, 2H, major rotamer), 5.87 (br s, 1H), 4.80 (s, 2H, minor rotamer), 4.54 (d, J = 5.6, 2H, minor rotamer), 4.28 (s, 2H, minor rotamer), 4.05 (d, J = 6.0, 2H, major rotamer), 2.03 (s, 3H, major rotamer), 2.01 (s, 3H, minor rotamer), 0.91 (s, 9H), 0.095 (s, 6H); ^{13}C NMR ($CDCl_3$, spectrum shows amide bond rotamers) δ 170.09 (major rotamer), 169.65 (minor rotamer), 145.26 (minor rotamer), 139.89 (minor rotamer), 135.08 (major rotamer), 131.41 (major rotamer), 126.63 (major rotamer), 125.64 (minor rotamer), 123.79 (major rotamer), 123.52 (minor rotamer), 64.83 (major rotamer), 60.76 (minor rotamer), 43.70 (major rotamer), 38.65 (minor rotamer), 25.83 (minor rotamer), 25.74 (major rotamer), 23.17, 18.29, −5.31 (minor rotamer), −5.42 (major rotamer); MS (LSIMS, m/z) 331 (M^+). Desilylation of dithiin **35** (52 mg, 0.152 mmol) according to procedure C gave 24 mg (71%) of dithiin **36** as an orange oil, eluent EtOAc: ^{1}H NMR ($CDCl_3$) δ 6.79 (m, 2H), 6.31 (d, J = 6.4, 1H, major rotamer), 6.27 (d, J = 5.6, 1H, major rotamer), 6.82 (br s, 1H), 4.28 (br s, 2H, minor rotamer), 4.51 (d, J = 5.6, 2H, minor rotamer), 4.23 (br s, 2H, major rotamer), 4.02 (d, J = 6.0, 2H, major rotamer), 2.05 (s, 1H), 1.99 (s, 3H, major rotamer); ^{13}C NMR ($CDCl_3$) δ 170.12, 144.10 (minor rotamer), 141.21 (minor rotamer), 134.83 (major rotamer), 132.38 (major rotamer), 126.53 (major rotamer), 125.81 (minor rotamer), 125.25 (minor rotamer), 125.18 (major rotamer), 64.50 (major rotamer), 60.10 (minor rotamer), 43.69 (major rotamer), 38.63 (minor rotamer), 23.14 (major rotamer), 21.01 (minor rotamer); MS (LSIMS, m/z) 217 (M^+).

3-(Azidomethyl)-6-(chloromethyl)-1,2-dithiin (37). To a stirred solution of the dithiin **29b** (100 mg, 0.31 mmol) in THF (5 mL) was added at room temperature water (6.7 μL), followed by the sequential addition, in one portion, of triphenylphosphine (97 mg; 0.37 mmol) and triphosgene (460 mg, 1.55 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was purified by chromatography, eluting with EtOAc–hexane (1:9), to afford 27.4 mg (40.4%) of chloride **37**: ^{1}H NMR ($CDCl_3$) δ 6.42 (dd, J = 6.4, 6.0, 2H), 4.27 (s, 2H), 4.00 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 128.54, 128.42, 127.72, 127.58, 54.86, 46.63; MS (EI, m/z) 221.0 ($M+2^+$), 219.0 (M^+); IR (neat) 2096 cm^{-1}. Anal. ($C_6H_6ClN_3S_2$) C, H, N.

3-(Hydroxymethyl)-6-[(2-hydroxybenzamido)methyl]-1,2-dithiin (41). To a stirred solution of the dithiin **29b** (194 mg, 0.616 mmol) in dry THF (3.0 mL) was added 50 μL of water, followed by triphenylphosphine (220 mg, 0.839 mmol) and 4*H*-1,3-benzodioxine-2,4-dione,[44] **38** (260 mg, 1.59 mmol). The reaction mixture was stirred for 2.5 h. The reaction mixture was diluted with EtOAc (50 mL), washed with 10% aqueous $NaHCO_3$ (2 × 30 mL) and brine (2 × 30 mL), then dried, and concentrated to give an orange oil. Purification by chromatography, eluting with EtOAc–hexane (1:4), gave 55 mg (22%) of the benzamide **39**: ^{1}H NMR ($CDCl_3$) δ 12.09 (s, 1H), 7.48–7.35 (m, 1H), 7.01 (d, J = 8.0, 1H), 6.88 (t, J = 7.6, 1H), 6.61 (br s, 1H), 6.38 (dd, J = 15.2, 6.4, 2H), 4.30 (s, 2H), 4.27 (d, J = 6, 2H), 0.92 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 169.94, 161.60, 135.69, 134.55, 130.40, 127.15, 125.41, 123.71, 118.78, 118.71, 64.81, 43.57, 25.76, 18.32, −5.40; MS (LSIMS, m/z) 409.1 (M^+). Desilylation of benzamide **39** (52 mg; 0.127 mmol) according to procedure C gave 24.4 mg (65%) of benzamide **41** as an orange oil, eluent EtOAc–hexane (1:

1); ^{1}H NMR (CD_3OD; spectrum shows amide bond rotamers) δ 7.77 (dd, J = 8.0, 1.6, 1H), 7.38 (dt, J = 8.4, 1.6, 1H), 6.92–6.86 (m, 2H), 6.37 (br s, 2H), 4.69 (s, 2H, minor rotamer), 4.67 (s, 2H, minor rotamer), 4.20 (s, 2H, major rotamer), 4.17 (s, 2H, major rotamer); ^{13}C NMR (CD_3OD; spectrum shows amide bond rotamers) δ 170.98, 161.08, 136.25, 134.96, 133.29, 129.05, 127.06, 125.98, 120.17, 118.42, 116.82, 64.78 (major rotamer), 60.08 (minor rotamer), 44.03 (major rotamer), 39.11 (minor rotamer); MS (LSIMS, m/z) 296.1 (MH^+).

3,6-Diformyl-1,2-dithiin (44). To a solution of dithiin **1d** (844 mg, 4.78 mmol) in THF (50 mL) at 0 °C was added quickly the Dess–Martin periodinane reagent (4.78 g, 11.49 mmol), and the mixture was stirred at 0 °C for 30 min and then at room temperature for another 40 min. Upon completion of the reaction, H_2O (25 mL) was added and the mixture was extracted with ether (3×). The combined organics were washed with H_2O, $NaHCO_3$ (3% solution), and brine, then dried, and evaporated. Chromatography, eluting with hexane–EtOAc (1:1), gave 820 mg (100%) of dialdehyde **44** as a deep purple, crystalline compound: mp 62.0–63.1 °C; R_f 0.31 hexane–EtOAc (1:1); ^{1}H NMR ($CDCl_3$) δ 9.56 (s, 2H), 7.25 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 186.45, 142.03, 141.41; MS (EI, m/z) 172.0 (M^+); HRMS (EI) calcd for $C_6H_4O_2S_2$ 171.9654, found 171.9653. Anal. ($C_6H_4O_2S_2$) C, H.

3,6-Bis[(*N*-hydroxyimino)methyl]-1,2-dithiin (45). To a solution of 3,6-diformyl-1,2-dithiin (**44**) (1.10 g, 6.39 mmol) in anhydrous glyme (40 mL) at room temperature was added anhydrous pyridine (1.08 mL, 13.41 mmol), followed by hydroxylamine hydrochloride (932 mg, 13.41 mmol). Upon completion of the reaction (5 h, mechanical stirring, monitored by TLC), the mixture was poured onto ice water (40 mL), diluted with ether, and separated. The aqueous layer was extracted with ether (3×), and the combined organics were washed with 0.4 M HCl and brine, then dried, and evaporated. Chromatography (applied to the column as an adsorbate, eluting with hexane–EtOAc (2:1, 1000 mL), hexane–EtOAc (1:1, 200 mL), and then EtOAc (200 mL), gave 574 mg (2.84 mmol, 44%) of bisoxime **45**, mp color change from red to brown at 173 °C, melting at 216.5–216.7 °C: R_f 0.25 hexane–EtOAc (2:1); ^{1}H NMR (DMSO-d_6) δ 11.86 (s, 2H), 8.05 (s, 2H), 6.85 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 147.97, 130.73, 129.56; MS (EI, m/z) 202.1 (M^+), 170.1 ($M - S^+$), 159.0 (100); IR (KBr) 3189 (OH), 3002 cm^{-1}; HRMS (EI) calcd for $C_6H_6N_2O_2S_2$ 201.9875, found 201.9871.

3,6-Bis[(*N*-methoxyimino)methyl]-1,2-dithiin (46). To a solution of 3,6-diformyl-1,2-dithiin (**44**) (820 mg, 4.76 mmol) in anhydrous glyme (30 mL) at room temperature was added anhydrous pyridine (845 μL, 10.47 mmol), followed by methoxylamine hydrochloride (875 mg, 10.47 mmol). Upon completion of the reaction (5 h, mechanical stirring, monitored by TLC), the mixture was poured onto ice water (30 mL), diluted with ether, and separated. The aqueous layer was extracted with ether (3×), and the combined organics were washed sequentially with 0.4 M HCl and brine, dried, and evaporated. Chromatography, eluting with hexane–EtOAc (3:1), gave 528 mg (2.29 mmol, 48%) of bisoxime **46**: mp 133.2–134.1 °C; R_f 0.39 hexane–EtOAc (3:1); ^{1}H NMR ($CDCl_3$) δ 7.83 (s, 2H), 6.57 (s, 2H), 3.99 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 147.51, 131.13, 62.79; MS (EI, m/z) 230.0 (M^+), 198.1 ($M - S)^+$, 173.0 (100, M – CN – OCH_3^+); HRMS (EI) calcd for $C_8H_{10}N_2O_2S_2$ 230.0187, found 230.0184.

3-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-6-formyl-1,2-dithiin (47). To a solution of dithiin **1e** (600 mg, 2.07 mmol) in THF (25 mL) at 0 °C was added quickly the Dess–Martin periodinane reagent (1.20 g, 2.83 mmol), and the mixture was stirred at 0 °C for 30 min and then at room temperature for another 30 min. Upon completion of the reaction, 12 mL of H_2O was added and the mixture was extracted with ether (3×). The combined organics were washed with H_2O, $NaHCO_3$ (3% solution), and brine, dried, and then concentrated. Flash chromatography, eluting with hexane–EtOAc (3:1), gave 560 mg (94%) of aldehyde **47** as a dark red, almost purple, crystalline compound: mp 42.5–43.6 °C; R_f 0.44 hexane–EtOAc, 3:1; ^{1}H NMR ($CDCl_3$) δ 9.72 (s, 1H), 7.33 (d, J = 6.4, 1H), 6.88 (d, J = 6.4, 1H), 4.55 (s, 2H), 1.15 (s, 9H), 0.34 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 187.39, 148.63, 144.20, 132.02, 123.00, 64.61, 25.71, 18.28, −5.47; MS (EI, m/z) 288.1 (M^+), 231.1 (M – $C_4H_9^+$), 201.1 (100); HRMS (EI) calcd for $C_{12}H_{20}S_2O_2Si$ 288.0669, found 288.0672. Anal. (C_{12} $H_{20}S_2O_2Si$) C, H, S.

General Procedure for Desilylation of TBDMS-Protected Functionalized Methylene Dithiins. General Procedure D. A stirred solution of silylated dithiins **47–59** (0.15–2 mmol, 100 mol %) in THF at 0 °C was treated with a premixed solution of tetrabutylammonium fluoride (TBAF, 300–700 mol % of a 1 M solution in THF) and acetic acid (3000–7000 mol %) at 0 °C. The mixture was stirred at 0 °C for 1 h and then at room temperature until the starting material was consumed by TLC (1–3 h). The mixture was concentrated to a small volume and then partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (2×), the combined organics were washed sequentially with $NaHCO_3$ (3% solution), and brine, dried (Na_2SO_4), and then concentrated. Purification was done by flash chromatography on silica gel, eluting with EtOAc or EtOAc–hexane mixtures to obtain the desilylated dithiin. In cases where the product was contaminated with thiophene, further purification over preparative HPLC was done before biological testing.

3-(Hydroxymethyl)-6-formyl-1,2-dithiin (48). Dithiin **47** (120 mg, 0.416 mmol) in THF (10 mL) was desilylated according to procedure D to obtain 60 mg (83%) of aldehyde **48** as a red oil, eluent EtOAc: R_f 0.54 EtOAc; ^{1}H NMR ($CDCl_3$) δ 9.51 (s, 1H), 7.13 (d, J = 6.0, 1H), 6.70 (d, J = 6.0, 1H), 4.36 (s, 2H), 2.00 (br, 1H), ^{13}C NMR ($CDCl_3$) δ 187.56, 147.99, 144.10, 132.70, 124.00, 64.26; MS (EI, m/z) 174.0 (M^+), 142.0 ($M - S^+$) 113.0 (100).

3-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-6-[(*N*-hydroxyimino)methyl]-1,2-dithiin (49). To a mechanically stirred solution of dithiin **47** (690 mg, 2.39 mmol) in anhydrous glyme (24 mL) at room temperature was added anhydrous pyridine (203 μL, 2.51 mmol), followed by hydroxylamine hydrochloride (175 mg, 2.51 mmol). After stirring at room temperature for 5 h, another 105 mol % of pyridine (203 μL, 2.51 mmol) and hydroxylamine hydrochloride (175 mg, 2.51 mmol) was added, and the mixture was stirred for 17 h at room temperature. Upon completion of the reaction, the mixture was poured onto ice water, diluted with ether, and separated. The aqueous layer was extracted with ether (3×), and the combined organics were washed with 0.4 M HCl and brine, then dried, and evaporated. Flash chromatography, eluting with hexane–EtOAc (3:1), gave 602 mg (1.98 mmol, 83%) of oxime **49**: R_f 0.38 hexane–EtOAc (3:1); ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1H), 6.54 (m, 2H), 4.34 (s, 2H), 1.7 (br, 1H), 0.93 (s, 9H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 149.33, 140.22, 132.25, 125.90, 123.47, 64.89, 25.75, 18.31, −5.43; MS (EI, m/z) 303.1 (M^+), 286.1, 246.0, 214.0 (100).

3-(Hydroxymethyl)-6-[(*N*-hydroxyimino)methyl]-1,2-dithiin (50). Oxime **49** (602 mg, 1.98 mmol) in THF (40 mL) was desilylated according to procedure D to obtain 289 mg (1.53 mmol, 77%) of oxime **50** as orange crystals: mp 126.8–127.3 °C; eluent hexane–EtOAc (1:1); R_f 0.29 hexane–EtOAc (1:1); ^{1}H NMR (DMSO-d_6) δ 11.67 (s, 1H), 8.00 (s, 1H), 6.70 (d, J = 6.8, 1H), 6.52 (dd, d, J = 6.4; 1.2, 1H), 5.47 (m, 1H), 4.13 (d, J = 5.6, 2H); ^{13}C NMR (DMSO-d_6) δ 148.03, 138.61, 130.83, 126.67, 124.05, 63.33; MS (EI, m/z) 189.0 (M^+, 100); HRMS (EI) calcd for $C_6H_7NO_2S_2$ 188.9924, found 188.9918. Anal. ($C_6H_7NO_2S_2$) C, H, N, S.

3-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-6-[(*N*-methoxyimino)methyl]-1,2-dithiin (51). To a solution of dithiin **47** (105 mg, 0.36 mmol) in anhydrous glyme (5 mL) was added methoxylamine hydrochloride (30 mg, 0.36 mmol) and pyridine (29 μL, 0.36 mmol) at room temperature. After 5 h, another 100 mol % of methoxylamine hydrochloride (30 mg) and 4-methylmorpholine (33 μL, 0.36 mmol) were added, and the mixture was stirred 24 h at room temperature. The reaction mixture was then poured onto ice water, the aqueous layer was extracted with ether (3×), and then the combined organics were washed with 0.5 M HCl and brine, dried, and concentrated. Flash chromatography, eluting with hexane–EtOAc (5:1), gave 6 mg (0.019 mmol) of one isomer of oxime **51** plus 52 mg (0.164 mmol) of a mixture of both isomers of **51**: total yield, 51%; 10 mg (0.029 mmol, 8%) of unreacted starting material was also isolated; R_f 0.52 hexane–EtOAc (5:1) one isomer; R_f 0.46 hexane–EtOAc (5:1) other isomer; ^{1}H NMR ($CDCl_3$) δ 7.82 (s, 1H), 6.49 (s, 2H), 4.32 (s, 2H), 3.97 (s, 3H),

0.93 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 147.90, 139.66, 131.83, 126.0, 123.55, 64.93, 62.54, 25.78, 18.34, −5.39; MS (EI, m/z) 317.1 (M^+, 100), 286.0 ($M - OCH_3^+$), 260.0 ($M - C{=}N - OCH_3^+$).

3-(Hydroxymethyl)-6-[(*N*-methoxyimino)methyl]-1,2-dithiin (52). Dithiin **51** (52 mg, 0.164 mmol) in THF (5 mL) was desilylated according to procedure D to obtain 30 mg (90%) of oxime **52** as orange crystals: mp 48.4−49.3 °C; eluent hexane−EtOAc (1:1); R_f 0.37 hexane−EtOAc (1:1); ^{1}H NMR ($CDCl_3$) δ 7.82 (s, 1H), 6.50 (m, 2H), 4.32 (s, 2H), 3.97 (s, 3H), ^{13}C NMR ($CDCl_3$) δ 147.72, 139.04, 131.56, 126.94, 124.85, 64.61, 62.57; MS (EI, m/z) 203.0 (M^+, 100); HRMS (EI) calcd for $C_7H_9NO_2S_2$ 203.0073, found 203.0075.

3-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-6-(2-carbethoxyethenyl)-1,2-dithiin (53). To a solution of triethyl phosphonoacetate (131 μL, 0.329 mmol) in THF (5 mL) at −78 °C was added *n*-BuLi (66 μL, 0.329 mmol) dropwise, and the mixture was stirred for 10 min. This mixture was then transferred by means of a cannula to a solution of dithiin **47** (100 mg, 0.346 mmol) in THF (5 mL) at −78 °C. After 3 h at −78 °C, no reaction had occurred (as monitored by TLC). A second solution of triethyl phosphonoacetate (131 μL, 0.329 mmol) in THF (5 mL) at −78 °C and *n*-BuLi (66 μL, 0.329 mmol) was prepared and added as described above. After another 3 h at −78 °C, the mixture was allowed to warm up to 0 °C, and was stirred for 1 h. At this time the starting material was almost gone (TLC). A solution of Na_2SO_4 (2 mL, 1 M in H_2O) and H_2O (10 mL) was added, the mixture was extracted with ether (4×), and then the combined organics were washed with Na_2CO_3 (1 M) and brine, dried and evaporated. Flash chromatography, eluting with hexane−EtOAc (3:1), gave 65 mg (52%) of dithiin **53** as a red oil and 29 mg of a mixture of **53** and unreacted starting material: ^{1}H NMR ($CDCl_3$) δ 7.39 (d, J = 15.2, 1H), 6.61 (d, J = 6.4, 1H), 6.53 (d, J = 6.4, 1H), 6.25 (d, J = 15.2, 1H), 4.34 (s, 2H), 4.24 (q, J = 7.2, 2H), 1.32 (t, J = 7.2, 3H), 0.93 (s, 9H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 166.54, 141.89, 141.84, 133.98, 127.70, 124.09, 122.57, 64.88, 60.61, 25.75, 18.29, 14.22, −5.44; MS (EI, m/z) 358.1 (M^+), 326.1 ($M - S^+$), 301.0 ($M - C_4H_9^+$), 269.1 (100, $M - S - C_4H_9^+$).

3-(Hydroxymethyl)-6-(2-carbethoxyethenyl)-1,2-dithiin (54). Dithiin **53** (65 mg, 0.18 mmol) in THF (8 mL) was desilylated according to procedure D to obtain 35 mg (80%) of dithiin **54** as a red oil: eluent EtOAc; R_f 0.41 EtOAc; ^{1}H NMR ($CDCl_3$) δ 7.39 (d, J = 15.2, 1H), 6.61 (d, J = 6.4, 1H), 6.56 (d, J = 5.6, 1H), 6.27 (d, J = 15.2, 1H), 4.35 (s, 2H), 4.25, (q, J = 6.8, 2H), 2.08 (s, br, 1H), 1.32 (t, J = 7.2, 3H); ^{13}C NMR ($CDCl_3$) δ 166.51, 141.71, 141.19, 133.79, 128.46, 125.33, 123.02, 64.53, 60.71, 14.20; MS (EI, m/z) 244.0 (M^+); HRMS (EI) calcd for $C_{10}H_{12}O_3S_2$ 244.0228, found 244.0228.

3-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-6-(2-carbomethoxyethenyl)-1,2-dithiin (55). To a solution of trimethyl phosphonoacetate (130 μL, 0.90 mmol) in THF (4 mL) at −78 °C was added *n*-BuLi (360 μL, 0.90 mmol) dropwise, and the mixture was stirred for 10 min. This mixture was then slowly transferred by means of a cannula to a solution of dithiin **47** (130 mg, 0.45 mmol) in THF (8 mL) at −78 °C. After 3 h at −78 °C, TLC showed incomplete reaction. The mixture was allowed to warm up to 0 °C and was stirred at 0 °C for 1 h, after which time TLC showed disappearance of dithiin **47**. A solution of Na_2SO_4 (3 mL, 1 M in water) and water (5 mL) was added, the mixture was extracted with ether (4×), and then the combined organics were washed sequentially with Na_2CO_3 (1 M) and brine, dried, and evaporated. Flash chromatography, eluting with hexane−EtOAc (3:1), gave 132 mg (85%) of dithiin **55** as a red oil: ^{1}H NMR ($CDCl_3$) δ 7.29 (d, J = 15.2, 1H), 6.50 (d, J = 6.4, 1H), 6.42 (dt, J = 6.8, 1.6, 1H), 6.14 (d, J = 15.2, 1H), 4.23 (s, 2H), 3.67 (s, 3H), 0.82, (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 169.93, 142.11, 141.95, 134.10, 127.51, 124.01, 121.98, 64.81, 51.71, 25.69, 18.29, −5.47; MS (EI, m/z) 344.0 (M^+), 312.1, 287.0, 255.0 (100).

3-(Hydroxymethyl)-6-(2-carbomethoxyethenyl)-1,2-dithiin (56). Dithiin **55** (121 mg, 0.35 mmol) in THF (16 mL) was desilylated according to procedure D to obtain 70 mg (87%) of dithiin **56** as orange crystals: mp 80.5−81 °C; eluent EtOAc; R_f 0.47 EtOAc; ^{1}H NMR ($CDCl_3$) δ 7.40 (d, J = 15.2, 1H), 6.62 (d, J = 6.4, 1H), 6.56 (d, J = 6.4, 1H), 6.28 (d, J = 15.2, 1H), 4.35 (d, J = 6.0, 2H), 3.70 (s, 3H), 1.99 (t, J = 6.0, 1H); ^{13}C NMR ($CDCl_3$; quaternary carbons missing) δ 141.97, 133.93, 125.40, 122.60, 64.60, 51.87; MS (EI, m/z) 230.1 (M^+, 100); HRMS (EI) calcd for $C_9H_{10}O_3S_2$ 230.0071, found 230.0071.

3-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-6-(2-cyanoethen-1-yl)-1,2-dithiin (57). $NaNH_2$ (44 mg, 1.067 mmol) was weighed quickly into an oven-dried flask, suspended in THF (4 mL), and cooled to −78 °C. To this suspension, was added $(EtO)_2P(O)CH_2CN$ (173 μL, 1.067 mmol) dropwise, and the mixture was stirred for 10 min at −78 °C. This mixture was transferred by means of a cannula to a solution of dithiin **47** (154 mg, 0.533 mmol) in THF (5 mL) and held at −78 °C. The reaction mixture was stirred at −78 °C for 3 h and then at 0 °C for 90 min. The reaction was quenched by adding a solution of Na_2SO_4 (5 mL, 1 M in water) and water (10 mL), and then the mixture was extracted with ether (4×). The combined organics were washed with Na_2CO_3 (1 M) and brine, dried, and then concentrated. Chromatographies, eluting with hexane−EtOAc (3:1), then separation of mixed fractions by eluting with hexane−EtOAc (4:1) gave a total of 91 mg (55%) of dithiin **57**. Unreacted **47**, 5 mg (6%), was also isolated; R_f 0.51 hexane−EtOAc (4:1); ^{1}H NMR ($CDCl_3$) δ 7.12 (d, J = 16.0, 1H), 6.59 (m, 2H), 5.76 (d, J = 16.0, 1H), 4.36 (s, 2 H), 0.92, (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 147.33, 144.23, 134.76, 125.80, 123.83, 117.74, 100.36, 64.80, 25.72, 18.28, −5.44; MS (EI, m/z) 311.1 (M^+), 245.0, 224.0 (100, $M - C_6H_{15}^+$).

3-(Hydroxymethyl)-6-(2-cyanoethen-1-yl)-1,2-dithiin (58). Dithiin **57** (54 mg, 0.173 mmol) in THF (5 mL) was desilylated according to procedure D to obtain 32 mg (94%) of nitrile **58** as an orange powder: mp 96.6−97.9 °C; eluent hexane−EtOAc (1:1); R_f 0.31 hexane−EtOAc (1:1); ^{1}H NMR ($CDCl_3$) δ 7.13 (d, J = 15.6, 1H), 6.60, (s, 2H), 5.78 (d, J = 16.0, 1H), 4.37 (s, 2H), 2.06 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 147.21, 143.51, 134.61, 126.53, 124.99, 117.64, 100.84, 64.39; MS (EI, m/z) 197.0 (M^+), 167.0 (100, $M - CN^+$); HRMS (EI) calcd for $C_8H_7NOS_2$ 196.9971, found 196.9969.

3-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-6-cyano-1,2-dithiin (59). To a solution of dithiin **49** (71 mg, 0.234 mmol) in CH_2Cl_2 (5 mL) at room temperature was added BDDC[50] [139 mg, 0.515 mmol, followed by the addition of Cu^ICl (51 mg, 0.515 mmol)], and the mixture was stirred for 5 h. Upon completion of the reaction, the mixture was diluted with EtOAc, sequentially washed with 0.2 M HCl, $NaHCO_3$ (3% solution) and brine, then dried, and concentrated. Chromatography, eluting with hexane−EtOAc (4:1), gave 45 mg (68%) of the nitrile **59** as a dark red oil: R_f 0.39 hexane−EtOAc (4:1); ^{1}H NMR ($CDCl_3$) δ 6.98 (d, J = 6.4, 1H), 6.57 (m, 1H), 4.33 (s, 2H), 0.93 (s, 9H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 147.21, 142.22, 122.95, 114.87, 98.07, 64.49, 25.69, 18.26, −5.49; MS (EI, m/z) 285.1 (M^+), 228.0, 196.0 (100).

3-(Hydroxymethyl)-6-cyano-1,2-dithiin (60). Dithiin **59** (43 mg, 0.150 mmol) in THF (5 mL) was desilylated according to procedure D to obtain 23 mg (90%) of nitrile **60** as a dark red oil; eluent hexane−EtOAc (1:1); R_f 0.30 hexane−EtOAc (1:1); ^{1}H NMR ($CDCl_3$) δ 7.05 (d, J = 6.4, 1H), 6.66 (d, J = 6.4, 1H), 4.41 (d, J = 4.4, 2H), 2.16 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 146.55, 142.19, 123.88, 114.73, 98.85, 64.07; MS (EI, m/z) 171.0 (M^+), 153.1, 141.0 (100); HRMS (EI) calcd for $C_6H_5NOS_2$ 170.9812, found 170.9813.

Biological Methods. Test Fungi Preparation. Eleven fungi, *C. albicans* (ATCC 10259), *C. albicans* (A-26), *C. albicans* (B311), *C. krusei* (GK7831), *C. parapsilosis* (CP18), *C. tropicalis* (1525), *C. neoformans* (ATCC 36556), *C. neoformans* (MI-106), *A. fumigatus* (ATCC 13073), *A. fumigatus* (WM-1), and *T. rubrum* (ATCC 18762) were used in the antifungal susceptibility test. All test fungi are part of the fungal collection at Shaman Pharmaceuticals. *C. albicans* (ATCC 10259), *C. neoformans* (ATCC 36556), and *A. fumigatus* (ATCC 13073) were used routinely in the antifungal screening assay. *Candida* species and *C. neoformans* were grown on YM agar (Difco, Michigan) for 24 h and 48 h at 35 °C, respectively. *A. fumigatus* was grown on SAB agar (Sabourad Agar Modified, Difco, Michigan) for 3−4 d at 35 °C. *T. rubrum* was cultured on SAB agar for 5−7 d at 25 °C. The yeast inoculum suspensions were prepared by incubating the yeast cells from the agar plate cultures in GYB broth (2% of glucose, 1% yeast

extract) for 6 h at 35 °C with rotation. The conidia of *A. fumigatus* and *T. rubrum* were used as the inocula.

Fungal Microplate Broth Assay. U-Bottom 96-well microplates were used in the assay. To each well of a microplate was added with 75 μL of SAB broth (Sabouraud Dextrose Broth, Difco, MI). The dithiin compounds were dissolved in ethanol or DMSO and diluted with SAB broth. The diluted compound was added into wells of the microplate at column no. 1 at 75 μL/well. A series of 2-fold dilutions were done by transferring aliquots of 75 μL from wells at the previous column to wells at the next column. Column no. 12 served as the fungal growth control. The fungal inoculum was applied into each well of rows B, C, D, E, F, G, and H of the microplate at 74 μL/well, except for all wells on rows A and H, to which was added SAB broth as a blank control. Amphotericin B was used in this assay as the reference antifungal compound. The final fungal inoculum concentrations for all *Candida* species was 2×10^3 cfu/mL. The final inoculum concentrations for *C. neoformans*, *A. fumigatus*, and *T. rubrum* were 2×10^4, 1×10^3, and 1×10^4 cfu/mL, respectively. The inoculated microplates with all *Candida* species were incubated for 24 h at 35 °C. The microplates containing *C. neoformans* or *A. fumigatus* were incubated for 48 h at 35 °C. The microplates containing *T. rubrum* were incubated for 7 d at 25 °C. All microplates were examined for antifungal activity with the aid of a concave viewing mirror after the incubation period, with all wells being compared to the growth in the fungal control wells. The lowest concentration which inhibited the fungal growth, as indicated by no visible growth in the well, was recorded as the minimum inhibition concentration (MIC) of the compound.

Molecular Modeling Geometry Optimizations. The Hartree–Fock molecular orbital calculations were performed with the SPARTAN program, version 3.1.[51] Geometry optimizations were performed using the 3-21G* basis set.[52] Final electronic structures were generated using single point calculations on the optimized geometry using the 6-31G* basis set. Charges were calculated using the electrostatic field fit method implemented within SPARTAN.

Molecular mechanics optimizations were performed using the Macromodel program version 4.5,[57] AMBER all atom force field parameter set as implemented within MacroModel, and GB/SA solvation parameter set.[58] Optimizations were done using AMBER, electrostatic field fit atomic charges calculated in SPARTAN, and the GB/SA water solvation model to ensure reasonable charges for the 1,2-dithiin ring system and simulate an aqueous environment. Comparison of a model 1,2-dithiin, 3,6-dimethyl-1,2-dithiin **61**, optimized using AMBER/molecular mechanics and that from Hartree–Fock/3-21G* optimizations produced a ring atom superimposition with rms deviations of 0.06 Å. Molecular mechanics were used for subsequent conformational searches without modification of the supplied force field parameter set.

MNDO or AM1 semiempirical molecular orbital optimizations as implemented within SPARTAN were found to produce 1,2-dithiin ring geometries considerably flattened with respect to those calculated using Hartree–Fock methods. The disulfide torsion (C_6–S_1–S_2–C_3) in 3,6-dimethyl-1,2-dithiin **61** changed from 53.8° calculated using Hartree–Fock/3-21G* to 25.1° for AM1. The final AM1 optimized geometry had optimized for conjugated double bond planarity resulting in a decrease in the cyclodiene torsion C_3–C_4–C_5–C_6 from 27.6° to 12.0° and an overall flattening of the 1,2-dithiin ring. AM1 optimized geometries also produced substantially higher energies when recomputed using Hartree–Fock/6-31G*, and made this method inappropriate for the 1,2-dithiin ring system and was not used for any optimizations in this study.

Transition State Search. The dithiin ring inversion transition state geometry was located using SPARTAN by transition state geometry optimization using the Hartree–Fock/3-21G* basis set.[52,59,60] The transition state energy was determined by single point calculation with the 6-31G* basis set using the 3-21G* optimized geometry. The transition state was optimized to a gradient of <0.0001. The search was seeded using various geometries with the transition state found starting from the optimized ground state geometry. Searches starting from sharply flattened ring geometries thought to be geometrically close to the transition state failed to converge.

Surfaces. LUMO Isoorbital surfaces were generated by mapping the LUMO onto the 0.002 electron/au^3 isodensity surface using SPARTAN. The location and degree of surface penetration of the LUMO was color-coded blue, with the largest and darkest patches indicating those sites susceptible to nucleophilic attack. Comparison of patch size and intensity provided a qualitative measure of selectivity between multiple patches on a single molecule.

Alignments. Atomic coordinate alignments using rigid body RMS fits on selected atom pairs was accomplished in MacroModel. Surface alignments were performed manually by maximizing alignment of nucleophilic susceptibility regions and common volume.

Conformational Search. Global minimum structures were determined for low flexibility molecules such as **45** using manual conformation generation followed by Hartree–Fock/3-21G* geometry optimization as described above. The global minimum structure of more flexible molecules such as **18i** were determined using the Multiple Minimum Monte Carlo conformational search procedure,[61] the AMBER force field, and the GB/SA water solvation model as implemented in MacroModel. All internal degrees of freedom were searched. The single global minimum structure was used to represent the many conformations with comparable energies and different geometries for electronic structure determination and surface generation.

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