Total Synthesis of (±)-Aspirochlorine

Gregory F. Miknis and Robert M. Williams*

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523. *Received August 14, 1992*

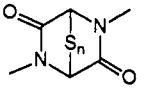
Abstract: (±)-Aspirochlorine was synthesized in a diastereoselective fashion from commercially available 5-chlororesorcinol in 13 steps. The synthesis involves an efficient stereoselective cycloaddition reaction of a hydroxamic ester to form the parent spiro[benzofuran-2(3*H*),2'-piperazine] ring system. In addition the synthesis employs a 2-nitrobenzyl group as an amide protecting group which is easily removed under photolytic conditions.

Introduction

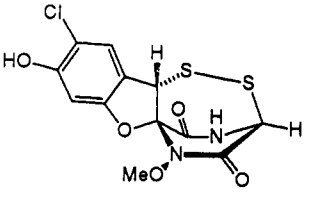
The epipolythiapiperazine-2,5-dione (**1**) containing compounds comprise a diverse and interesting class of fungal metabolites. Historically, these compounds have been the focus of a tremendous amount of investigation not only as attractive synthetic targets[1] but also for their ever increasing array of biological properties which range from potent antiviral/antifungal activities, immunosuppressive activities such as the inhibition of phagocytosis, oxidative damage to DNA, and more recently have been shown to be potent inhibitors of histamine release.[2] Furthermore, compounds which contain the epipolythiapiperazine-2,5-dione moiety have been shown to be effective inhibitors of the enzyme reverse transcriptase,[3] a key enzyme in the life cycle of retro viruses which is currently an attractive target for drug design.[4]

In all cases the disulfide bridge is required for biological activity.[5] Despite the possible therapeutic uses, no drug containing this ring system as a pharmacophore has been developed due to the high mammalian toxicity exhibited by most of these compounds.[6] Aspirochlorine (A30641, **2**) is a novel seven-membered epidithiapiperazine-2,5-dione isolated from *Aspergillus tamari* in 1976.[7] Since its isolation, aspirochlorine has also been identified as the major active constituent from extracts of *Aspergillus flavus* and *Aspergillus oryzae*.[8,9] The structure originally assigned to aspirochlorine (**3**) was proposed to have a unique bicyclo [3.2.1] N-1,3 disulfide bridge, but the structure (correctly shown as **2**) was revised in 1987 from a crystal structure of a semisynthetic derivative.[10] Aspirochlorine is the only known epipolythiapiperazine-2,5-dione-containing natural product derived from glycine, which places a free amide (i.e., NH) adjacent to the S-S bridge. In addition, it is a rare example of an amino acid metabolite to incorporate the unusual *N*-methoxyl moiety in a diketopiperazine ring.

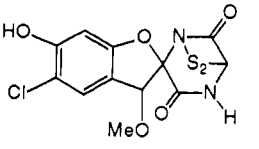
Aspirochlorine *does not* display the same potent antiviral activity which is characteristic of six-membered disulfide containing compounds and exhibits only mild antifungal properties. The relative lack of activity displayed by aspirochlorine might be attributed to differences in ring strain and redox potential for the potent six-membered bicyclo [2.2.2] disulfide ring systems versus the seven-membered bicyclo [3.2.2] disulfide ring system found in **2**.[11]



1 n = 1,2,3,4



2 Aspirochlorine (A30641)



3

(1) (a) General review of the chemistry of epipolythiapiperazine-2,5-diones see: Leigh, C.; Taylor, A. *Adv. Chem. Ser.* **1976**, *149*, 228. Representative synthetic endeavors: (b) Kirby, G. W.; Rao, G. V.; Robins, D. J.; Stark, W. M. *Tetrahedron Lett.* **1986**, *27*, 5539. (c) Plate, R.; Akkerman, M. A. J.; Otteheijm, H. C. J.; Smits, J. M. M. *J. Chem. Soc., Perkin Trns. 1* **1987**, 2481. (d) Fukuyama, T.; Nakatsuka, S.; Kishi, Y. *Tetrahedron* **1981**, *37*, 2045.

(2) General reviews on the biological activity, see: (a) Waring, P.; Eichner, R. D.; Mullbacher, A. *Med. Res. Rev.* **1988**, *8*, 499. (b) Mullbacher, A.; Waring, P.; Braithwaite, A. W.; Eichner, R. D. *Drugs of the Future* **1987**, *12*, 565. (c) Jordan, T. W.; Cordiner, S. J. *TIPS* **1987**, *8*, 144. (d) Nagarajan, R. In *Mycotoxins—Production, Isolation, Separation and Purification*, Betina, U., Ed.; Elsevier Science Publishing: New York, 1984; p 351. Antiviral/antifungal, see: Rightsel, W. A.; Schneider, H. G.; Sloan, B. J.; Graf, P. R.; Miller, F. A.; Bartz, Q. R.; Ehrlich, J.; Dixon, G. J. *Nature* **1964**, *204*, 1333. Trown, P. W. *Biochem. Biophys. Res. Commun.* **1968**, *33*, 402. Immunosuppresive activity, see: Mullbacher, A.; Moreland, A. F.; Waring, P.; Sjaarda, A.; Eichner, R. D. *Transplantation* **1988**, *46*, 120. Mullbacher, A.; Waring, P.; Eichner, R. D. *J. Gen. Microbiol.* **1985**, *131*, 1251. Mullbacher, A.; Eichner, R. D. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 3835. DNA cleavage related, see: Waring, P. *J. Biol. Chem.* **1990**, *265*, 14476. Waring, P.; Eichner, R. D.; Mullbacher, A.; Sjaarda, A. *J. Biol. Chem.* **1988**, *263*, 18493. Eichner, R. D.; Waring, P.; Geue, A. M.; Braithwaite, A. W.; Mullbacher, A. *J. Biol. Chem.* **1988**, *262*, 3772. Braithwaite, A. W.; Eichner, R. D.; Waring, P.; Mullbacher, A. *Mol. Immun.* **1987**, *24*, 47. Inhibition of histamine release, see: Kawahara, N.; Nozawa, K.; Yamazaki, M.; Nakajima, S.; Kawai, K. *Chem. Pharm. Bull.* **1990**, *38*, 73. Kawahara, N.; Nakajima, S.; Yamazaki, M.; Kawai, K. *Chem. Pharm. Bull.* **1989**, *37*, 2592. Kawahara, N.; Nozawa, K.; Nakajima, S.; Kawai, K.; Yamazaki, M. *J. Chem. Soc., Chem. Commun.* **1989**, 951. Kawai, K.; Nozawa, K. In *Mycotoxins and Phycotoxins*; Elsevier Science Publishers: Amsterdam, 1989. Inhibition of platelet aggregation, see: Sakai, M.; Watanuki, M. *Agric. Biol. Chem.* **1987**, *51*, 2167.

(3) (a) DeClerq, E.; Billiau, A.; Ottenheijm, H. C. J.; Herscheid, J. D. M. *Biochem. Pharm.* **1978**, *27*, 635. (b) Smith, G. R.; Gallo, R. C. *Life Sciences* **1974**, *15*, 1711. (c) Ottenheijm, H. C. J.; Herscheid, J. D. M.; Tijhuis, M. W.; Oosterbaan, M.; DeClerq, E. *J. Med. Chem.* **1978**, *21*, 796, 799. (d) Miller, P. A.; Milstrey, K. P.; Trown, P. W. *Science* **1968**, *159*, 431.

(4) (a) Connolly, K. J.; Hammer, S. M. *Antimicrob. Ag. Chemother.* **1992**, *36*, 245 and 509. (b) Goff, S. P. *J. AIDS* **1990**, *3*, 817. (c) Nakamura, S.; Inouye, Y. *Novel Microbial Products for Medicine and Agriculture*; Demain, A. L., Somkuti, G. A., Hunter-Cevera, J. C., Rossmoore, H. W. Eds.; Society for Industrial Microbiology: 1989; Chapter 11. (d) Tisdale, M.; Larder, B. A.; Lowe, D. M.; Stammers, D. K.; Purifoy, D. J. M.; Erth, P.; Bradley, C.; Kemp, S.; Darby, G. K.; Powell, K. L. *J. Antimicrob. Chemother* **1989**, *23A*, 47. (e) Mitsuya, H.; Broder, S. *Nature* **1987**, *325*, 773. (f) Chandra, P.; Vogel, A.; Gerber, T. *Cancer Res.* **1985**, *45*, 46775.

(5) (a) Mullbacher, A.; Waring, P.; Tiwari-Palni, U.; Eichner, R. D. *Mol. Immun.* **1986**, *23*, 231. (b) Billard, W.; Peets, E. *Antimicrob. Ag. Chemother.* **1974**, *5*, 19. (c) Middleton, M. C. *Biochem. Pharm.* **1974**, *23*, 811. (d) Trown, P. W.; Bilello, J. A. *Antimicrob. Ag. Chemother.* **1972**, *2*, 261.

(6) Review, see: Taylor, A. In *Microbial Toxins*, Kadis, S., Ciegler, A., Ajl., S. J., Eds.; Academic Press: New York, 1971; Volume 7, Chapter 10. Munday, R. *Chem. Biol. Interactions* **1982**, *41*, 361. Middleton, M. C. *Biochem. Pharm.* **1974**, *23*, 801, 811. Possible role of fungal toxins in AIDS, see: Eichner, R. D.; Mullbacher, A. *Aust. J. Exp. Biol. Med. Sci.* **1984**, *62*, 479.

(7) Berg, D. H.; Massing, R. P.; Hoehn, M. M.; Boeck, L. D.; Hamill, R. L. *J. Antibiot.* **1976**, *29*, 394.

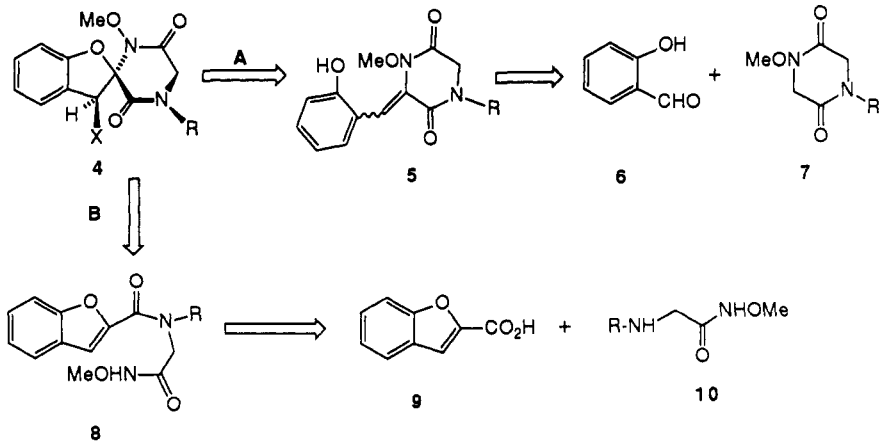
(8) Sakata, K.; Masago, H.; Sakurai, A.; Takahashi, N. *Tetrahedron Lett.* **1982**, *28*, 5607.

(9) Sakata, K.; Kuwatsuka, T.; Sakurai, A.; Takahashi, N.; Tamura, G. *Agric. Biol. Chem.* **1983**, *47*, 2673.

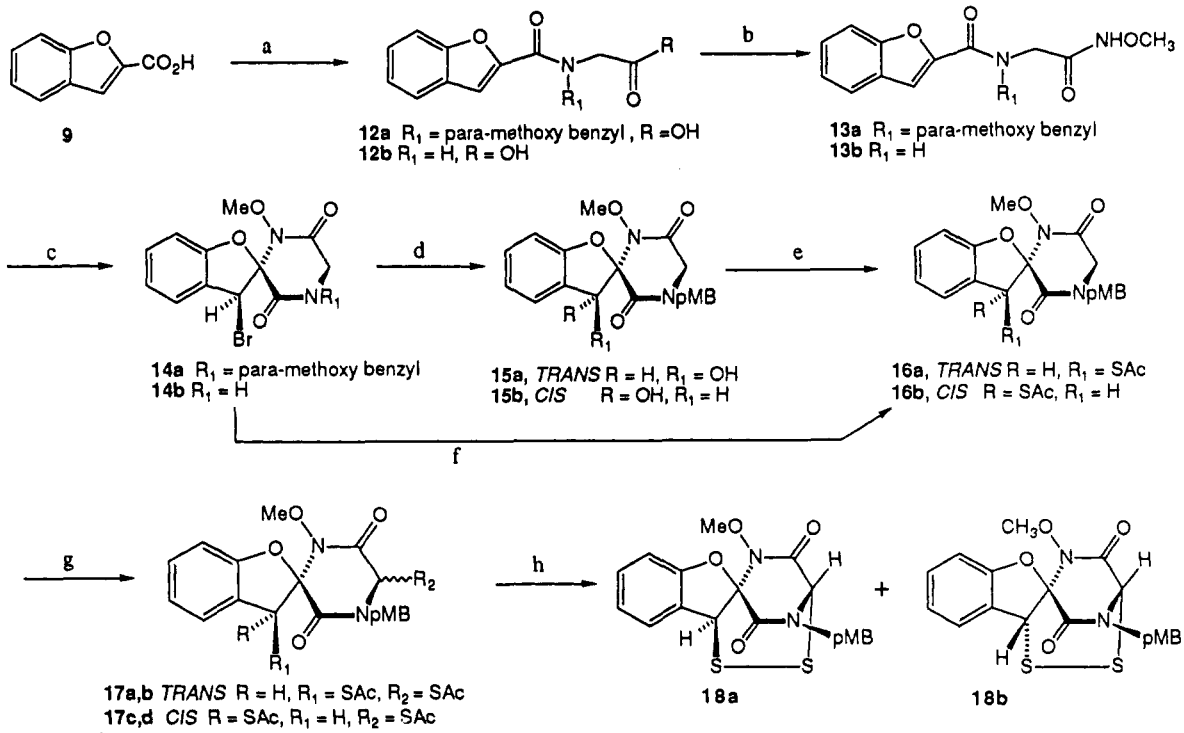
(10) Sakata, K.; Maruyama, M.; Uzawa, J.; Sakurai, A.; Lu, H. S. M.; Clardy, J. *Tetrahedron Lett.* **1987**, *28*, 5607.

0002-7863/93/1515-536$04.00/0 © 1993 American Chemical Society

Scheme I



Scheme II[a]



[a] Reagents and conditions: (a) (1) $SOCl_2$, benzene, reflux; (2) *N*-(4-methoxybenzyl)glycine ethyl ester **11**, NaOH; (3) LiOH, EtOH; three steps 60%; (b) pivaloyl chloride, Et_3N followed by NH_2OCH_3; 80–95%; (c) NBS, $CHCl_3$, room temperature, 50%; (d) silver triflate, THF/H_2O; 75%; (e) 12 equiv of HSAc, 6 equiv BF_3–Et_2O, CH_2Cl_2, 70%; (f) excess thiolacetic acid, $ZnCl_2$ benzene; 32–69%; (g) NBS, CCl_4 reflux, followed by thiolacetic acid, pyridine; 65% (h) HCl/EtOH, room temperature 5 h or NaOH, EtOH, room temperature 10 min; followed by aqueous KI_3, CH_2Cl_2, 32%.

Our interest in aspirochlorine is 2-fold; the first objective was to develop an efficient synthesis of this unusual natural product and secondly to explore the mechanism of action/biological activity of **2** and similar compounds as it relates to the physical properties of respective disulfides. In a preliminary communication, we outlined our synthetic approach to aspirochlorine in a model system.[12] In this paper we would like to describe the details of that model study and report its successful application to the first total synthesis of (±)-aspirochlorine.

Results and Discussion

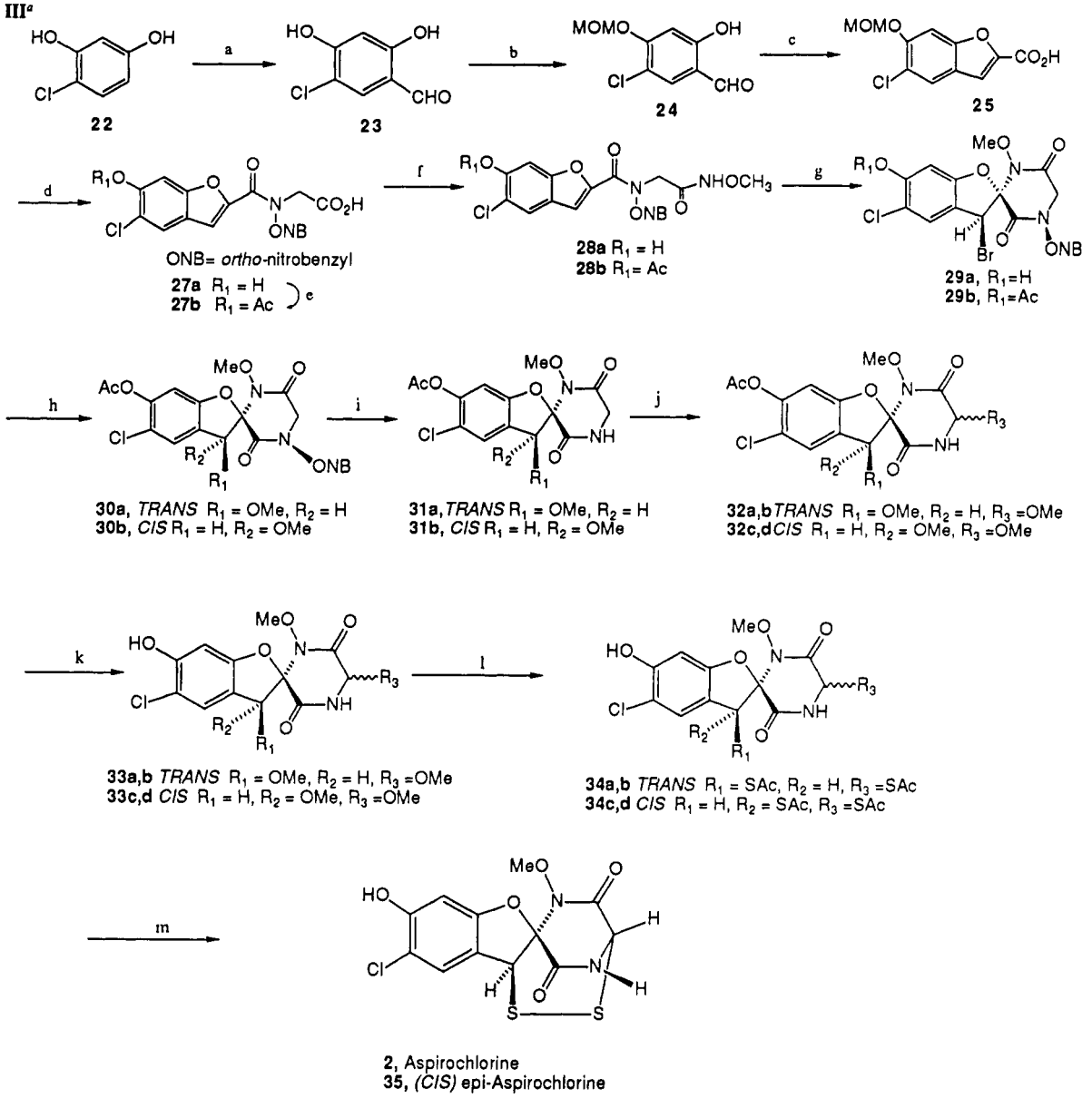
A major goal of the model system was to develop an efficient methodology to construct the spiro[benzofuran-2(3*H*),2′-piperazine] moiety **4** which encompasses the core structure. Two possible retrosynthetic routes are shown in Scheme I. The spiro center could be created by coupling an appropriate piperazine-2,5-dione **7** with a 2-hydroxybenzaldehyde **6** in a convergent approach as depicted in path A. A similar approach was used by Shin and co-workers in the synthesis of the skeleton of aspirochlorine before the structural revision appeared in the literature.[13] Applying this approach toward the synthesis of aspirochlorine had several potential drawbacks which made it less attractive. The foremost concern would be the difficult task of controlling the regiochemical outcome in the aldol condensation/dehydration between an unsymmetrically substituted piperazinedione **7** and the 2-hydroxybenzaldehyde derivative **6**. In

(11) (a) Burns, J. A.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 6296. (b) Singh, R.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 1190. (c) **1990**, *112*, 6304. (d) Houk, J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1987**, *109*, 6825. (e) Whitesides, G. M.; Houk, J.; Patterson, M. A. K. *J. Org. Chem.* **1983**, *48*, 112. (f) Szajewski, R. P.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 2011. (g) Whitesides, G. M.; Lilburn, J. E.; Szajewski, R. P. *J. Org. Chem.* **1977**, *42*, 332. (h) Allinger, N. L.; Hickey, M. J.; Kao, J. *J. Am. Chem. Soc.* **1976**, *98*, 741.

(12) Williams, R. M.; Miknis, G. F. *Tetrahedron Lett.* **1990**, *31*, 4297.

(13) Shin, C.; Nakajima, Y.; Sato, Y. *Chem. Lett.* **1984**, 1301.

Scheme III[a]



[a] Reagents and conditions: (a) $Zn(CN)_2$, HCl; 40%; (b) MOM-Cl, Et_3N, 50%; (c) diethyl bromomalonate, K_2CO_3, MEK reflux, followed by KOH/EtOH, reflux, 72%; (d) oxalyl chloride, followed by *o*-nitrobenzyl glycine ethyl ester **26**, $NaHCO_3$, followed by aqueous HCl/dioxane reflux, 84%; (e) excess acetic anhydride, pyridine, 98%; (f) isobutyl chloroformate, *N*-methylmorpholine, THF, followed by methoxylamine, 70%; (g) NBS, EtOH-free $CHCl_3$, room temperature, 67%; (h) silver triflate, MeOH/THF, reflux, 80%; (i) *hν*, 10% H_2O/THF, 72%; (j) *tert*-butyl hypochlorite, NaOMe, 0 °C to room temperature, 56–72%; (k) NaOEt, EtOH, 0 °C, 30 min, 74%; (l) excess thiolacetic acid, BF_3–Et_2O, 65%; (m) excess methoxylamine, CSA, THF, 20–34%.

addition the desired aldol condensation/dehydration reaction did not appear likely due to the well documented rearrangement of *N*-alkoxy amides to α-alkoxy amides in the presence of base.[1,14] In addition, a potentially difficult problem would be to control the stereochemistry in the subsequent electrophilic cyclization (**5** → **4**) leading up to the parent tricyclic system.

Based on these potential problems, we envisioned the desired tricyclic system **4** could be created in a stereospecific manner via an intramolecular cyclization reaction of a suitable hydroxamic ester **8** as depicted in path B. The requisite hydroxamic ester **8** could easily be obtained from simple peptide coupling of coumarilic acid **9** and the appropriate N-protected glycine ester **10**. The successful application of this approach is shown in Scheme II.

Commercially available coumarilic acid **9** was coupled with *N*-(*p*-methoxybenzyl)glycine ester **11** to give the desired benzofuranylglycine ethyl ester which was saponified (LiOH, EtOH) to give coumarilic glycinate **12a** in 66% overall yield for the two steps. A variety of methods was used to prepare *O*-methyl hydroxamic ester **13a**; the most satisfactory procedure utilized mixed anhydride formation (pivaloyl chloride, triethyl amine) followed by treatment with methoxylamine to give **13a** in 80–95% yields. Treatment of **13a** with 1.2 equiv of NBS in ethanol-free chloroform resulted in formation of the desired tricyclic bromide **14a** in 50% isolated yield as a single diastereomer possessing the desired relative stereochemistry (i.e., trans). Confirmation of the relative stereochemistry shown for **14a** was obtained from a single crystal X-ray analysis.[12]

Having firmly established an efficient methodology to construct the spirocyclic skeleton of aspirochlorine (31% overall yield of **14** from **9**), we further investigated the scope of the facile spirocyclization reaction by carrying out the NBS oxidation on the analogous system utilizing the unprotected amide **12b** which was obtained by coupling glycine ethyl ester with **9**. To our dismay

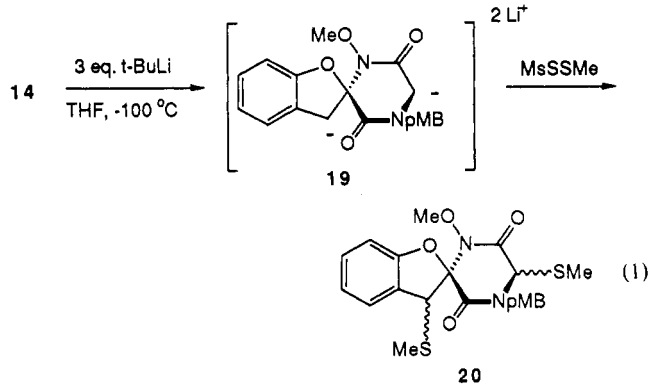
(14) For a review of *N*-alkoxy amino acids, see: Ottenheijm, H. C. J.; Herscheid, J. D. M. *Chem. Rev.* **1986**, *86*, 697. For related work, see: (a) Otteheijm, H. C. J.; Plate, R.; Noordik, J. H.; Herscheid, J. D. M. *J. Org. Chem.* **1982**, *47*, 2147. (b) Herscheid, J. D. M.; Nivard, R. J. F.; Tijhuis, M. W.; Ottenheijm, H. C. J. *J. Org. Chem.* **1980**, *45*, 1885. (c) Herscheid, J. D. M.; Nivard, R. J. F.; Tijhuis, M. W.; Scholten, H. P. H.; Ottenheijm, H. C. J. *J. Org. Chem.* **1980**, *45*, 1880.

none of the desired tricyclic bromide **14b** was obtained from treating **13b** with NBS even when reactions were conducted in refluxing CCl_4. The only products obtained were a mixture of α-brominated acyclic compounds and acyclic compounds and acyclic N-brominated compounds as determined from analysis of the ^1H NMR spectra.

The lack of any spirocyclized material from reactions involving **13b** can be readily explained by considering the conformation about the central amide bond in **13** as illustrated in Figure 1. Compounds such as **13b** containing a secondary amide should adopt the lower energy extended conformation (s-trans form) forcing the benzofuran and hydroxamic ester moieties to be distal. Conversely, cyclization of the tertiary amide-containing compound **13a** can be attributed to the amide significantly populating the s-cis conformation (the *p*-methoxylbenzyl moiety can be considered to be sterically larger than the hydroxamic ester group), allowing the benzofuran and hydroxamic ester functionalities to lie in close proximity allowing cyclization to readily occur. Based on the experimental observation that **13b** does not undergo cyclization, it is apparent that an efficient cyclization reaction requires the central amide to be capable of adopting the requisite folded conformation (assuming the hydroxamate moiety also adopts the s-cis conformation).

The cyclization of **13a** to **14a** proceeds via *anti*-addition resulting in the net desired relative stereochemistry between the *N*-methoxyl moiety and benzylic bromide. Based on the well established reactivity of benzylic halides as good leaving groups in S_N2 reactions, it was anticipated that the natural stereochemistry at the benzylic position could be established using a double inversion protocol involving initial formation of an alcohol or ether followed by a subsequent displacement by thiolate.[15]

An attractive alternative approach to directly convert **14a** to a dithiol containing compound was predicated on the assumption that halogen–metal exchange may proceed with net retention of configuration. This approach was attempted and involved treating **14a** with 3 equiv of *tert*-butyllithium at −100 °C followed by trapping of the intermediate dianion **19** with methyl methanethiolsulfonate to give the disulfenylated compound **20** (eq 1). In the event, only a trace of the desired compound was isolated from the reaction mixture under the conditions shown in eq 1, and synthetically useful amounts of **20** were never realized by this approach.



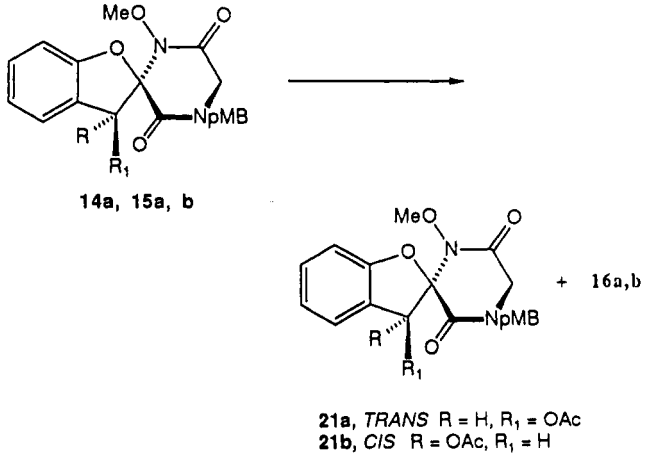
Functionalization of **14a** was ultimately achieved using Lewis acid (S_N1-type) conditions. Formation of alcohols **15a,b** was achieved simply by treating **14a** with a slight excess of silver triflate in aqueous THF. The reaction proceeds in a nonselective fashion giving a 1.6:1 (trans/cis, **15a/15b**) ratio of diastereomers in 75% overall yield; fortunately the epimeric alcohols were easily separated by column chromatography and carried on individually.

The relative configurations at the benzylic position for alcohols **15a,b** and subsequent related compounds were determined by ^1H NMR/NOE experiments. In the case of the trans diastereomer **15a**, irradiation of the benzylic methine proton at 5.80 ppm resulted in a positive NOE enhancement of the *N*-methoxyl signal at 3.88 ppm. Likewise irradiation of the *N*-methoxyl group exhibited a positive NOE enhancement of the signal assigned to the benzylic proton. Analogous NOE experiments involving the cis diastereomer **15b** did not reveal significant NOE enhancements for either signal (benzylic methane 5.59 ppm, *N*-methoxyl 3.81 ppm). The slight preference for the formation of the trans diastereomer as the major isomer is attributed to steric interactions between the *N*-methoxyl group and the approaching nucleophile on the incipient benzylic oxonium ion.

In our preliminary account, it was reported treatment of **15a,b** with 6 equiv of BF_3–Et_2O in the presence of 12 equiv thiolacetic acid resulted in the exclusive formation of the *trans*-thioacetate **16a**. However, more careful examination of the crude reaction revealed a mixture of benzylic thioacetates **16a** and **16b**. Surprisingly, along with thioesters **16a,b** a mixture of the O-acetylated compounds **21a,b** was also isolated from the reaction mixture and characterized. The identity of the O-acetylated compounds **21a,b** was confirmed by acetylation of **15a** and **15b** with acetyl chloride and comparison of the ^1H NMR spectra. The NMR of the O-acetylated compounds exhibited a downfield shift of the benzylic methines to 6.42 and 6.33 ppm for the trans and cis, while the signals due to the acetate methyl group were shifted upfield to 1.86 and 2.14 ppm for the trans and cis diastereomers, respectively. The formation of the O-acetylated compounds can be rationalized to occur via complexation of the thiol group of thiolacetic acid with the Lewis acid rendering the carbonyl oxygen more prone to react in a nucleophilic capacity. The incipient thionoacetates presumably undergo S to O exchange upon workup, although the intermediacy of such species proved elusive.

Subsequent experiments utilizing individual alcohols **15a,b** demonstrated that the product ratio of **16a,b** is dependent upon the stereochemistry of the starting alcohol. Treatment of *trans*-**15a** under the reaction conditions (12 equiv thiolacetic acid, 6 equiv BF_3–Et_2O) gave a 1.4:1 ratio of **16a/16b** in 70% yield as determined by integration of the benzylic methine signals at 5.74 and 5.81 ppm for the trans and cis diastereomers, respectively, in the crude NMR. Analogous reactions using *cis*-**15b** gave rise to a 3:1 ratio of **16a/16b** in 64% yield. Interestingly, in each case the major thioacetate diastereomer possessed the desired natural stereochemistry (i.e., *trans*-**16a**). The relative stereochemistry in **16a,b** was verified using the same NOE experiments as previously described for alcohols **15a,b**.

Despite the moderate success using BF_3–Et_2O, more stereoselective conditions to convert alcohols **15** to the thioacetates **16** was sought, and a variety of examples are shown in Table I. Treatment of **15a** or **15b** with 3 equiv of thiolacetic acid in the presence of excess anhydrous zinc chloride in refluxing benzene gave almost exclusive formation of the *O*-acetyl compounds **21a,b**



(entries 1 and 5). Analysis of the crude ^1H NMR spectra showed complete disappearance of starting material, and the mixture of *O*-acetates **21a,b** could be isolated in 50–54% yield. Again the formation of **21a,b** presumably arises from a Fisher-type transesterification process in which the zinc chloride forms a S–Zn complex with the thiolacetic acid.

(15) Wardell, J. L. In *The Chemistry of the Thiol Group*; Patai, S., Ed.; John Wiley and Sons: New York, 1974; Chapter 4.

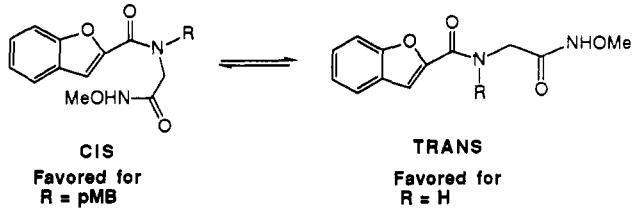


Figure 1.

Treatment of alcohols **15a,b** under a variety of conditions (entries 2–9) routinely gave mixtures of the O- and S-acetylated material. Only reactions using an excess of both thiolacetic acid and BF_3–Et_2O favored formation of the *S*-acetates.

Treatment of bromide **14a** with an excess of thiolacetic acid (>30 equiv, essentially solvolysis conditions) in the presence of zinc chloride in various solvents at room temperature resulted in exclusive formation of a mixture of **16a,b** as determined by crude ^1H NMR under a variety of conditions (entries 10–13). Surprisingly, treatment of bromide **14a** under the same conditions routinely gave higher ratios of **16a,b** (e.g., compare entry 2 and 12) and in every case the major diastereomer possessed the desired trans relative stereochemistry.

To determine if the product ratio of **16a/16b** might reflect an intrinsic thermodynamic stability for the trans configuration versus cis, both **16a** and **16b** were resubjected to the reaction conditions using excess thiolacetic acid/$ZnCl_2$ in benzene. Analysis of the crude NMRs showed epimerization did not take place under the reaction conditions indicating the product ratio reflects kinetic, not thermodynamic factors.

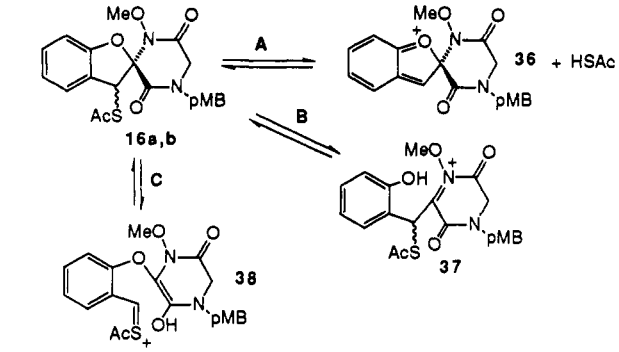
Introduction of the thiol group at the α-position of the diketopiperazine was achieved by bromination with NBS in refluxing carbon tetrachloride followed by treatment of the unstable bromides with thiolacetic acid in the presence of pyridine. The reaction gives essentially a 1:1 mixture of bisthioacetates **17a,b** in 65% combined yield presumably epimeric at the α-position only. Treatment of **16b** under the same conditions gave **17c,d** in 50% isolated yield as a 1:1 mixture of epimers. Attempts to firmly establish the stereochemistry at the α-position in each of the individual diastereomers **17a–d** by NOE experiments were ambiguous. Furthermore, since the conversion of *trans*-dithiols to disulfides has been observed previously,[1,16] the exact determination of the stereochemistry at the α-position in **17a–d** was not critical for subsequent transformations. Although the individual diastereomers could be separated, it was more convenient to carry each pair on as the mixture of epimers.

Deprotection of the thiol groups in **17a,b** under acidic conditions (HCl saturated ethanol, room temperature 6 h) followed by oxidation of the intermediate dithiols with aqueous KI_3/CH_2Cl_2 system resulted in a 1:1.4 ratio of the natural and unnatural disulfides **18a** and **18b** in a modest 32–44% combined yield. The ratio of **18a,b** was the same regardless of which diastereomeric bisthioacetate (e.g., **17a** or **b**) was used as the starting material. The relative configurations of both disulfide diastereomers were deduced from single X-ray crystal structural analysis.[12] Deprotection of the diastereomeric bisthioacetates **17c,d** containing the cis configuration under the same acidic conditions gave a surprisingly high 1:5 to 1:11 ratio of **18a/18b** in 30–49% yield.

In an attempt to gain further insight into when epimerization occurred and apparent stability of the cis thioacetates **17c,d**, the individual monothioacetates **16a,b** were subjected to the acid hydrolysis conditions, and the intermediate thiols were reacetylated with acetic anhydride. Analysis of the NMR for the *trans*-thioacetate **16a** revealed a 3:1 ratio of trans/cis in 40% combined yield, while **16b** gave a 1:5.6 trans/cis ratio in 60% isolated yield. These results indicate the cis diastereomer is in fact more stable to acidic conditions than the trans isomer.

A possible explanation for the stability of the cis configuration versus the trans may involve stereoelectronic effects. In the trans diastereomer, the *S*-acetyl bond can adopt an antiperiplanar orientation with respect to the C–N bond of the diketopiperazine ring which can lead to a weakening of the S–C bond (analogous to the anomeric affect). The cis diastereomers do not possess this type of interaction; therefore, the S–C bond is stronger and less readily cleaved leading to epimerization. Alternative mechanisms which cannot be ruled out given the available experimental evidence are the possibility of C–O or C–N bond cleavage followed by reclosure to generate the epimeric thioacetate.[17] Further investigation of this unusual isomerization reaction is currently underway.

Scheme IV



The acid-catalyzed epimerization was avoided by conducting the final sequence under basic, anaerobic conditions. Deprotection of either **17a,b** under basic conditions (0.2 M sodium hydroxide in aqueous ethanol followed by oxidation with KI_3) resulted in formation of the desired disulfide **18a** in 32% yield and only a trace of the unnatural isomer. The same result could be obtained using NH_4OH/methanol; formation of disulfide **18a** was instantaneous as evidenced by the crude NMR prior to KI_3 oxidation, but the overall yield dropped to 18%. Comparable results were obtained using the diastereomeric thioacetates **17c,d**.

Having demonstrated the feasibility of the model study for the synthesis of aspirochlorine, we undertook the task of applying this approach toward the total synthesis. The strategy which emerged included several modifications foremost of which was the incorporation of a new amide protecting group and incorporation of both sulfur atoms in a single step.

A shortcoming of the model system was the inability to remove the glycine amide protecting group. As discussed above, a tertiary amide was required for the spirocyclization reaction to proceed. Our initial choice of the *p*-methoxybenzyl protecting group was predicated on the assumption strongly acidic media would be capable of removing this group, and literature precedent indicated epipolythiapiperazinediones were reasonably stable to strong acid. Unfortunately, we were unable to remove the *N*-*p*-methoxybenzyl group of **18** (or related spirocyclic precursors) using CAN or concentrated acids such as H_2SO_4 or TFA.[18] The lack of a good experimental procedure to remove the *p*-methoxybenzyl group in the model study thus precluded the use of this group for the total synthesis. Furthermore, the benzofuran moiety in the natural product contains substantially more electron density due to the presence of an additional hydroxyl group para to the benzylic position. This net increase in electron density around the aromatic ring might increase the likelihood of competing electrophilic aromatic substitution reactions in any type of oxidative deprotonation sequence. In order to avoid this problem we decided to incorporate a new protecting group which could be removed under

(16) Eguchi, C.; Kakuta, A. *J. Am. Chem. Soc.* **1974**, *96*, 3983. Ohler, E.; Tataruch, F.; Schmidt, U. *Chem. Ber.* **1973**, *106*, 165. Kishi, Y.; Fukuyama, T.; Nakatsuka, S. *J. Am. Chem. Soc.* **1973**, *95*, 6490.

(17) The epimerization of thioacetates **16a,b** was thought to occur via path A involving the benzofuranyl cation **36**. The absence of any products which resemble trapping of **36** with solvent (i.e., ethanol) suggests that another mechanism(s) may be occurring. Reasonable possibilities include path B which involves hydrolysis of the hemiaminal function resulting in the formation of intermediate **37**. Subsequent bond rotation followed by ring closure would allow epimerization to take place. A similar mechanism is illustrated by path C and involves formation of an incipient thionoacetate **38** as a possible intermediate.

(18) Smith, A. B.; Rano, T. A.; Chida, N.; Sulikowski, G. A. *J. Org.* 4Chem. **1990**, *55*, 1136. Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.* **1983**, 1001.

Table I. Conversion of **14a** and **15a,b** to Thioacetates **16a,b**

entry	substrate	conditions[a]	ratio O vs S acetylation[b]	ratio of trans/cis[c]	combined yield (%)
1	**15a**	3 eq. HSAc, $ZnCl_2$, benzene, reflux 6 h	1:trace		50
2	**15a**	ex HSAc, $ZnCl_2$, benzene, rt, 24 h	9:1	2.5:1	77
3	**15a**	ex HSAc, $ZnCl_2$, benzene, rt, 6 days	4:1	2:1	75
4	**15a**	12 eq. HSAc, 6 eq. BF_3–Et_2O, CH_2Cl_2	1:3	1.5:1	70
5	**15b**	3 eq. HSAc, $ZnCl_2$, benzene, reflux 6 h	1:trace		54
6	**15b**	ex HSAc, $ZnCl_2$, benzene, rt, 24 h	9:1	3:1	63
7	**15b**	ex HSAc, $ZnCl_2$, benzene, rt, 6 days	1:1	2:1	80
8	**15b**	3 eq. HSAc, 0.5 eq. BF_3–Et_2O, CH_2Cl_2	1:trace		50
9	**15b**	12 eq. HSAc, 6 eq. BF_3–Et_2O, CH_2Cl_2	1:3	3:1	64
10	**14a**	ex HSAc, $ZnCl_2$, $CHCl_3$, rt, 24 h	trace:1	3:1	52
11	**14a**	ex HSAc, $ZnCl_2$, acetone, rt, 24 h	trace:1	5:1	32
12	**14a**	ex HSAc, $ZnCl_2$, benzene, rt, 24 h	trace:1	3.6:1	62
13	**14a**	ex HSAc, $ZnCl_2$, benzene, rt, 36 h	trace:1	3:1	83

more mild, selective conditions.

After reviewing the various moieties which have been used as amide protecting groups,[19] we decided to try the *o*-nitrobenzyl (oNB) group which has the distinct advantage of being photolabile under mild conditions. The oNB group has been used extensively in peptide chemistry as an amine and carboxyl protecting group[20] and has been used as an alcohol protecting group as well. The use of oNB as an *amide protecting group* has not been widely used,[21] and our synthesis demonstrates the potential utility of oNB as an amide protecting group.

The total synthesis summarized in Scheme III commences with the synthesis of 2,4-dihydroxy-5-chlorobenzaldehyde **23**. Compound **23** can be obtained from 2,4-dihydroxybenzaldehyde via electrophilic chlorination using NaOCl[22] or via formylation of 4-chlororesorcinol **22**.[23] Both methodologies were investigated with varying degrees of success.

Attempted chlorination of 2,4-dihydroxybenzaldehyde with basic NaOCl did not generate the desired 5-chloro isomer **23** as originally reported.[24] Benzaldehyde **23** was obtained selectively via Gatterman formylation of commercially available 4-chlororesorcinol **22** using zinc cyanide in the presence of HCl. Selective protection of the 4-hydroxyl to give **24** was achieved with moderate success (49%) using chloromethyl methyl ether (MOM chloride) in the presence of triethylamine. As expected, the major side product in this reaction is the over-protected product which is easily removed during workup.

Conversion of **24** to the corresponding coumarilic acid derivative was performed using Tanaka's procedure although the yields obtained did not match those reported for similar systems.[25] Treating **24** with diethyl bromomalonate and potassium carbonate followed by hydrolysis of the intermediate diester under basic conditions resulted in formation of the desired coumarilic acid **25** in 72% yield along with a small amount of the deprotected acid as a side product. The unprotected compound arises from the acidic workup required and could be suppressed by careful control of the pH.

Schotten–Baumann coupling of acid chloride **25** with *N*-(2-nitrobenzyl)glycine ethyl ester **26** (prepared from 2-nitrobenzyl bromide and glycine ethyl ester) went smoothly. The crude ester was routinely carried on without purification, immediately being subjected to acid hydrolysis (aqueous HCl, dioxane, reflux) to remove both the ethoxy and methoxymethyl groups giving carboxylic acid **27a** in 84–95% overall yield from **25**. Conversion of **27a** to the desired hydroxamic acid **28a** was achieved in a modest 41% yield by diimide coupling (1-(3-(dimethylamino)-propyl)-3-ethylcarbodiimide hydrochloride, methoxylamine, aqueous THF).

Attempted ring closure of **28a** did not result in any of the desired spiro[benzofuran-piperazine] compound **29a** under identical conditions (NBS, $CHCl_3$), and starting material was recovered unchanged. The lack of ring closure for the free hydroxyl containing **28a** compared to the facile ring closure for the hydroxamic ester **13a** in the model study strongly suggests that the 6-hydroxy group has a pronounced influence on the electronic nature of the 2,3 double bond presumably via a resonance effect. In order to minimize the effects of the distant hydroxy group on the double bond, the 6-hydroxy group was protected with an electron-withdrawing ester moiety. Initial reactions were conducted with pivalate, but this group proved too difficult to remove in subsequent transformations and was abandoned (data not shown). The desired transformation was obtained using acetate as the protecting group which was efficiently introduced by treating **27a** with excess acetic anhydride. Compound **27b** was further converted into hydroxamic ester **28b** in 70% yield via mixed anhydride formation (isobutyl chloroformate, *N*-methylmorpholine, methoxylamine). Treatment of **28b** with NBS gave the desired tricyclic compound **29b** in 57–63% isolated yield after workup.

Conversion of **29b** into a mixture of alcohols using the procedure developed in the model study (silver triflate, aqueous THF, 73%, ~1:1 ratio) was straightforward, but we opted for converting **29b** into a protected form of the alcohols, the analogous methyl ethers. Conversion of **29b** into **30a,b** was achieved in 73% yield by simply performing the reaction in the presence of methanol instead of water. Much to our surprise, the conversion of **29b** to **30a,b** proceeds in a stereoselective fashion resulting in a 4:1 ratio of **30a**:**30b**. If the reaction was conducted at reflux the ratio of **30a**/**30b** dropped to 2:1, but the overall yield was increased to 80%. Methyl ethers **30a,b** could be separated by careful column chromatography and carried on independently. Determination of the stereochemistry for the methyl ethers was carried out by NOE experiments and comparison of the ^1H NMR spectra with NMR data obtained from the model study.

The photolytic deprotection of **30a,b** was examined under a variety of conditions (Table II). Using a variety of aqueous THF solutions resulted in the desired **31a,b** in 40–50% yield. As the deprotection proceeds the solution darkens, and it was assumed the change in color may be quenching the reaction. Addition of Pyrex beads to the solution (entry 2) as a means of increasing the transmittance through the solution improved the yield to 58%. Further improvements in the yield were obtained by decreasing

(19) Smith, M. B.; Wand, C.; Keusenkothen, P. F.; Dembofsky, B. T.; Fay, J. G.; Zezza, C. A.; Kwon, T. W.; Sheu, J.; Son, Y. C.; Menezes, R. F. *Chem. Lett.* **1992**, 247 and references cited therein. See, also: Nakatsuka, S.; Miyazaki, H.; Goto, T. *Tetrahedron Lett.* **1980**, *21*, 2817. Kishi, Y.; Nakatsuka, S.; Fukuyama, T.; Havel, M. *J. Am. Chem. Soc.* **1973**, *95*, 6493.

(20) Review of photolabile protecting groups, see: Pillai, V. N. R. *Synthesis* **1980**, 1. For related work using *o*-nitrobenzyl groups see: (a) Walker, J. W.; Reid, G. P.; McCray, J. A.; Trentham, D. R. *J. Am. Chem. Soc.* **1988**, *110*, 7170. (b) Kalbag, S. M.; Roeske, R. W. *J. Am. Chem. Soc.* **1975**, *97*, 440. (c) Patchornik, A.; Amit, B.; Woodward, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 6333. (d) Barltrop, J. A.; Schofield, P. *J. Chem. Soc.* **1965**, 4758.

(21) Milburn, T.; Matsubara, N.; Billington, A. P.; Udgaonkar, J. B.; Walker, J. W.; Carpenter, B. K.; Webb, L. W.; Marque, J.; Denk, W.; McCray, J. A.; Hess, G. P. *Biochemistry* **1989**, *28*, 49.

(22) Hopkins, C. Y.; Chisholm, M. J. *Can. J. Res.* **1946**, *24B*, 208.

(23) Chakravarti, D.; Ghosh, B. *J. Ind. Chem. Soc.* **1935**, *12*, 791. Adams, R.; Levine, I. *J. Am. Chem. Soc.* **1923**, *45*, 2373.

(24) The regiochemical assignment was made based on ^1H NMR coupling constants for the 3- and 5-chloro regio isomers. The 200 MHz ^1H NMR of **23** exhibits two singlets at 7.61 and 6.59 ppm which is consistent with *para*-substitution in aromatic rings. The ^1H NMR of 3-chlororesorcylaldehyde, on the other hand, exhibits two doublets at 7.57 and 6.68 ppm (J = 8.69 Hz) consistent for *ortho* protons indicating chlorination must have taken place at the 3-position.

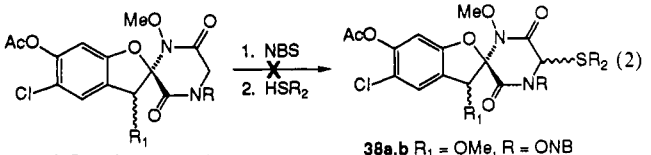
(25) Tanaka, S. *J. Am. Chem. Soc.* **1951**, *73*, 872.

Table II. Photolysis Conditions for the Conversion of **30a,b** to **31a,b**[a]

entry	solvent, conditions	time (h)	% yield **30a,b**[b]
1	30% H_2O/THF	18	40–50
2	30% H_2O/THF, beads	18	58
3	10% H_2O/THF, beads	18	66
4	10% H_2O/THF, beads	5	72
5	10% H_2O/THF, beads 10 eq. semicarbazide-HCl	5	68

[a] All reactions were carried out at 10 mmol concentrations in a quartz tube. Photolysis was carried out using a 450-W Conrad-Hanovia medium-pressure mercury vapor lamp at 37 °C. [b] Reported yields are isolated yields.

the amount of water from 30% to 10% in the reaction mixture resulting in the yield increasing to 66%. A final change in the duration of the photolysis from 18 h to 5 h increased the yield to an optimal 72%. Addition of an aldehyde trapping agent (10 equiv semicarbazide hydrochloride, entry 5) did not affect the overall yield for the photolysis. Under the reaction conditions no epimerization at the benzylic position was observed in either case. As an interesting side note, the photolytic deprotection could also be carried out efficiently using direct sunlight.



30a,b R_1 = OMe, R = ONB
31a,b R_1 = OMe, R = H

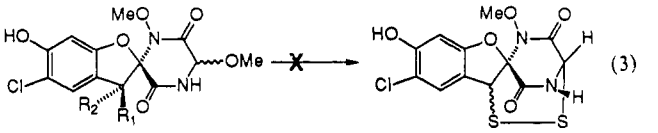
38a,b R_1 = OMe, R = ONB
39a,b R_1 = OMe, R = H

Attempted functionalization of the α-position of the diketopiperazine ring of both the *o*-nitrobenzyl protected substrate **30a,b** or the deprotected compounds **31a,b** under a variety of conditions did not give satisfactory results. Attempted bromination (NBS, benzoyl peroxide carbon tetrachloride, reflux) of **30** followed by trapping the unstable bromide with thiolacetic acid did not result in any of the desired functionalized compounds **38** in appreciable yields (eq 2). Likewise **31** was resistant to NBS under a variety of conditions which have been used to brominate α to NH groups in dipeptides (e.g., NBS/CCl_4 or NBS/$CHCl_3$)[26,27] and did not give any of the desired **39**.

The oxidation of the diketopiperazine could be carried out efficiently via N-chlorination using *tert*-butyl hypochlorite.[28] Treatment of **31a,b** with *tert*-butyl hypochlorite followed by sodium methoxide gave the bismethyl ethers *trans*-**32a,b** and *cis*-**32c,d** each as a mixture of epimers at the α-position. The reaction displays a pronounced solvent dependency; reactions carried out in chlorinated solvents gave the best synthetic yields (50–58%). The N-chlorination/rearrangement reaction proceeds with slight stereoselectivity giving a 1.6:1 ratio of **32a**/**32b** when the reaction were carried out in methylene chloride and a 3:1 ratio of **32a**/**32b** when the reaction was carried out in chloroform. Diastereomers **32a,b** could be easily separated by column chromatography, while epimers **32c,d** were inseparable and carried on as a mixture.

The acetate protecting group in **32** was efficiently removed by treating the individual diastereomers (in the case of **32a,b**) or the mixture **32c,d** with sodium ethoxide in absolute ethanol at 0 °C to give the free phenols **33a–d** in 72–74% yields. All the various diastereomers of **33** could be separated by chromatography. Direct conversion of **31** to **33** could be carried out using excess base, but better overall yields were obtained if the reactions were carried out separately.

Incorporation of the sulfur moieties into **33a–d** was anticipated to lead directly to aspirochlorine (eq 3). Unfortunately this was not borne out experimentally. Treating **33a,b** with H_2S in the presence of $ZnCl_2$ or BF_3–Et_2O under numerous conditions followed by KI_3 oxidation resulted in complex mixtures and only trace amounts of the natural product. Treatment of **33c,d** with H_2S, $ZnCl_2$ followed by oxidation gave aspirochlorine in a disappointing 5–10% isolated yield.



33a-d **2, 35** (3)

Conversion of methyl ethers **33a,b** or **33c,d** to the corresponding bisthioacetates **34a–d** was achieved (12 equiv of thiolacetic acid, 6 eqiv of BF_3–Et_2O, CH_2Cl_2 reflux, 8 h) yielding a mixture of diastereomers in 65% combined yield. The compounds could be separated into two sets of two diastereomers: the nonpolar minor group (ca. < 20%) and the more polar major set of thioacetates. Based on the precedence observed in the model study, the major diastereomers were tentatively assigned the desired trans stereochemistry at the benzylic position and carried on. This stereochemical assignment was verified by reduction of an authentic sample of aspirochlorine (excess methyl mercaptan, pyridine) followed by trapping of the dithiol intermediate with acetyl chloride to generate **34**. Comparison of the ^1H NMR spectra of the products from this reaction with the ^1H NMR of the major thioacetates obtained via BF_3–Et_2O catalysis established that these thioacetates were identical.

Conversion of thioacetates **34a–d** into aspirochlorine also proved to be problematic. Basic conditions such as NaOMe/MeOH, aqueous $NaHCO_3$/EtOH, NaSH/EtOH, or NH_4OH/MeOH under either anaerobic or aerobic conditions resulted in disappearance of starting material but did not produce any aspirochlorine upon workup. Deprotections using a nonbasic nucleophile such as cyanide anion[29] (0.1 equiv of aqueous NaCN, MeOH, reflux) only gave traces of the natural produce by ^1H NMR, while reactions using chloroaniline, which has been used to cleave base sensitive thioacetates, gave no reaction at all.[30]

Removal of the acetate protecting groups under acidic conditions was achieved but with limited success. Treatment of thioacetates **34** with saturated ethanolic HCl followed by oxidation resulted in a complex mixture of products from which aspirochlorine could be isolated in 5–15% yield. Numerous attempts at varying the conditions (aqueous HCl/EtOH, catalytic HCl, aqueous acid, neat TFA/thioanisole, etc.) did not substantially improve the yield.

The low yield for the desired product along with the substantial amount of decomposition which was being observed lead us to believe the thioacetates were either unstable to the reaction conditions and/or the oxidation to the disulfide did not proceed readily. To test whether the dithiol/disulfide oxidation was contributing to the low yield, a sample of natural aspirochlorine was reduced ($NaBH_4$, EtOH, 0 °C), and the intermediate dithiols immediately oxidized with aqueous KI_3. Although the oxidation appeared to be clean by TLC, aspirochlorine was only isolated in 38% from the reaction, indicating the oxidation does not take place as readily as anticipated.

The substantial decomposition in the deprotection reactions must be due to the instability of the thioacetates under the various conditions examined. The elimination of 2 equiv of thiolacetic acid from **34** could readily occur due to the presence of strategically located activating groups (i.e., the OH activates the benzylic position, and the NH activates the α-position of the diketopiperazine ring). Evidence for this type of elimination/addition was observed in the model study and used to account for the epimerization of thioacetates **16a,b** and the formation of the mixture of disulfides **18a,b**. Thus, acid catalyzed loss of 1 equiv of thiolacetic acid could generate either a quinone methide species or an *N*-acyl iminium ion both of which are reactive intermediates,

(26) Yamaura, M.; Suzuki, T.; Hashimoto, H.; Yoshimura, J.; Shin, C. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2812.
(27) Lidert, Z.; Gronowitz, S. *Synthesis* **1980**, 322.
(28) (a) Poisel, H.; Schmidt, U. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 294. (b) Poisel, H.; Schmidt, U. *Chem. Ber.* **1975**, *108*, 2547.
(29) Aminolysis of esters using catalytic cyanide, see: Hogberg, T.; Strom, P.; Ebner, M.; Ramsby, S. *J. Org. Chem.* **1987**, *52*, 2033. Transesterification of esters using catalytic cyanide, see: Mori, K.; Tominaga, M.; Takigawa, T.; Matsui, M. *Synthesis* **1973**, 790.
(30) Fuchs, G. *Acta Chem. Scand.* **1965**, *4*, 1490.

which can undergo further loss of thiolacetic acid and decomposition.

To take advantage of the possibility that elimination was indeed occurring, the deprotection was carried out using saturated H_2S in a nonnucleophilic solvent in order to increase the amount of sulfur nucleophile in solution. Therefore if the elimination occurred, the probability of the intermediate being quenched by thiol would be increased. Saturating a benzene solution of thioacetate **34a,b** and camphor sulfonic acid (CSA) with H_2S resulted in *clean* conversion to aspirochlorine in 28% isolated yield (51% based on recovered starting material). Unfortunately this reaction proved to be rather unpredictable and could not be repeated with any consistency. Determination of whether transesterification or elimination/addition of hydrogen disulfide is the mechanism is not clear. Treatment of methyl ethers **33c,d** under the same conditions resulted in no reaction, and only starting material was evident by TLC.

After several more attempts, we were finally able to cleave the thioacetates under mild conditions using aminolysis. Treating a solution of **34a–d** with excess methoxylamine in the presence of camphor sulfonic acid (CSA) under aerobic conditions routinely gave aspirochlorine in 20–34% yield. The synthetic aspirochlorine possessed identical ^{1}H NMR and IR spectral characteristics and HPLC retention time when compared with the natural substance. At the present time, none of the epimeric disulfide **35** has been positively identified from either reactions involving the methyl ethers or thioacetates. The lack of evidence for **35** does not rule out the formation of such a compound and may reflect problems associated with stability.

The first total synthesis of (±)-aspirochlorine has been achieved in 13 steps from 4-chlororesorcinol. The synthesis proceeds with moderate stereoselectivity and exemplifies the use of the *o*-nitrobenzyl group as a photolabile amide protecting group. Efforts to study the redox properties of the aspirochlorine disulfide bridge as compared to other disulfides is currently under study in these laboratories.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker 300 MHz FT NMR or on an IBM WP270 MHz FT NMR in $CDCl_3$ or DMSO-d_6 and chemical shifts are reported relative to TMS. NMR data collected in methanol-d_4 are reported relative to the methanol peak at 3.30 ppm. IR were collected on a Perkin-Elmer 1600 FT IR. Melting points were obtained using a Mel Temp apparatus and are uncorrected. Elemental analysis were performed by MHW labs, Phoenix, AZ. Analytical thin-layer chromatography (TLC) was carried out using Merck Kieselgel 60 F_{254} glass plates. Preparative flash column chromatography was performed using Grade 60 230–400 mesh silica gel purchased from Aldrich, and radial chromatography was carried out on a Chromatotron Model 7924 using 1,2 or 4 mm silica plates as needed. HPLC separation of aspirochlorine was carried out using Waters 6000 pump equipped with a 254-nm fixed wavelength detector and a 8 × 10 cm silica radial compression cartridge, using 2% methanol/chloroform at a flow rate of 2 mL/min.

Unless otherwise stated, all reactions were carried out in flame-dried flasks under a N_2 or argon atmosphere. Compounds containing *o*-nitrobenzyl group were stored in flasks wrapped in aluminum foil to minimize photodecomposition. Tetrahydrofuran and diethyl ether were dried over sodium/benzophenone ketyl, while methylene chloride was dried over calcium hydride. Transfer of solvents were carried out via flame-dried syringe. Ethanol-free chloroform was obtained by first washing with water, drying over magnesium sulfate distillation from phosphorus pentoxide, and storing in an amber bottle. Triethylamine, pyridine, and acyl chlorides were first filtered through alumina prior to use. TLCs of thiol and thioacetate-containing compounds were visualized either using ethanolic I_2/NaN_3 stain or 5% Ellmans' reagent in DMF. Photolysis reactions were conducted using a 450-W Conrad-Hanovia 7825 medium-pressure lamp in a Pyrex well at 37 °C. Coumarilic acid was obtained from Lancaster Synthesis, and 5-chlororesorcinol was obtained from Aldrich. Methoxylamine hydrochloride was converted into the free base using the published procedure.[31] Methoxylamine was stored over KOH at 0 °C and filtered through a plug of alumina prior to use. *tert*-Butyl hypochlorite was prepared fresh and stored in an amber bottle over $CaCl_2$ at 0 °C.[32] All other reagents used were of commercial purity (Aldrich) unless otherwise stated.

Caution. Reactions involving the highly toxic H_2S and zinc cyanide/HCl mixtures were very carefully performed in a well ventilated fume hood. In addition, reactions carried out using the highly toxic carcinogen chloromethyl methyl ether (MOM-Cl) were conducted using appropriate lab attire (lab coat, rubber gloves, safety glasses) in a well-ventilated fume hood.

***N*-(4-Methoxybenzyl)glycine Ethyl Ester (11).** To a stirred solution of *p*-methoxybenzylamine (68.6 g, 0.5 mol, 1.0 equiv) and triethylamine (101 g, 1.0 mol, 2.0 equiv) in 300 mL of THF was added dropwise ethyl bromoacetate (87.7 g, 0.525 mol, 1.05 equiv) at 0 °C under N_2, and the mixture stirred at room temperature for 12 h. The reaction was filtered and evaporated, and the product was distilled under reduced pressure (bp 135–140 0 °C, 0.3 mmHg): obtained 94.4 g of a light yellow oil; 85% yield; ^{1}H NMR (270 mHz), $CDCl_3$) δ = 1.27 (3 H, t), 1.90 (1 H, s), 3.39 (2 H, s), 3.74 (2 H, s), 3.80 (3 H, s), 4.19 (2 H, qt), 6.87 (2 H, d), 7.25 (2 H, d); IR (NaCl, neat film) ν = 3340, 2975, 2930, 1735, 1610 cm^{-1}.

***N*-[Benzofuranyl-2-(3*H*)]-*N*-(4-methoxybenzyl)glycine (12a).** A solution of coumarilic acid (1.98 g, 12.2 mmol, 1.0 equiv) and thionyl chloride (3.1 mL, 38.9 mmol, 3.0 equiv) in 150 mL of dry benzene was refluxed for 4 h. The solution was concentrated. The crude acid chloride was taken up in methylene chloride and added to a vigorously stirred aqueous solution containing *N*-(4-methoxybenzyl)glycine ethyl ester **11** (3.0 g, 13.0 mmol, 1.1 equiv) and $NaHCO_3$ (1.1 g, 13.0 mmol, 1.1 equiv). The solution was stirred at room temperature for 1 h. The layers were separated, and the organic phase was washed with water, dried over $MgSO_4$, and filtered to give a yellow oil. The crude ester was taken up in 100 mL of ethanol, cooled to 0 °C, and saponified using LiOH (15 mL, 15.0 mmol, 1.2 equiv). The solution was warmed to room temperature and stirred for 24 h. The white solid was collected by filtration and taken up in water. After acidification with 2 M HCl, the acid was extracted into methylene chloride, dried with $MgSO_4$, filtered, and concentrated to a light yellow solid. The product was recrystallized from boiling ethyl acetate/hexanes: 66% yield; mp 153–154 °C; ^{1}H NMR (300 MHz, DMSO-d_6, T = 370 K) δ = 7.71 (1 H, d, J = 7.7 Hz), 7.54 (1 H, d, J = 8.1 Hz), 7.44–7.37 (2 H, m), 7.32–7.24 (3 H, m), 6.89 (2 H, d, J = 8.6 Hz), 4.75 (2 H, s), 4.17 (2 H, s), 3.74 (3 H, s); IR (NaCl, film) ν = 2938, 1738, 1611, 1248, 1176 cm^{-1}. Anal. Calcd for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.19; H, 5.11; N, 4.18.

***N*-[Benzofuranyl-2-(3*H*)]-*N*-glycine (12b).** Coumarilic acid (1.0 g, 6.16 mmol, 1.0 equiv) was dissolved in 100 mL of dry benzene and thionyl chloride (1.45 mL, 18.5 mmol, 3.0 equiv) was added, and the solution was refluxed for 3 h. The reaction was cooled, and the solvent was removed to give the crude acid chloride as an off-white colored solid. The acid chloride was taken up in CH_2Cl_2 and added to a vigorously stirred suspension of glycine ethyl ester hydrochloride (947 mg, 6.78 mmol, 1.1 equiv) and $NaHCO_3$ (569 mg, 6.78 mmol, 1.1 equiv) in 100 mL of water. The reaction was stirred for 1 h, the layers separated, and the organic phase was collected, washed with water, dried over $MgSO_4$, filtered, and concentrated to a white crystalline material.

The ester was dissolved in 50 mL of ethanol cooled to 0 °C. An aqueous solution of LiOH (2.8 mL, 1.1 equiv) was added, and the solution was warmed to room temperature and stirred for 24 h. The solvent was removed, and the residue was taken up in water, washed with diethyl ether, and acidified with 1 M HCl. The white precipitate was extracted into CH_2Cl_2, washed with water, dried over $MgSO_4$, filtered, and concentrated to a white solid which was recrystallized from ethyl acetate/hexanes: mp 189–191 °C; 65% yield; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 12.71 (1 H, brs), 9.0 (1 H, t, J = 5.9 Hz), 7.79 (1 H, d, J = 7.6 Hz), 7.67 (1 H, d, J = 8.4 Hz), 7.58 (1 H, s), 7.51–7.45 (1 H, m), 7.37–7.32 (1 H, m), 3.94 (2 H, d, J = 6.0 Hz); IR (KBr) ν = 3267, 3057, 1725, 1660, 1567, 1228, 748 cm^{-1}. Anal. Calcd for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.25; H, 4.25; N, 6.28.

***N*-Benzofuranylglycine Hydroxamate (13a).** To a solution containing 1 g **12a** (2.94 mmol, 1.0 equiv) dissolved in 250 mL of THF cooled to 0 °C was added triethylamine (616 mL, 4.42 mmol, 1.5 equiv). Pivaloyl chloride (400 mL, 1.1 equiv) was added causing the solution to turn bright yellow. The reaction was stirred at 0 °C for 90 min before added methoxylamine (500 mL, 9.4 mmol, 3.2 equiv). Solution stirred at 0 °C until the yellow color dissipated (about 2 h). The reaction was poured into ethyl acetate, washed with saturated $NaHCO_3$ and water, dried over $MgSO_4$, filtered, and concentrated to a thick, colorless oil which left standing crystallized. The hydroxamic ester was purified by recrystallization from boiling ethyl acetate/hexanes: obtained 1.03 of a white solid; typical yields 80–95%; ^{1}H NMR (300 MHz, DMSO-d_6, T = 370

(31) Fujii, T.; Wu, C. C.; Yamada, S. *Chem. Pharm. Bull.* **1967**, *15*, 345. Bissot, T. C.; Parry, R. W.; Campbell, D. H. *J. Am. Chem. Soc.* **1957**, *79*, 796.

(32) Mintz, M. J.; Walling, C. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. 5, p 184.

K) δ = 10.78 (1 H, brs), 7.48 (1 H, d, J = 7.7 Hz), 7.55 (1 H, d, J = 8.2 Hz), 7.44–7.37 (2 H, m), 7.33–7.24 (3 H, m), 6.89 (2 H, d, J = 8.6 Hz), 4.74 (2 H, s), 4.0 (2 H, s), 3.75 (3 H, s), 3.58 (3 H, s); IR (NaCl, film) ν = 3203, 2999, 2936, 1677, 1613, 1513 cm^{-1}. Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.20; H, 5.47; N, 7.61. Found: C, 65.25; H, 5.61; N, 7.69.

***N*-Benzofuranylglycine Hydroxamate (13b).** To an aqueous THF solution of **12b** (1.6 g, 7.3 mmol, 1.0 equiv) and 1-(3-(dimethylamino)-propyl)-3-ethylcarbodiimide hydrochloride (2.79 g, 14.6 mmol, 2.0 equiv) was added methoxylamine (686 mg, 14.6 mol, 2.0 equiv). The solution was stirred at room temperature for 48 h. The reaction was poured into water, extracted with CH_2Cl_2, washed with saturated $NaHCO_3$ and water, dried over $MgSO_4$, filtered, and concentrated to a white solid. The solid was recrystallized from ethyl acetate/hexanes to give 976 mg of a crystalline material: mp 181 °C; 53% yield; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 11.23 (1 H, brs), 8.93 (1 H, brt), 7.78 (1 H, d, J = 7.6 Hz), 7.67 (1 H, d, J = 8.4 Hz), 7.58 (1 H, s), 7.50–7.45 (1 H, m), 7.37–7.32 (1 H, m), 3.80 (2 H, d, J = 5.7 Hz), 3.6 (3 H, s); IR (KBr) ν = 3275, 3196, 3001, 1684 (shoulder), 1648, 1572, 1305, 747 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.26; H, 4.99; N, 11.25.

Trans Spiro Cyclic Bromide (14a). To a solution of glycine hydroxamate **13a** (1 g, 2.71 mmol, 1 equiv) in 50 mL of EtOH-free $CHCl_3$ was added NBS (578 mg, 3.25 mmol, 1.2 equiv) in one portion, and the solution was stirred at room temperature overnight. The reaction was diluted with additional $CHCl_3$ and extracted with saturated $Na_2S_2O_3$ and twice with H_2O, and the organic layer was dried over Na_2SO_4, filtered, and evaporated to give a thick yellow oily residue. The residue was taken up in ethyl acetate, and the white precipitate which subsequently forms collected. The mothor liquor was chromatographed using 3:2 hexane/ethyl acetate, and the product was recrystallized from boiling ethyl acetate/hexanes: 50% combined yield; mp 142–143 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) ∂ = 7.33–7.26 (4 H, m), 7.28 (1 H, d, J = 8.6 Hz, super imposed over multiplet), 7.07–7.02 (1 H, m), 6.97–6.95 (1 H, m), 6.86 (1 H, d, J = 8.6 Hz), 6.01 (1 H, s), 4.69 (1 H, $^1/_2$ABq, J = 14.3 Hz), 4.50 (1 H, $^1/_2$ABq, J = 14.3 Hz), 5.99 (2 H, d, J = 1.4 Hz), 3.92 (3 H, s), 3.80 (3 H, s); ^{1}H NMR (DMSO-d_6, 270 MHz) ∂ = 7.34–7.29 (5 H, m), 7.06–7.02 (2 H, m), 6.92 (1 H, d, J = 8.6 Hz), 6.24 (1 H, s), 4.69 (1 H, $^1/_2$ABq, J = 14.3 Hz), 4.38 (1 H, $^1/_2$ABq, J = 14.3 Hz), 4.19 (1 H, $^1/_2$ABq, J = 18.3 Hz), 4.04 (1 H, $^1/_2$ABq, J = 18.3 Hz), 3.74 (3 H, s); ^{13}C NMR ($CDCl_3$, 75.47 MHz) ∂ = 162.1 (C), 160.93 (C), 159.8 (C), 157.9 (C), 131.18 (CH), 131.08 (CH), 130.63 (CH), 125.93 (C), 125.44 (CH), 122.68 (CH), 114.28 (CH), 109.69 (CH), 100.68 (C), 65.71 (CH_3), 55.28 (CH_3), 50.15 (CH), 49.24 (CH_2), 47.96 (CH_2); IR (neat, NaCl) ν = 1693, 1613, 1513, 1245 cm^{-1}. Anal. Calcd for $C_{20}H_{19}N_2O_5Br$: C, 53.70; H, 4.28; N, 6.26; Br, 17.87. Found: C, 53.62; H, 4.22; N, 6.26; Br, 18.00.

Trans and Cis Spiro Cyclic Alcohols (15a,b). **14a** was dissolved in a solution of 1:1 THF/H_2O at room temperature. Silver triflate (1.2 equiv) dissolved in THF was added, and the resulting solution was stirred for 30 min. The solution was diluted with ethyl acetate, and saturated NaCl solution added. The solution was filtered through a plug of Celite to remove the silver salts. The filtrate was washed with brine and water, dried over $MgSO_4$, filtered, and afterwards evaporated to a colorless oil which upon standing solidifies. The residue was taken up in ethyl acetate and chromatographed using 1:1 ethyl acetate/hexanes. Both isomers were recrystallized from ethyl acetate/hexanes: 80% combined yield.

***trans*-15a**: R_f 0.17, 1:1 ethyl acetate/hexanes; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.39–7.19 (4 H, m), 7.06–7.01 (1 H, m), 6.91–6.87 (3 H, m), 5.80 (1 H, d, J = 12.3 Hz, singlet in D_2O), 4.60 (1 H, $^1/_2$ABq, J = 14.4 Hz), 4.49 (1 H, $^1/_2$ABq, J = 14.4 Hz), 3.98 (2 H, s), 3.88 (3 H, s), 3.80 (3 H, s), 3.55 (1 H, d, J = 12.4 Hz, exchangeable in D_2O); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ = 161.49 (C), 160.99 (C), 159.73 (C), 158.47 (C), 130.65 (CH), 129.97 (CH), 127.19 (C), 125.81 (C), 125.0 (CH), 122.44 (CH), 114.46 (CH), 109.86 (CH), 99.92 (C), 77.50 (CH), 65.30 (CH_3), 55.29 (CH_3), 48.95 (CH_2), 47.99 (CH_2); IR (NaCl, neat film) ν = 3407, 1683 cm^{-1}; mp 135–136 °C. Anal. Calcd for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.29. Found: C, 62.49; H, 5.25; N, 7.26.

***cis*-15b**: R_f 0.1, 1:1 ethyl acetate/hexanes); ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.36–7.28 (3 H, m), 7.24 (1 H, $^1/_2$ABq, J = 8.6 Hz), 7.07–6.96 (3 H, m), 6.98 (1 H, $^1/_2$ABq, J = 8.6 Hz), 5.59 (1 H, d, J = 12.6 Hz, singlet in D_2O), 4.69 (1 H, $^1/_2$ABq, J = 14.3 Hz), 4.48 (1 H, $^1/_2$ABq, J = 14.3 Hz), 4.01 (2 H, s), 3.81 (3 H, s), 3.78 (3 H, s), 3.0 (1 H, d, J = 12.8 Hz, exchangeable in D_2O); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ = 162.95 (C), 161.78 (C), 159.75 (C), 157.46 (C), 130.79 (CH), 130.16 (CH), 126.27 (C), 126.20 (C), 124.57 (CH), 122.58 (CH), 114.47 (CH), 109.76 (CH), 98.28 (C), 79.08 (CH), 65.54 (CH_3), 55.33 (CH_3), 49.28 (CH_2), 48.11 (CH_2); IR (NaCl, neat film) ν = 3392, 1683 cm^{-1}; mp 140–142 °C. Anal. Calcd for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.29. Found: C, 62.44; H, 5.21; N, 7.20.

Trans and Cis Spiro Cyclic Thioacetates (16a,b). **14a** (75 mg) was dissolved in 4 mL of benzene, and excess thiolacetic acid (0.5 mL) was added followed by a spatula tip of anhydrous zinc chloride. The solution was stirred for 36 h at room temperature. The reaction was filtered, diluted with ethyl acetate, washed three times with saturated $NaHCO_3$ and water, dried over $MgSO_4$, filtered, and concentrated to a foul-smelling yellow film. The products were purified via column chromatography using 10% acetone in CCl_4 as the eluent: yield 69–80%.

***trans*-16a**: R_f 0.3, 20% acetone/CCl_4; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.28–7.24 (4 H, m), 7.14 (1 H, d, J = 7.5 Hz), 6.97–6.85 (3 H, m), 5.74 (1 H, s), 4.87 (1 H, $^1/_2$ABq, J = 14.1 Hz), 4.16 (1 H, $^1/_2$ABq, J = 14.1 Hz), 3.94 (1 H, $^1/_2$ABq, J = 18 Hz), 3.91 (3 H, s), 3.83 (1 H, $^1/_2$ABq, J = 18.2 Hz), 3.79 (3 H, s), 2.14 (3 H, s); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ = 195.2 (C), 161.48 (C), 160.58 (C), 159.7 (C), 158.1 (C), 130.69 (CH), 129.91 (CH), 126.41 (C), 124.31 (CH), 123.91 (C), 122.17 (CH), 114.25 (CH), 109.36 (CH), 101.3 (C), 65.4 (CH_3), 55.31 (CH_3), 50.11 (CH), 49.24 (CH_2), 48.45 (CH_2), 29.62 (CH_3); IR (NaCl, neat film) ν = 1694, 1513, 1462, 1244 cm^{-1}; white crystals from ethyl acetate/petroleum ether; mp 164–165 °C. Anal. Calcd for $C_{22}H_{22}N_2O_6S$: C, 59.71; H, 5.01; N, 6.33; S, 7.25. Found: C, 59.93; H, 5.18; N, 6.07; S, 7.48.

***cis*-16b**: R_f 0.4, 20% acetone/CCl_4; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.29–7.28 (4 H, m), 7.14 (1 H, d, J = 7.5 Hz), 7.11–6.88 (3 H, m), 5.81 (1 H, s), 4.81 (1 H, $^1/_2$ABq, J = 14.3 Hz), 4.47 (1 H, $^1/_2$ABq, J = 14.3 Hz), 3.91 (1 H, $^1/_2$ABq, J = 18 Hz), 3.81 (3 H, s), 3.77 (3 H, s) superimposed over 3.73 (1 H, $^1/_2$ABq, J = 18 Hz), 2.36 (3 H, s); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ = 195.61 (C), 162.9 (C), 160.32 (C), 159.67 (C), 157.19 (C), 130.33 (CH), 129.78 (CH), 126.14 (C), 123.97 (CH), 123.59 (C), 122.33 (CH), 114.31 (CH), 109.26 (CH), 99.50 (C), 65.04 (CH_3), 55.29 (CH_3), 52.74 (CH), 49.45 (CH_2), 48.16 (CH_2), 29.91 (CH_3); IR (NaCl, neat film) ν = 1706, 1691, 1612, 1513, 1461, 1239 cm^{-1}; white plates from ethyl acetate/petroleum ether; mp 102–104 °C. Anal. Calcd for $C_{22}H_{22}N_2O_6S$: C, 59.71; H, 5.01; N, 6.33; S, 7.25. Found: C, 59.61; H, 5.23; N, 6.11; S, 7.00.

***trans*-*O*-Acetate 21a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.27–7.25 (4 H, m), 7.03–7.02 (2 H, m), 6.87 (2 H, d, J = 8.6 Hz), 6.42 (1 H, s), 4.63 (1 H, $^1/_2$ABq, J = 14.1 Hz), 4.32 (1 H, $^1/_2$ABq, J = 14.1 Hz), 3.99 (2 H, d, J = 1.8 Hz-collapsed AB quartet), 3.86 (3 H, s), 3.79 (3 H, s), 1.86 (3 H, s); IR (NaCl, neat film) ν = 2941, 1739, 1687, 1513, 1248 cm^{-1}.

***cis*-*O*-Acetate 21b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.35–7.26 (4 H, m), 7.06–6.98 (2 H, m), 6.9 (2 H, d, J = 8.6 Hz), 6.33 (1 H, s), 4.72 (1 H, $^1/_2$ABq, J = 14.4 Hz), 4.53 (1 H, $^1/_2$ABq, J = 14.4 Hz), 3.87 (2 H, d, J = 1.2 Hz), 3.81 (3 H, s), 3.78 (3 H, s), 2.13 (3 H, s); IR (NaCl, neat film) ν = 2941, 1739, 1685, 1513, 1243 cm^{-1}.

Spiro Cyclic Bisthioacetates (17a–d). **16a** or **16b** (600 mg, 1.35 mmol, 1.0 equiv) and NBS (362 mg, 2.03 mmol, 1.5 equiv) were dissolved in 50 mL of CCl_4 under argon, and the solution was heated and refluxed for 3.5 h. The solution was cooled, and the solvent was removed. The orange residue was taken up in CH_2Cl_2, and a CH_2Cl_2 solution of pyridine (408 μL, 5.42 mmol, 4.0 equiv) and thiolacetic acid (387 μL, 5.42 mmol, 4.0 equiv) was added. The combined solution was stirred at room temperature for 30 min. The solution was extracted with saturated $NaHCO_3$ and water, dried over $MgSO_4$, filtered, and concentrated to an obnoxious smelling foam. The products were purified using flash column chromatography using 5% acetone in CCl_4: obtained 493 mg of both diastereomers; 65% combined yield. Same experimental procedure was used for **17c,d** in 55% yield.

17a: R_f 0.4, 1:1 ethyl acetate/hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.32 (2 H, d, J = 8.5 Hz), 7.26–7.21 (1 H, m), 7.13–7.10 (1 H, m), 7.00–6.95 (1 H, m), 6.90–6.85 (3 H, m), 6.12 (1 H, s), 5.74 (1 H, s), 5.19 (1 H, $^1/_2$ABq, J = 14.5 Hz), 3.91 (3 H, s), 3.80 (3 H, s), 3.74 (1 H, $^1/_2$ABq, J = 14.5 Hz), 2.50 (3 H, s), 2.18 (3 H, s); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ = 195.18 (C), 192.31 (C), 161.64 (C), 161.13 (C), 159.72 (C), 157.35 (C), 130.97 (CH), 129.60 (CH), 126.52 (C), 125.14 (C), 124.05 (CH), 122.38 (CH), 114.14 (CH), 109.54 (CH), 101.52 (C), 64.85 (CH_3), 60.04 (CH), 55.29 (CH_3), 48.95 (CH), 46.73 (CH_2), 30.45 (CH_3), 29.64 (CH_3); IR (NaCl, neat film) ν = 1695, 1612, 1513, 1459, 1243 cm^{-1}; white crystals from ethyl acetate/hexanes; mp 204–205 °C. Anal. Calcd for $C_{24}H_{24}N_2O_7S_2$: C, 55.80; H, 4.68; N, 5.42; S, 12.41. Found: C, 55.64; H, 4.76; N, 5.24; S, 12.51.

17b: R_f 0.32, 1:1 ethyl acetate/hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.30–7.21 (3 H, m), 7.13–7.11 (1 H, m), 7.01–6.87 (4 H, m), 5.89 (1 H, s), 5.88 (1 H, s), 5.14 (1 H, $^1/_2$ABq, J = 14.4 Hz), 3.95 (3 H, s), 3.88 (1 H, $^1/_2$ABq, J = 14.4 Hz), 3.81 (3 H, s), 2.48 (3 H, s), 2.46 (3 H, s); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ = 193.41 (C), 191.96 (C), 161.9 (C), 160.01 (C), 159.74 (C), 157.85 (C), 130.57 (CH), 129.79 (CH), 126.49 (C), 125.18 (C), 124.28 (CH), 122.37 (CH), 114.2 (CH), 109.35 (CH), 101.0 (C), 65.55 (CH_3), 59.83 (CH), 55.28 (CH_3), 49.28 (CH),

47.05 (CH_2), 30.27 (CH_3), 30.17 (CH_3); IR (NaCl, neat film) ν = 1706, 1691, 1612, 1513, 1461, 1239 cm^{-1}; white solid from ethyl acetate/petroleum ether; mp 168–170 °C dec. Anal. Calcd for $C_{24}H_{24}N_2O_7S_2$: C, 55.80; H, 4.68; N, 5.42; S, 12.41. Found: C, 55.68; H, 4.84; N, 5.58; S, 12.16.

Cis Bisthioacetate Diastereomers. 17c: R_f 0.42, 1:1 ethyl acetate/hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.27–7.25 (3 H, m), 7.15–7.13 (1 H, m), 7.05–6.87 (2 H, m), 6.85 (2 H, d, J = 8.54 Hz), 6.23 (1 H, s), 5.36 (1 H, s), 5.28 (1 H, $^1/_2$ABq, J = 8.54 Hz), 3.99 (1 H, $^1/_2$ABq, J = 14.5 Hz), 3.81 (3 H, s), 3.68 (3 H, s), 2.44 (3 H, s), 2.37 (3 H, s); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ = 194.24 (C), 192.23 (C), 162.45 (C), 159.96 (C), 159.7 (C), 156.75 (C), 130.60 (CH), 129.47 (CH), 126.23 (C), 124.73 (C), 123.60 (CH), 122.56 (CH), 114.15 (CH), 109.31 (CH), 99.73 (C), 64.16 (CH_3), 60.09 (CH), 55.27 (CH_3), 52.45 (CH); 47.61 (CH_2), 30.48 (CH_3), 29.96 (CH_3); IR (NaCl, neat film) ν = 2940, 1702, 1612, 1513, 1239 cm^{-1}.

17d: R_f 0.32, 1:1 ethyl acetate/hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.32 (2 H, d, J = 8.5 Hz), 7.26–7.22 (1 H, m), 7.13 (1 H, d, J = 7.4 Hz), 7.03–6.89 (4 H, m), 5.94 (1 H, s), 5.83 (1 H, s), 5.27 (1 H, $^1/_2$ABq, J = 14.47 Hz), 3.82 (1 H, $^1/_2$ABq, J = 14.47 Hz), 3.83 (3 H, s), 3.77 (3 H, s), 2.51 (3 H, s), 2.46 (3 H, s); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ = 194.57 (C), 192.02 (C), 163.23 (C), 159.79 (C), 159.72 (C), 156.92 (C), 130.56 (CH), 129.7 (CH), 126.58 (C), 124.19 (C), 123.92 (CH), 122.52 (CH), 114.23 (CH), 109.16 (CH), 99.0 (C), 65.34 (CH_3), 60.03 (CH), 55.27 (CH_3), 51.75 (CH), 47.24 (CH), 30.24 (CH_3); IR (NaCl, neat film) ν = 2942, 1699, 1513, 1238 cm^{-1}; light yellow crystals from ethyl acetate/hexanes; mp 168–169 °C. Anal. Calcd for $C_{24}H_{24}N_2O_7S_2$: C, 55.80; H, 4.68; N, 5.42, S, 12.41. Found: C, 55.83; H, 4.73; N, 5.25; S, 12.14.

Spiro Cyclic Disulfides (18a,b). Acid Hydrolysis Procedure. Twenty-five milligrams (0.048 mmol, 1 equiv) of a mixture of **17a–d** was suspended in 10 mL of absolute ethanol and cooled to 0 °C. Dry HCl gas was bubbled through the solution for 30 min and stirred at room temperature for an additional 5 h. The ethanol was removed under vacuum, and the yellow residue was taken up in CH_2Cl_2. The CH_2Cl_2 layer was shaken with aqueous 2% KI_3 until the organic layer was a persistent pink/purple. The organics were washed with water, dried over Na_2SO_4, filtered, and concentrated to a dark brown film which was purified via preparative thin-layer chromatography using 3:2 hexane/ethyl acetate as the eluent. The two bands which stain white with I_2/NaN_3 were isolated: obtained 6.7 mg of white solid; combined yield 32%.

Basic Hydrolysis Procedure. Twenty milligrams (0.041 mmol, 1 equiv) of a mixture of **17a–d** was suspended in 7 mL of absolute ethanol, and argon was bubbled through the solution for 20 min. NaOH (1.5 mL, 0.2 N) was added with continued degassing, and the solution was stirred for 10 min. The reaction was poured into a separatory funnel containing CH_2Cl_2, and aqueous 2% KI_3 was added until the CH_2Cl_2 layer was purple. The organic layer was washed with water, dried over Na_2SO4, filtered, and concentrated to a brown film which was PTLC'd using 3:2 hexane/ethyl acetate (or radial chromatography using 3:1 hexane/ethyl acetate): isolated 5.4 mg of **18a** or **b** as a white solid; yield 32%.

18a: R_f 0.38, 2:3 ethyl acetate/hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.34–7.18 (4 H, m), 7.09 (1 H, d, J = 8.2 Hz), 7.04–6.99 (1 H, m), 6.89 (2 H, $^1/_2$ABq, J = 8.7 Hz), 5.27 (1 H, $^1/_2$ABq, J = 14.4 Hz), 5.00 (1 H, s), 4.89 (1 H, s), 3.96 (1 H, $^1/_2$ABq, J = 14.4 Hz), 3.96 (3 H, s), 3.81 (3 H, s); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ = 165.53 (C), 164.24 (C), 159.97 (C), 157.98 (C), 131.23 (CH), 130.66 (CH), 125.25 (C), 124.79 (CH), 122.68 (CH), 121.19 (C), 114.56 (CH), 110.48 (CH), 101.62 (C), 66.44 (CH_3), 62.29 (CH), 55.33 (CH_3), 52.45 (CH), 47.44 (CH_2); IR (NaCl, neat film) ν = 2942, 1712, 1612, 1513, 1232 cm^{-1}; colorless crystals from diethyl ether/pentane; mp 188–189 °C.

18b: R_f 0.29, 2:3 ethyl acetate/hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.26–7.16 (4 H, m), 7.08–7.03 (2 H, m), 6.90 (2 H, $^1/_2$ABq, J = 8.6 Hz), 5.20 (1 H, s), 5.14 (1 H, s), 4.88 (1 H, $^1/_2$ABq, J = 14.6 Hz), 4.39 (1 H, $^1/_2$ABq, J = 14.6 Hz), 3.87 (3 H, s), 3.82 (3 H, s); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ = 166.09 (C), 162.97 (C), 160.05 (C), 158.1 (C), 130.78 (CH), 130.45 (CH), 125.94 (C), 123.9 (CH), 123.07 (CH), 121.48 (C), 114.76 (CH), 109.88 (CH), 100.21 (CH), 66.35 (CH_3), 64.64 (CH), 56.27 (CH), 55.34 (CH_3), 48.47 (CH_2); IR (NaCl, neat film) ν = 2943, 1708, 1513, 1458, 1249, 1030 cm^{-1}; mp 163–164 °C.

Chlororesorcylaldehyde (23). Prepared following the procedure of Chakravarti and Ghosh.[22] In a flame-dried, 1-L, three-necked flask equipped with a condensor and a mercury seal stirrer under an inert atmosphere was added 4-chlororesorcinol (25 g, 0.17 mol, 1 equiv) and anhydrous zinc cyanide (40 g, 0.34 mol, 2.0 equiv). Anhydrous diethyl ether (200 mL) was added, and the reaction was cooled to 0 °C. Dry HCl gas was passed through the rapidly stirred solution for 2 h until a solid mass formed. The ether was decanted, and 250–300 mL of water was added. The reaction was heated to reflux, and any residual ether was distilled off. The reaction was refluxed until the solid mass dissolved entirely. Upon cooling the crude chlororesorcylaldehyde separates as a red solid and was collected. Recrystallization from water gave the desire product in sufficient purity to carry on. Repeated recrystallizations gave chlororesorcylaldehyde as yellow needles in 40% yield: ^1H NMR (300 MHz, DMSO-d_6) δ = 11.39 (1 H, brs, exchangeable), 10.89 (1 H, brs, exchangeable), 9.98 (1 H, s), 7.60 (1 H, s), 6.58 (1 H, s); IR (KBr) ν = 3378, 1630, 1495, 1266, 723 cm^{-1}.

2-Hydroxy-4-(methoxymethyl)-5-chlorobenzaldehyde (24). A solution containing 20 g (116 mmol, 1.0 equiv) of chlororesorcylaldehyde **23** and triethylamine (16.2 mL, 116 mmol, 1.0 equiv) in 750 mL of THF was cooled to 0 °C. Chloromethyl methyl ether (13.2 mL, 173.8 mmol, 1.5 equiv) was added subsurface, and the solution was warmed to room temperature and stirred for 3 h. The solution was filtered through a Celite plug diluted with diethyl ether and extracted three times with 0.2 M NaOH. The etheral layer (containing dialkylated material) was discarded, while the aqueous layer was carefully acidified to pH 4–5 with cold 0.1 M H_2SO_4 and extracted with ethyl acetate. The ethyl acetate was washed with water, dried over $MgSO_4$, filtered, and concentrated to an orange solid which was taken up in a 3:1 hexane/ethyl acetate solution and filtered through a plug of 25% alumina in silica gel. The colorless filtrate was concentrated, and the product was recrystallized from hexane: obtained 12.5 g of a white crystalline solid; 49% yield; mp 68–70 °C; ^1H NMR (300 MHz, $CDCl_3$) δ = 11.29 (1 H, s, exchangeable in D_2O), 9.70 (1 H, s), 7.35 (1 H, s), 6.76 (1 H, s), 5.31 (2 H, s), 3.52 (3 H, s); IR (NaCl film) ν = 2962, 2839, 1647, 1487 cm^{-1}. Anal. Calcd for $C_9H_9O_4Cl$: C, 49.90; H, 4.19; Cl, 16.36. Found: C, 50.15; H, 4.29; Cl, 16.42.

5-Chloro-6-(methoxymethyl)coumarilic Acid (25). A slurry consisting of 4 g (18.46 mmol, 1.0 equiv) of **24**, diethyl bromomalonate (3.5 mL, 20.31 mmol, 1.1 equiv), and potassium carbonate (5.1 g, 36.9 mmol, 2.0 equiv) were heated to reflux in 15 mL of acetone. After 5 h the solution was concentrated to a thick yellow oil which was taken up in water, acidified to pH 5 with cold 0.1 M H_2SO_4, and extracted with ethyl acetate. The ethyl acetate was washed with water and concentrated, and the residue was taken up in 20 mL of ethanol, and an alcoholic solution of KOH (3.0 equiv) was added and refluxed for 2 hours. The solution was cooled and concentrated, and the residue was taken up in dilute NaOH and extracted with diethyl ether which was discarded. The aqueous layer was acidified to pH 3–4 with 0.1 M H_2SO_4 and the precipitate which gradually forms collected. The carboxylic acid was further purified by recrystallization from ethyl acetate/hexanes: obtained 3.4 g of a fine white solid; mp 193–194 °C; 72% yield; ^1H NMR (300 MHz, DMSO-d_6) δ = 13.55 (1 H, br s, exchangeable in D_2O), 7.89 (1 H, s), 7.59 (1 H, s), 7.56 (1 H, s), 5.39 (2 H, s), 3.44 (3 H, s); IR (KBr) ν = 3415, 2907, 2554, 1684, 1571 cm^{-1}. Anal. Calcd for $C_{11}H_9O_5Cl$: C, 51.48; H, 3.53; Cl, 13.81. Found: C, 51.38; H, 3.54; Cl, 13.64.

***N*-(2-Nitrobenzyl)glycine Ethyl Ester (26).** Glycine ethyl ester hydrochloride (52 g, 370.3 mmol, 4.0 equiv) was dissolved in 1.5 L of 95% ethanol. $NaHCO_3$ (38.8 g, 462.8 mmol, 5.0 equiv) was added, and after 5 min 2-nitrobenzyl bromide (20 g, 92.5 mmol, 1.0 equiv) was added and the solution refluxed for 20 h. The solution was cooled, filtered, and concentrated to a viscous yellow oil which was taken up in ethyl acetate, washed with water, dried over $MgSO_4$, filtered, and concentrated to a thick yellow/brown oil. Product (14.5 g) (yellow oil) was obtained from flash column chromatography using 3:2 hexane/ethyl acetate as the eluent along with 2 g of dialkylated side product: 65% yield; ^1H NMR (300 MHz) ($CDCl_3$) δ = 7.97 (1 H, d, J = 8.0 Hz), 7.66–7.57 (2 H, m), 7.45–7.40 (1 H, m), 4.18 (2 H, qt, J = 7.1 Hz), 4.10 (2 H, s), 3.44 (2 H, s), 1.27 (3 H, t, J = 7.1 Hz); IR (NaCl, neat film) ν = 3354, 1736, 1526 cm^{-1}.

***N*-Benzofuranylglycine (27a).** 6-Chloro-7-(methoxymethyl)coumarilic acid **25** (9 g, 35.1 mmol, 1.0 equiv) was suspended in 500 mL of CH_2Cl_2 under N_2. THF was added to the solution until all the starting material was completely dissolved. DMF (1 mL) was added followed by 3.5 mL of oxalyl chloride (38.57 mmol, 1.1 equiv). After approximately 5 min the solution turned cloudy and was stirred at room temperature for 1 h. The acid chloride solution was concentrated to approximately half the original volume and was added to a vigorously stirred solution containing *N*-(2-nitrobenzyl)glycine ethyl ester **26** (8.35 g, 35.1 mmol, 1.0 equiv) and sodium bicarbonate (4.4 g, 52.6 mmol, 1.5 equiv) in 100 mL of water. The resulting solution was stirred for 45 min. The layers were separated, and the organic layer was washed with 0.1 M K_2CO_3, acidified with 10% HCl, washed with water, dried over $MgSO_4$, filtered, and concentrated to a thick yellow oil which solidifies on standing: obtained 16.5 g of crude ester (>95% by TLC). The crude ester was taken up in 500 mL of dioxane, 55 mL of 2 M HCl was added, and the solution was refluxed for 36 h. The solution was cooled, made basic with 0.2 M NaOH, and washed with diethyl ether. The aqueous solution reacidified with aqueous HCl. The crude acid was extracted into ethyl acetate, washed with water, dried over $MgSO_4$, filtered, and concentrated to a

light yellow colored solid: obtained 12.9 g of crude acid which was carried on without further purification; ^{1}H NMR (300 MHz, DMSO-d_6, T = 357 K) δ = 12.5 (1 H, br s, exchangeable in D_2O), 10.5 (1 H, br s, exchangeable in D_2O), 8.04 (1 H, d, J = 8.1 Hz), 7.74–7.54 (3 H, m), 7.27 (1 H, s), 7.01 (1 H, s), 5.11 (2 H, s), 4.31 (2 H, s); IR (KBr) ν = 3413, 3141, 1733, 1608, 1556, 1525 cm^{-1}.

***N*-Benzofuranylglycine (27b).** To 12.9 g of crude **27a** (31.97 mmol, 1.0 equiv) dissolved in 30–50 mL of pyridine was added excess acetic anhydride (30 mL at least 10 equiv), and the solution was stirred at room temperature for 4 h. The majority of the solvent was removed in vacuo, and the residue was taken up in ethyl acetate, washed with 10% HCl followed by water, dried over $MgSO_4$, filtered, and concentrated to 14 g of a yellow/orange foam (>95% by TLC) which was also carried on without further purification: ^{1}H NMR (300 MHz, DMSO-d_6, T = 370 K) δ = 7.97 (1 H, d, J = 8 Hz), 7.85 (1 H, s), 7.67–7.47 (4 H, m), 7.34 (1 H, s), 5.03 (2 H, s), 3.95 (2 H, s), 2.32 (3 H, s); IR (KBr) ν = 3430, 3105, 2941, 1772, 1615 (br), 1525, 1196 cm^{-1}.

***N*-Benzofuranylglycine Hydroxamate (28a).** To a solution of **27a** (250 mg, 0.617 mmol, 1.0 equiv) dissolved in 60 mL of THF was added 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (178 mg, 0.926 mmol, 1.5 equiv). (A few milliliters of water was added to help dissolve the carbodiimide.) The yellow solution was stirred for 10 min before methoxylamine (96 mL, 1.85 mmol, 3.0 equiv) was added causing the color to dissipate. The solution was stirred for 16 h before dilution with ethyl acetate, extracted with saturated $NaHCO_3$, and dried over Na_2SO_4. The residue was purified using 20% methanol/chloroform: obtained 172 mg of a white solid which was recrystallized from ethyl acetate/hexanes; 64% yield; ^{1}H NMR (300 MHz, T = 357 K, DMSO-d_6) δ = 10.81 (1 H, br s), 8.21 (1 H, s), 8.05 (1 H, d, J = 7.9 Hz), 7.7–7.52 (4 H, m), 7.29 (1 H, s), 7.06 (1 H, s), 5.10 (2 H, s), 4.24 (2 H, s), 3.59 (3 H, s); IR (KBr) ν = 3171, 2975, 1665, 1610, 1523, 1338, 1142 cm^{-1}.

***N*-Benzofuranylglycine Hydroxamate (28b).** To a solution containing 2.77 g of **27b** (6.2 mmol, 1.0 equiv) dissolved in 200 mL of THF cooled to 0 °C was added *N*-methylmorpholine (750 mL, 6.82 mmol, 1.1 equiv). After 10 min isobutyl chloroformate (880 mL, 6.82 mmol, 1.1 equiv) was added causing the solution to turn yellow. After 45 min the ice bath was removed and methoxylamine (630 mL, 12.4 mmol, 2.0 equiv) was added causing the intense yellow color to dissipate, and the reaction was stirred for an additional 45 min at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate was washed with 10% HCl followed by water, dried over $MgSO_4$, filtered, and concentrated to a yellow/orange oil. The hydroxamic ester was purified from column chromatography using 2:1 ethyl acetate/hexanes: obtained 2.1 g of a white foam which was further purified by recrystallization from ethyl acetate/hexanes; mp 151–152 °C; 70% yield; ^{1}H NMR (300 MHz, DMSO-d_6, T = 370 K) δ 10.81 (1 H, br s), 8.02 (1 H, d, J = 8 Hz), 7.91 (1 H, s), 7.73–7.27 (4 H, m), 7.0 (1 H, s), 5.10 (2 H, s), 4.23 (2 H, s), 3.57 (3 H, s), 2.32 (3 H, s); IR (NaCl film) ν = 3210, 2998, 1771, 1677, 1637, 1526 cm^{-1}. Anal. Calcd for $C_{21}H_{18}N_3O_8Cl$: C, 53.01; H, 3.81; N, 8.83; Cl, 7.45. Found: C, 52.92; H, 3.88; N, 8.68; Cl, 7.25.

Trans Spiro Cyclic Bromide (29b). NBS (4.0 g, 22.69 mmol, 1.2 equiv) was added in one portion to a solution of **28b** (9.0 g, 18.9 mmol, 1.0 equiv) in 600 mL of ethanol-free chloroform under N_2 at room temperature, and the reaction was stirred at room temperature for 20 h. The reaction was poured into a separatory funnel containing additional $CHCl_3$, washed with saturated sodium thiosulfate followed by water, dried over $MgSO_4$, filtered, and concentrated to a thick, light yellow colored oil which if let standing solidifies. The oily product was immediately purified by column chromatography using 3:2 hexane/ethyl acetate as the eluent: obtained 6.67 g of a white solid which was recrystallized from ethyl acetate/hexanes; mp 160–162 °C; 67% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.04 (1 H, d, J = 8.0 Hz), 7.67–7.60 (2 H, m), 7.55–7.50 (1 H, m), 7.35 (1 H, s), 6.79 (1 H, s), 6.01 (1 H, s), 5.05 (1 H, $^1/_2$ABq, J = 15.7 Hz), 5.01 (1 H, $^1/_2$ABq, J = 15.7 Hz), 4.18 (2 H, s), 3.95 (3 H, s), 2.35 (3 H, s); ^{13}C NMR (75.47 (MHz, $CDCl_3$) δ 168.02 (C), 161.33 (C), 161.22 (C), 156.68 (C), 148.88 (C), 148.81 (C), 133.9 (CH), 130.59 (CH), 129.42 (C), 129.30 (CH), 126.36 (CH), 125.19 (CH), 124.41 (C), 120.71 (C), 105.92 (CH), 101.75 (C), 65.81 (CH_3), 49.06 (CH_2), 48.18 (CH), 46.49 (CH_2), 20.55 (CH_3); IR (NaCl film) ν = 2992, 1772, 1697, 1527 cm^{-1}. Anal. Calcd for $C_{21}H_{17}N_3O_8ClBr$: C, 45.47; H, 3.09; N, 7.57; total halogen content (calculated as 2Cl) 12.78. Found: C, 45.55; H, 3.15; N, 7.58; total halogen 12.67.

Trans and Cis Spiro Cyclic Methyl Ethers (30a,b). A solution of silver triflate (735 mg, 4.36 mmol, 1.2 equiv) in 15 mL of THF was added in 1 portion to a rapidly stirring solution of 2.0 g of **29b** (3.6 mmol, 1.0 equiv) dissolved in 150 mL of THF in which 30 mL of methanol had been added. The resulting solution was stirred at room temperature for 45 min. The reaction was diluted with ethyl acetate followed by the addition of saturated brine solution. The reaction was filtered through a plug of celite, and the filtrate washed with brine, water, dried over $MgSO_4$, filtered, and concentrated to a white solid. The diastereomers were purified by column chromatography using 2% acetone in $CHCl_3$. 950 mg of the trans diastereomer (nonpolar) and 315 mg of the cis diastereomer (polar) were obtained in 69% combined yield (81% based on recovered starting material). Each diastereomer was recrystallized from ethyl acetate/hexanes.

***trans*-30a**: R_f 0.3, 5% acetone/chloroform; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (1 H, d, J = 8.1 Hz), 7.62–7.49 (3 H, m), 7.43 (1 H, s), 6.82 (1 H, s), 5.52 (1 H, s), 5.26 (1 H, $^1/_2$ABq, J = 16.2 Hz), 4.88 (1 H, $^1/_2$ABq, J = 16.2 Hz), 4.12 (2 H, s), 3.93 (3 H, s), 3.61 (3 H, s), 2.35 (3 H, s); ^{13}C NMR (75.47 (MHz, $CDCl_3$) δ = 168.07 (C), 161.97 (C), 161.15 (C), 158.03 (C), 148.67 (C), 148.65 (C), 133.85 (CH), 129.97 (C), 129.62 (CH), 128.98 (CH), 126.02 (CH), 125.19 (CH), 124.12 (C), 119.93 (C), 106.37 (CH), 101.15 (C), 84.62 (CH), 65.69 (CH_3), 59.28 (CH_3), 49.24 (CH_2), 46.56 (CH_2), 20.56 (CH_3); IR (NaCl film) ν = 2943, 1773, 1697, 1527 cm^{-1}; white crystals from ethyl acetate/hexanes; mp 132–134 °C. Anal. Calcd for $C_{22}H_{20}N_3O_9Cl$: C, 52.23; H, 4.98; N, 8.31; Cl, 7.01. Found: C, 52.13; H, 4.20; N, 8.17; Cl, 6.92.

***cis*-30b**: R_f 0.2, 5% acetone/chloroform; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (1 H, d, J = 8.1 Hz), 7.86 (1 H, t, J = 7.5 Hz), 7.54 (1 H, t, J = 8.1 Hz), 7.43–7.39 (2 H, m), 6.73 (1 H, s), 5.63 (1 H, s), 5.0 (2 H, s), 4.13 (1 H, $^1/_2$ABq, J = 18.1 Hz), 4.09 (1 H, $^1/_2$ABq, J = 18.2 Hz), 3.80 (3 H, s), 3.64 (3 H, s), 2.34 (3 H, s); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ = 168.0 (C), 162.89 (C), 162.37 (C), 156.05 (C), 148.74 (C), 148.07 (C), 134.1 (CH), 129.54 (CH), 129.52 (C), 129.45 (CH), 125.43 (CH), 125.12 (CH), 124.44 (C), 120.1 (C), 105.84 (CH), 98.2 (C), 84.6 (CH), 64.58 (CH_3), 60.13 (CH_3), 49.17 (CH_2), 47.04 (CH_2), 20.57 (CH_3); IR (NaCl film) ν = 2946, 1772, 1688, 1527 cm^{-1}; white needles from ethyl acetate/hexanes; mp 163–164 °C. Anal. Calcd for $C_{22}H_{20}N_3O_9Cl$: C, 52.23; H, 3.98; N, 8.31; Cl, 7.01. Found: C, 52.49; H, 4.20; N, 8.39; Cl, 7.09.

Trans and Cis Spiro Cyclic Methyl Ethers (31a,b). Methyl ether **30a** (250 mg, 0.494 mmol) was dissolved in 50 mL of 10% water in THF in a quartz tube containing Pyrex beads. The solution was photolyzed at 37 °C for 5 h using a 450-W Conrad-Hanovia medium-pressure mercury vapor lamp. The reaction was filtered into a separatory funnel, containing ethyl acetate, washed with water, dried over $MgSO_4$, filtered, and concentrated to a brown film which was chromatographed using 15% acetone/chloroform: obtained 131 mg of product **31a**; 72% yield. Analogous reaction using the cis diastereomer **30b** gave **31b** as a white solid in 71% yield.

***trans*-31a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.41 (1 H, s), 7.30 (1 H, s, exchangeable in D_2O), 6.80 (1 H, s), 5.44 (1 H, s), 4.15 (1 H, $^1/_2$ABq, J = 18.4 Hz, broadened by NH, d, J = 2.8 Hz), 4.07 (1 H, $^1/_2$ABq, J = 18.4 Hz), 3.90 (3 H, s), 3.60 (3 H, s), 2.35 (3 H, s); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ = 168.12 (C), 162.59 (C), 162.28 (C), 157.92 (C), 148.69 (C), 126.13 (CH), 124.19 (C), 120.04 (C), 106.3 (CH), 100.93 (C), 84.79 (CH), 65.71 (CH_3), 59.5 (CH_3), 44.0 (CH_2), 20.62 (CH_3); IR (NaCl film) ν = 3273, 2942, 1772, 1708 cm^{-1}; white needles from ethyl acetate/petroleum ether; mp 181–182 °C. Anal. Calcd for $C_{15}H_{15}N_2O_7Cl$: C, 48.59; H, 4.08; N, 7.56; Cl, 9.56. Found: C, 48.46; H, 4.21; N, 7.35; Cl, 9.46.

***cis*-31b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.39 (1 H, s), 6.73 (i H, s), 6.57 (1 H, s, exchangeable in D_2O), 5.5 (1 H, s), 4.19 (1 H, $^1/_2$ABq, J = 2.0 Hz), 4.28 (1 H, $^1/_2$ABq, J = 1.3 Hz), 3.79 (3 H, s), 3.65 (3 H, s), 2.34 (3 H, s); ^{13}C NMR (75.47 MHz, DMSO-d_6) δ = 168.13 (C), 162.79 (C), 162.73 (C), 156.14 (C), 147.64 (C), 125.29 (CH), 125.19 (C), 118.5 (C), 105.83 (CH), 97.71 (C), 83.33 (CH), 63.70 (CH_3), 59.70 (CH_3), 43.21 (CH_2), 20.35 (CH_3); IR (NaCl film) ν = 3274, 2942, 1770, 1703 cm^{-1}; white solid from ethyl acetate/petroleum ether; mp dec >230 °C. Anal. Calcd for $C_{15}H_{15}N_2O_7Cl$: C, 48.59; H, 4.08; N, 7.56. Found: C, 48.61; H, 4.19; N, 7.31.

Spiro Cyclic Bismethyl Ethers (32a–d). General Procedure. Methyl ether **31** (65 mg, 0.176 mmol, 1 equiv) was dissolved in 5 mL of dry ethanol-free at room temperature. Freshly prepared *tert*-butyl hypochlorite (25 μL, 0.193 mmol, 1.2 equiv) was added followed by the dropwise addition of a freshly prepared solution of 0.1 M sodium methoxide (1.5 equiv). The solution was stirred at room temperature for 1 h. The reaction was quenched with 10% aqueous HCl, extracted with ethyl acetate, washed with water, dried over Na_2SO_4, filtered, and concentrated to a yellow film. In the case of **31a**, the individual diastereomers **32a,b** were purified by column chromatography using 20% acetone/$CHCl_3$ as the eluent: obtained a white solid for a combined yield of 56%. Analogous reactions using **31b** gave **32c,d** as an inseparable mixture of diastereomers which was carried on directly.

***trans*-32a**: R_f 0.4, 2:1 ethyl acetate/hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.39 (1 H, s), 7.32 (1 H, br s, exchangeable in D_2O), 6.75

(1 H, s), 5.6 (1 H, s), 5.00 (1 H, d, J = 2.2 Hz), 3.91 (3 H, s), 3.57 (3 H, s), 3.49 (3 H, s), 2.35 (3 H, s); ^{13}C NMR (75.47 (MHz, $CDCl_3$) δ = 168.15 (C), 161.91 (C), 160.0 (C), 157.52 (C), 148.51 (C), 126.0 (CH), 124.49 (C), 120.10 (C), 106.23 (CH), 101.16 (C), 84.7 (CH), 80.82 (CH), 65.34 (CH_3), 60.0 (CH_3), 55.56 (CH_3), 20.59 (CH_3); IR (NaCl, film) ν = 3268, 2943, 1772, 1715, 1604, 1478, 1198, 1145 cm^{-1}; white needles from ethyl acetate/hexanes; mp 132–133 °C. Anal. Calcd for $C_{16}H_{17}N_2O_8Cl$: C, 47.95; H, 4.28; N, 6.99; Cl, 8.85. Found: C, 47.89; H, 4.40; N, 6.77; Cl, 9.03.

***trans*-32b**: R_f 0.3, 2:1 ethyl acetate/hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.72 (1 H, br s, exchangeable in D_2O), 7.42 (1 H, s), 6.83 (1 H, s), 5.21 (1 H, s), 4.90 (1 H, d, J = 4.2 Hz), 3.86 (3 H, s), 3.57 (3 H, s), 3.53 (3 H, s), 2.35 (3 H, s); ^{13}C NMR (75.47 (MHz, $CDCl_3$) δ = 168.02 (C), 163.17 (C), 160.66 (C), 158.12 (C), 148.77 (C), 126.0 (CH), 124.32 (C), 120.15 (C), 106.7 (CH), 100.33 (C), 85.9 (CH), 80.66 (CH), 65.92 (CH_3), 59.19 (CH_3), 56.35 (CH_3), 20.58 (CH_3); IR (NaCl, film) ν = 3281, 2942, 1772, 1716, 1604, 1476, 1197, 1147 cm^{-1}; white plates from ethyl acetate/hexanes; mp 178–180 °C. Anal. Calcd for $C_{16}H_{17}N_2O_8Cl$: C, 47.95; H, 4.28; N, 6.99; Cl, 8.85. Found: C, 47.88; H, 4.39; N, 6.71; Cl, 8.90.

Cis Diastereomers (32c,d). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.87 (1 H, d, J = 3.4 Hz), 7.60 (1 H, d, J = 2.36 Hz), 7.41 (1 H, s), 7.37 (1 H, s), 6.77 (1 H, s), 6.72 (1 H, s), 5.60 (1 H, s), 5.22 (1 H, s), 5.08 (1 H, d, J = 2.79 Hz), 4.91 (1 H, d, J = 3.6 Hz), 3.82 (3 H, s), 3.77 (3 H, s), 3.66 (3 H, s), 3.61 (3 H, s), 3.57 (3 H, s), 3.53 (3 H, s), 2.35 (3 H, s), 2.34 (3 H, s).

Spiro Cyclic Bismethyl Ethers (33a–d). General Procedure. A suspension of 44 mg (0.11 mmol, 1 equiv) of **32a,b** or **32c,d** in 2 mL of absolute ethanol was stirred at 0 °C. Exactly 1.1 equiv of 0.1 M sodium ethoxide at 0 °C was added dropwise. The resulting solution was stirred at 0 °C for 30 min before quenching the reaction by addition of 10% aqueous HCl. The reaction was poured into ethyl acetate, washed with saturated sodium chloride, dried over Na_2SO_4, filtered, and concentrated to a light yellow film. Crude NMR shows >90% product. The product was purified by column chromatography using 2:1 ethyl acetate hexanes or 15% acetone/$CHCl_3$; obtained 29 mg of a white solid. The individual diastereomers could be obtained routinely in 74% isolated yield.

***trans*-33a**: R_f 0.28, 2:1 ethyl acetate/hexanes; ^{1}H NMR (300 MHz, MeOH-d_4) δ = 7.28 (1 H, s), 6.49 (1 H, s), 5.44 (1 H, s), 5.08 (1 H, s), 4.86 (2 H, br s), 3.83 (3 H, s), 3.51 (3 H, s), 3.49 (3 H, s); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ = 163.54 (C), 162.36 (C), 160.04 (C), 156.53 (C), 127.06 (CH), 118.66 (C), 115.03 (C), 102.16 (C), 99.30 (CH), 86.77 (CH), 82.12 (CH), 65.67 (CH_3), 59.65 (CH_3), 55.76 (CH_3); IR (NaCl, film) ν = 3273 shoulder 3148, 2943, 1705, 1627.6, 1299, 1097, 1032 cm^{-1}; mp decomposes—no clean melting point (180–202 °C); white crystals from diethyl ether at −11 °C. Anal. Calcd for $C_{14}H_{15}N_2O_7Cl$: C, 46.87; H, 4.21; N, 7.81. Found: C, 47.00; H, 4.42; N, 7.69.

***trans*-33b**: R_f 0.18, 2:1 ethyl acetate/hexanes; ^{1}H NMR (300 MHz, MeOH-d_4) δ = 7.35 (1 H, s), 6.56 (1 H, s), 5.03 (1 H, s), 4.89 (1 H, s), 4.83 (2 H, br s), 3.79 (3 H, s), 3.50 (3 H, s), 3.48 (3 H, s); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ = 164.78 (C), 162.99 (C), 160.65 (C), 156.78 (C), 127.12 (CH), 119.78 (C), 118.66 (C), 115.16 (C), 99.24 (CH), 87.81 (CH), 82.04 (CH), 66.35 (CH_3), 58.71 (CH_3), 56.57 (CH_3); IR (KBr) ν = 3342 shoulder 3225, 2945, 1710, 1631, 1497, 1186, 1099, 1041 cm^{-1}; mp decomposes—no clean melting point; white solid from acetone/petroleum ether. Anal. Calcd for $C_{14}H_{15}N_2O_7Cl$: C, 46.87; H, 4.21; N, 7.81. Found: C, 46.95; H, 4.32; N, 7.7.

***cis*-33c**: R_f 0.32, 2:1 ethyl acetate/hexanes; ^{1}H NMR (300 MHz, MeOH-d_4) δ = 7.21 (1 H, d, J = 1.1 Hz), 6.46 (1 H, s), 5.48 (1 H, s), 5.12 (1 H, s), 4.84 (2 H, br s), 3.72 (3 H, s), 3.55 (3 H, s), 3.49 (3 H, s); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ = 166.41 (C), 163.57 (C), 158.19 (C), 156.06 (C), 125.96 (CH), 118.86 (C), 115.09 (C), 99.16 (CH), 99.03 (C), 87.22 (CH), 81.59 (CH), 64.59 (CH_3), 60.40 (CH_3), 55.71 (CH_3); IR (NaCl, film) ν = 3281, 2941, 1700, 1627, 1487, 1437, 1104 cm^{-1}; white crystals from diethyl ether/petroleum ether at 0 °C; mp 158–159 °C. Anal. Calcd for $C_{14}H_{15}N_2O_7Cl$: C, 46.87; H, 4.21; N, 7.81. Found: C, 46.66; H, 4.37; N, 7.63.

***cis*-33d**: R_f 0.23, 2:1 ethyl acetate/hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.29 (1 H, s), 6.49 (1 H, s), 5.10 (1 H, s), 4.93 (1 H, s), 4.85 (2 H, br s), 3.77 (3 H, s), 3.59 (3 H, s), 3.53 (3 H, s); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ = 167.66 (C), 162.64 (C), 158.73 (C), 156.40 (C), 126.66 (CH), 118.7 (C), 115.2 (C), 99.1 (C), 99.03 (CH), 86.07 (CH), 82.48 (CH), 65.24 (CH_3), 60.57 (CH_3), 57.37 (CH_3); IR (NaCl, film) ν = 3272, 3171 (shoulder), 2934, 1700, 1627, 1440, 1303, 1157, 1034 cm^{-1}; white crystals from carbon tetrachloride/methanol 0 °C; dec 198–200 °C. Anal. Calcd for $C_{14}H_{15}N_2O_7Cl$: C, 46.87; H, 4.21; N, 7.81. Found: C, 46.63; H, 4.33; N, 7.57; Cl, 9.84.

Spiro Cyclic Bisthioacetates (34a–d). Representative Procedure. BF_3–Et_2O (170 μL, 1.36 mmol, 8.0 equiv) was added to 60 mg of bismethyl ether **33a** (1.0 equiv, 0.167 mmol) in 15 mL of CH_2Cl_2. Thioacetic acid (150 μL, 2.07 mmol, 12.0 equiv) was added, and the solution was heated and refluxed for 8 h. The solution was cooled, diluted with additional CH_2Cl_2, washed once with saturated $NAHCO_3$, saturated NH_4Cl, and water, dried over Na_2SO_4, filtered, and concentrated to a foul-smelling yellow film. The products were purified by column chromatography using 3% MeOH/$CHCl_3$ or 10% acetone/$CHCl_3$; 47 mg of a mixture of inseparable diastereomers were obtained which were carried on without further purification; 65% yield.

Major Diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.08 (1 H, s), 7.07 (1 H, s), 6.61 (2 H, s), 6.50 (1 H, br s), 5.92 (1 H, d, J = 2.9 Hz), 5.83 (1 H, s), 5.70 (1 H, br s); 5.66 (1 H, d, J = 2.2 Hz), 3.98 (3 H, s), 3.93 (3 H, s), 2.48–2.41 (12 H, m); IR (NaCl, film) ν = 3401, 2938, 1707, 1367, 1197, 1145 cm^{-1}.

Methanethiol Reduction and Acetylation of Aspirochlorine. Aspirochlorine (15 mg) was dissolved in 1 mL of dry pyridine and cooled to 0 °C. Excess methanethiol was added, and the solution was stirred under argon for 15 min and at room temperature for 9 h. The solution was concentrated under vacuum, and the residue was taken up in 1 mL of fresh pyridine followed by the addition of 2 equiv of acetyl chloride. The reaction was stirred for 15 min before diluting with ethyl acetate, washed with water, dried over $MgSO_4$, filtered, and concentrated to a yellow film. ^{1}H NMR of the crude film showed the presence of thioacetates **34**.

Sodium Borohydride Reduction and KI_3 Oxidation of Aspirochlorine. Aspirochlorine (8 mg) was dissolved in 2 mL of absolute ethanol at 0 °C and the solution degassed by passing argon through the solution for 20 min. A small spatula tip of $NaBH_4$ was quickly added, and the solution was stirred for 30 min. The solution was concentrated under reduce pressure, and the residue was taken up in H_2O/$CHCl_3$ and acidified to pH 5–6 with 10% H_2SO_4. Aqueous KI_3 was added dropwise until the organic phase was a light pink color. The organics were washed with water, dried over Na_2SO_4, filtered, and concentrated to a brown film which was purified using PTLC. Aspirochlorine (3 mg) (38% yield) was obtained.

Aspirochlorine (2). **34** (10 mg) and a small amount of CSA were dissolved in 4 mL of THF, cooled to 0 °C, and saturated with oxygen. Methoxylamine (100 μL) was added, and the solution was warmed to room temperture and stirred for 6.5 h. The reaction was concentrated, and the yellow film was immediately purified by PTLC using 5% methanol/chloroform. A light yellow noncrystalline solid (2 mg) was obtained. On repeated attempts, yields of aspirochlorine routinely ranged from 20 to 34%. The synthetic and natural substances were identical by ^{1}H NMR, IR, TLC, and HPLC: R_f 0.2, 5% methanol/chloroform; 0.5 in 6:4 chloroform/acetone and 0.4 in 1:1 benzene/ethyl acetate; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.15 (1 H, s), 6.77 (1 H, s), 6.73 (1 H, br s, exchangeable, concentration dependent), 5.78 (1 H, br s, exchangeable, concentration dependent), 5.16 (1 H, d, J = 5.5 Hz), 4.90 (1 H, s), 3.96 (3 H, s); IR (NaCl, film) ν = 3268, 2996, 1715, 1624, 1482, 1338, 1174, 1042, 754 cm^{-1}.

Acknowledgment. The authors would like to thank Eli Lilly for the generous sample of natural aspirochlorine. Financial support from The National Science Foundation, The National Institutes of Health, Hoffman-La Roche, Inc., Symphony Pharmaceutical, Merck, Sharp & Dohme Research Laboratories, and Eli Lilly Co. is gratefully acknowledged.

Supplementary Material Available: ^{1}H NMR, IR, and HPLC analyses of natural and synthetic aspirochlorine (3 pages). Ordering information is given on any current masthead page.