# A Unified Strategy for the Synthesis of Sulfur-Containing Pyridoacridine Alkaloids: Antitumor Agents of Marine Origin

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*Received September 11, 1995*[⊗]

**Abstract:** Details of the total synthesis of the major classes of sulfur-containing pyridoacridine alkaloids, dercitins, kuanoniamines, diplamine, and shermilamine B, are described.

## Introduction

A family of remarkable marine alklaoids displaying the unique pyridoacridine architecture exemplified by cystodytins, e.g., **1**, began to emerge in the late 1980's.[1] Members of the group that incorporate a sulfur functionality, for instance, diplamine, **2**,[2] varamines, **3** and **4**,[3] shermilamines, **5** and **6**,[4] kuanoniamines, **7**,[5] and dercitins, **8** and **9**,[6] are especially interesting on accounts of their varying degrees of immunomodulatory and antitumor activity. Furthermore, the recent discovery that many heterocyclic quinonoid substances inhibit reverse transcriptase[7] raises the provocative possibility that **1**−**9** may be also active against retroviruses.[8]

Diplamine, **2**, and shermilamines, **5** and **6**, are orange pigments isolated from *Tridemnum* and *Diplosoma* species of tunicates, respectively. No biological data seem to be available for **5** and **6**, but **2** is known to be exceedingly cytotoxic against L1210 murine leukemia and quite active against *Escherichia coli* and *Staphylococcus aureus*. Another tunicate, *Lyssoclinum vareau*, yielded varamines, **3** and **4**, which are structurally similar to **2** and possess comparable activity.

Kuanoniamines, bright yellow metabolites from the mollusk, *Chelynotus semperi*, display only modest cytotoxicity. They strongly coordinate divalent ions ($Fe^{2+}$, $Co^{2+}$, $Cu^{2+}$, $Zn^{2+}$; $K_{eq} \approx 10^{10}$ $M^{-2}$) with a 2:1 ligand to ion stoichiometry, and the resulting complexes appear to bind to nucleic acids, possibly by intercalation into DNA base pairs.[6c] Little else is known regarding other biological activities, probably because of lack of sufficient quantities of isolated material. Kuanoniamines are pH indicators, their color changing from yellow ($\lambda_{max}$ = 430 nm in basic or neutral media) to deep burgundy ($\lambda_{max}$ = 480−510 nm) under acidic conditions. Indeed, their name is derived from the Hawaiian word, *kuanoni*, which conveys the idea of changing color. This property pertains to all pyridoacridines, for which yellow, burgundy, or purple colors are associated with chromophores **10**, **11**, and **12**, respectively (Scheme 2).

In contrast to kuanoniamines, considerable bioactivity is found in dercitins, especially **9**. These substances were obtained from deep-water sponges belonging to the *Stelletta* and *Dercitus* species (fam. *Pachastrellidae*). Compound **9** is a deep blue pigment similar in appearance to the mitomycins (notice chromophore **12**), while **8** is bright yellow, as the absence of an *N*-methyl on the pyridine ring nitrogen provides the molecule with a chromophore of the type **10**. Blue **9** ($\lambda_{max}$ = 590 nm) and yellow **8** ($\lambda_{max}$ = 430 nm) change to deep burgundy ($\lambda_{max}$ = 480−510 nm, chromophore **11**) in acidic media.

The new alkaloids provide useful lead structures for the development of new types of antitumor agents, a goal that would certainly be facilitated by the clarification of the mode of action of pyridoacridines.[10] Pursuit of either endeavor requires practical chemical syntheses, as the new natural products are extremely rare. We have recently accomplished such an objective,[10] and in this paper we describe full details of our work.

**Synthetic Strategy: A Common Intermediate for Pyridoacridine Alkaloids Emerges.** Our synthetic strategy was influenced by the biosynthetic hypothesis shown in Scheme 3. We surmise that sulfur-containing pyridoacridines probably arise through sulfenylation of an intermediate resembling the cystodytins, which are metabolites of the tunicate, *Cystodytes dellechiajei*,[11] e.g. cystodytin J, **1**. Such an intermediate is described below with the generic structure **16**, which, in turn, could arise through oxidative merger of tyramine, **13**, and kyurenin, **14**, followed by oxidative cyclization of the resultant **15**. This presumed progenitor of cystodytins could undergo oxidative sulfenylation, e.g., with cysteine, to furnish **17**. Formal $\beta$-elimination of the sulfur functionality and concomitant loss of dehydroalanine from **17** would provide a mercaptoquinone imine (or equivalent biosynthetic intermediates), which could undergo S-methylation to produce the diplamine−

[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1995.

(1) For excellent reviews covering isolation, properties, and past synthetic activity see: (a) Molinski, T. F. *Chem. Rev.* **1993**, *93*, 1825. (b) Moody, C. J.; Thomas, R. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI Press: Greenwich, CT, 1992; Vol. 2, p 377 ff.

(2) Charyulu, G. A.; McKee, T. C.; Ireland, C. M. *Tetrahedron Lett.* **1989**, *30*, 4201.

(3) Molinski, T. F.; Ireland, C. M. *J. Org. Chem.* **1989**, *54*, 4256.

(4) Carroll, A. R.; Cooray, N. M.; Poiner, A.; Scheuer, P. J. *J. Org. Chem.* **1989**, *54*, 4231.

(5) Scheuer, P. J.; Carroll, A. R. *J. Org. Chem.* **1990**, *55*, 4426.

(6) (a) Gunawardana, G. P.; Kohmoto, S.; Gunasekera, S. P.; McConnell, O. J.; Koehn, F. E. *J. Am. Chem. Soc.* **1988**, *113*, 4856. (b) Gunawardana, G. P.; Kohmoto, S.; Burres, N. S. *Tetrahedron Lett.* **1989**, *30*, 4359. (c) Gunawardana, G. P.; Koehn, F. E.; Lee, A. Y.; Clardy, J.; He, H.-Y.; Faulkner, D. J. *J. Org. Chem.* **1992**, *57*, 1523.

(7) (a) Okada, H.; Mukai, H.; Inouye, Y.; Nakamura, S. *J. Antibiot.* **1986**, *39*, 306. (b) Inouye, Y.; Take, Y.; Oogose, K.; Kubo, A.; Nakamura, S. *J. Antibiot.* **1987**, *40*, 105.

(8) Intriguing reports dealing with this issue have indeed appeared: (a) Taraporewala, I. B.; Cessac, J. W.; Chanh, T. C.; Delgado, A. V.; Schinazi, R. F. *J. Med. Chem.* **1992**, *35*, 2477. Antiviral activity for dercitins has been reported in the isolation paper (ref 8a).

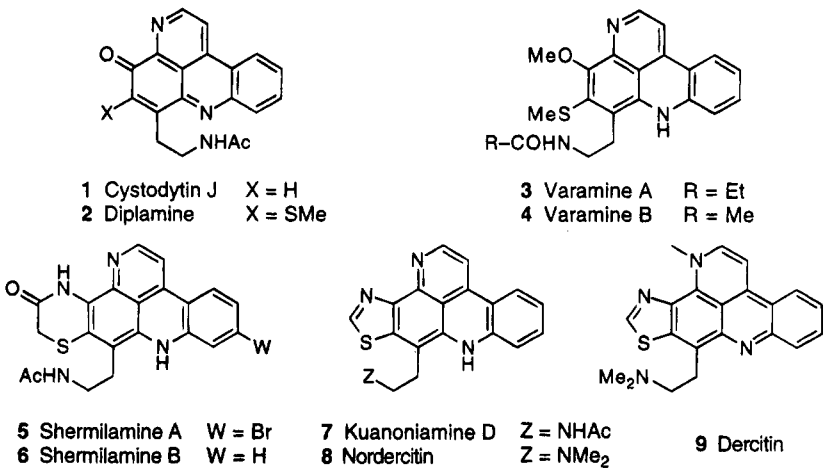
(9) Interesting data in this area are just beginning to emerge; cf.: McDonald, L. A.; Eldredge, G. S.; Barrows, L. R.; Ireland, C. M. *J. Med. Chem.* **1994**, *37*, 3819. For related studies see also: Lindsay, B. S.; Barrows, L. R.; Copp, B. R. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 739.

(10) (a) Bishop, M. J.; Ciufolini, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 10081. (b) Ciufolini, M. A.; Shen, Y.-C. *Tetrahedron Lett.* **1995**, *36*, 4709.

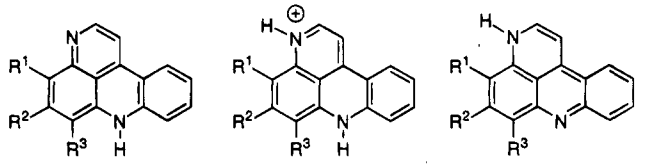
(11) (a) Kobayashi, J. I.; Cheng, J.-F.; Wälchli, M. R.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Ohizumi, Y. *J. Org. Chem.* **1988**, *53*, 1800. Kobayashi, J.; Tsuda, M.; Tanabe, A.; Ishibashi, M.; Cheng, J.-F.; Yamamura, S.; Sasaki, T. *J. Nat. Prod.* **1991**, *54*, 1634.

0002-7863/95/1517-12460$09.00/0 

**Scheme 1**




**Scheme 2**




varamine group of substances. Thiazine- and thiazole-containing alkaloids would also arise from **17**. In this case, however, the major events leading to the natural products would be cyclization of **17** to **18**, decarboxylation, and hydration–oxidation of the intervening **19** to give shermilamine-like compound **20**. A biosynthetic version of a well known oxidative transformation of thiazinones to thiazoles[12] might be involved in conversion of **20** to thiazole-containing alkaloids (cf. **20** → **24**).[13]

Useful methodology to accomplish the equivalent of transformations **13** + **14** → **15** and **15** → **16** below has recently emerged in the shape of a pyridine-forming reaction[14] and a nitrene insertion into C–H bonds,[15] respectively. The advent of these technologies allowed us to identify a common intermediate for structures **2**–**9** in the form of pyridoketone **25** (Scheme 4), which may be readily obtained from the known dienone **26**.[16] Key events in the advancement of **25** to **1**–**9** would be carbonyl α-sulfenylation and photochemically induced intramolecular nitrene insertion.

Two ancillary issues emerged immediately after formulation of our general synthetic plan. Sulfenylation of **25** may be accomplished in a number of ways, but the precise timing of such an operation required special consideration. Introduction of sulfur prior to photolysis could lead to troublesome side reactions in the diplamine/varamine manifold. Here, photoexcitation of the pyridyl ketone might induce Norrish-type H-atom transfer[17] (cf. **27** → **28**, Scheme 5), and the resulting diradical **28** could then decay to a multitude of undesirable products. Protection of the ketone and external sensitization of azide deazoniation, as a means to minimize the chance of unwanted side reactions, was unattractive, because the synthesis would then be several steps longer. The most direct strategy seemed to be direct mercaptanation of a quinoneimine of the type **1**. Coversely, geometric constraints greatly reduce the possibility of Norrish-type reactions in molecules of general structure **29**. Sulfenylated intermediates of that type were therefore anticipated to be plausible precursors to **5**–**9**, barring possible bimolecular H-atom transfers.

A second issue related to the timing of introduction of the acetamide function within the side chain "R" of **25**. This operation must be carried out prior to photolysis, as an amide group is well tolerated during that step, while nucleophilic transformations are best avoided once the pyridoacridine is in place.[16,18] Acetamide introduction may be achieved at the stage of **25** if R = $CH_2CH_2OH$, but then a carbonyl protection–deprotection maneuver becomes necessary.[18] Conversely, a side-chain amide or a free OH are not tolerated in **26** during the first step of the pyridine-forming sequence; namely, the inverse-demand heterocycloaddition with a vinyl ether catalyzed by a lanthanide diketonate complex (Scheme 6). Presumably, those highly Lewis basic units strongly ligate the metal, thereby inhibiting coordination by the enone carbonyl and repressing cycloaddition. By contrast, the acetate ester of **26** is a good substrate for the cycloaddition step. This led us to surmise that mesylate **31** may also be viable, with the added advantage that it would produce intermediates especially amenable to facile introduction of the side chain amide. This turned out to be the case.

Combination of **31** with ethyl vinyl ether provided pyrans **32**, obtained as a 1:1 mixture of side-chain epimers, but of mostly *cis* relative stereochemistry between aryl and ethoxy groups. The mesylate in **32** was smoothly displaced with *N*-sodioacetamide in DMF prior to pyridine formation, and ozonolysis of the emerging **34** afforded **35** in good overall yield after chromatography (the first one in the entire sequence). In an analogous fashion, ketone **36** was obtained from the acetate ester of **26**. These valuable ketones permitted rapid access to the entire group of pyridoacridine alkaloids.

**Total Synthesis of Cystodytin J (1) and Diplamine (2).** Diplamine was efficiently obtained through oxidative sulfeny-

(12) Discussion: Metzger, J. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, U.K., 1984; Vol. 6, part 4B; pp 235–331. See especially pp 324–325.

(13) A similar pathway has been suggested for the biosynthesis of firefly luciferin: McCapra, F.; Razavi, Z. *J. Chem. Soc., Chem. Commun.* **1975**, 42.

(14) Ciufolini, M. A.; Byrne, N. E. *J. Chem. Soc., Chem. Commun.* **1988**, 1230.

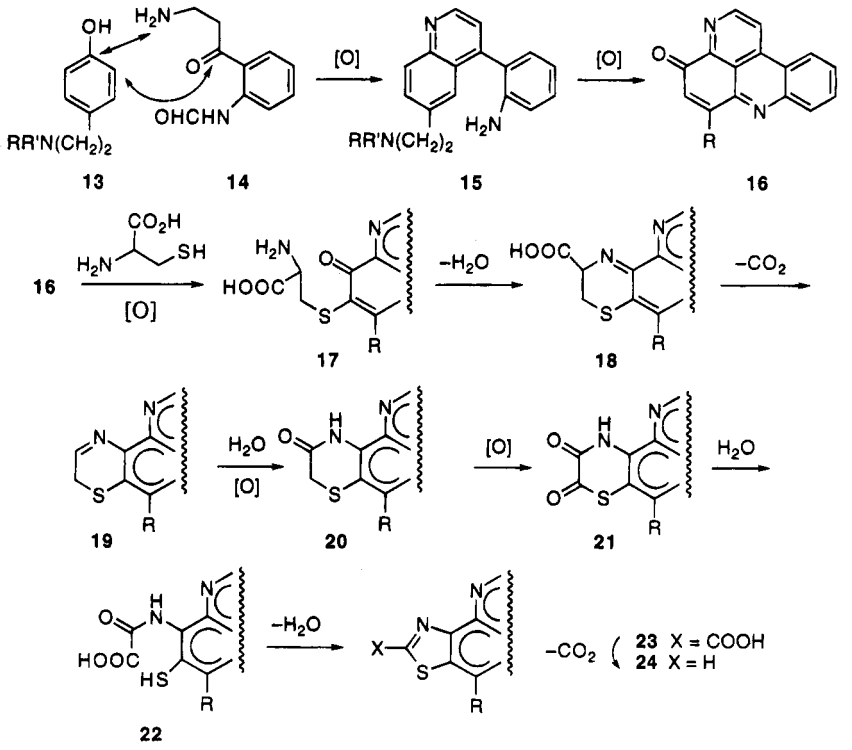
(15) (a) McRobbie, I. M.; Meth-Cohn, O.; Suschitzky, H. *J. Chem. Res.* **1977**, 17. (b) Lindley, J. M.; McRobbie, I. M.; Meth-Cohn, O.; Suschitzsky, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2194. (c) Ciufolini, M. A. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI Press: Greenwich, CT, 1995; Vol. 3, in press.

(16) Ciufolini, M. A.; Byrne, N. E. *Tetrahedron Lett.* **1989**, *30*, 5559.

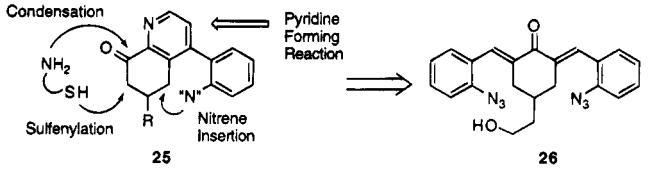
(17) For a discussion see, e.g., Cowan, D. O.; Drisko, R. L. *Elements of Organic Photochemistry*; Plenum Press: New York, 1976; Ch. 3, pp 116 ff.

(18) Ciufolini, M. A.; Byrne, N. E. *J. Am. Chem. Soc.* **1991**, *113*, 8016.

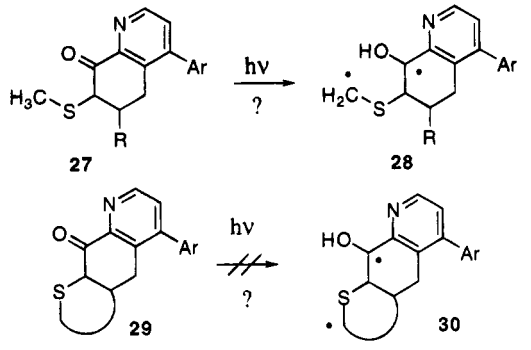
**Scheme 3**



**Scheme 4**



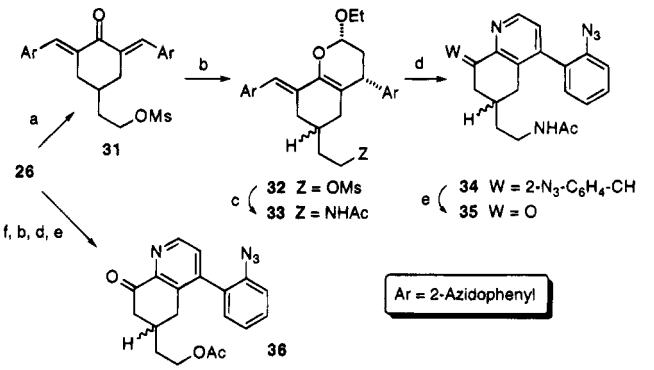
**Scheme 5**



lation of cystodytin J, demonstrating the plausibility of our biosynthetic hypothesis. Thus, ketone **35** was subjected to thermophotolysis under Meth–Cohn conditions (chlorobenzene, 110 °C, Sylvania sunlamp, Pyrex, argon), but without an external sensitizer, as the pyridyl ketone moiety of **35** provides effective internal triplet sensitization.[18] The emerging tetracyclic intermediate **37** was deep purple. We attribute this color to tautomeric equilibration with **38**, which incorporates a chromophore of the type **12**. The lumiproduct was oxidized in situ by titration with a solution of DDQ to give bright yellow cystodytin J, mp 196–197 °C dec, obtained in 31% chromatographed yield from **35**.

Moderately elevated temperatures are essential for the success of the thermophotolysis step, but, in accord with Meth–Cohn's observations, the efficiency of the reaction suffers at temperatures higher than about 110 °C. Thermal activation seemingly

**Scheme 6**[a]



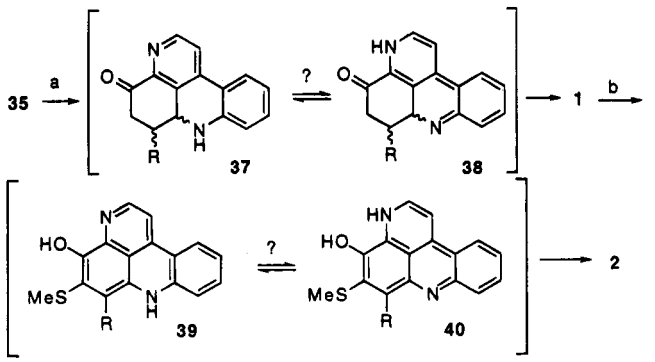
[a] (a) MsCl, $CH_2Cl_2$, $Et_3N$, 0 °C to rt, 99%; (b) $EtOCH{=}CH_2$, cat. Yb(fod)$_3$, DCE, reflux, 99%; (c) $AcNH_2$, NaH, DMF, 0 °C to rt, 97%; (d) moist $HONH_2{\cdot}HCl$, MeCN, reflux, 62%; (e) $O_3$, 4:1 $CH_2Cl_2$/MeOH, −78 °C and then $Me_2S$, −78 °C to rt, 67% chromatographed; (f) $Ac_2O$, pyridine, 97%.

facilitates hydrogen atom abstraction by a presumed triplet nitrene intermediate, which otherwise decays to unwanted side products.

Rapid and quantitative conversion to intensely purple **39** occurred when MeSH was bubbled into a 4:1 $CH_2Cl_2$/AcOH solution of **1** at room temperature.[19] The color of **39** may also be attributed to equilibration with tautomer **40**. Removal of the volatiles left the sulfenylated intermediate as an air-sensitive, dark purple solid. This substance was redissolved in $CH_2Cl_2$ and titrated with a solution of DDQ in $CH_2Cl_2$ until a color change from dark blue to dull orange was observed. This indicated formation of the diplamine chromophore. The orange solution was directly applied to a column of silica gel, and totally synthetic diplamine, mp 200–201 °C dec (lit. 202–204 °C dec)

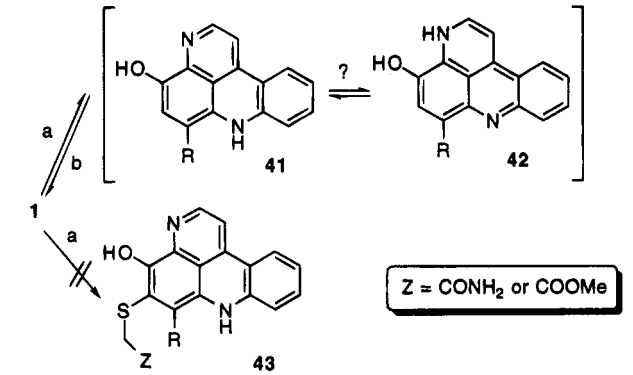
(19) For similar reactions see: (a) Finley, K. T. In *The Chemistry of the Quinonoid Compounds*; Patai, S., Ed.; John Wiley & Sons: London, UK, 1974; Vol. 1, part 2; Ch. 17, especially pp 881–900. (b) Chatterjee, M.; Rokita, S. E. *J. Am. Chem. Soc.* **1990**, *112*, 6397, and references cited therein.

**Scheme 7**[a]



[a] (a) *hv*, PhCl, 110 °C and then cool to rt and titrate with DDQ, 31% chromatographed; (b) MeSH, 4:1 $CH_2Cl_2$/AcOH, rt and then remove volatiles, take up in $CH_2Cl_2$, and titrate with DDQ, 94%.

**Scheme 8**[a]

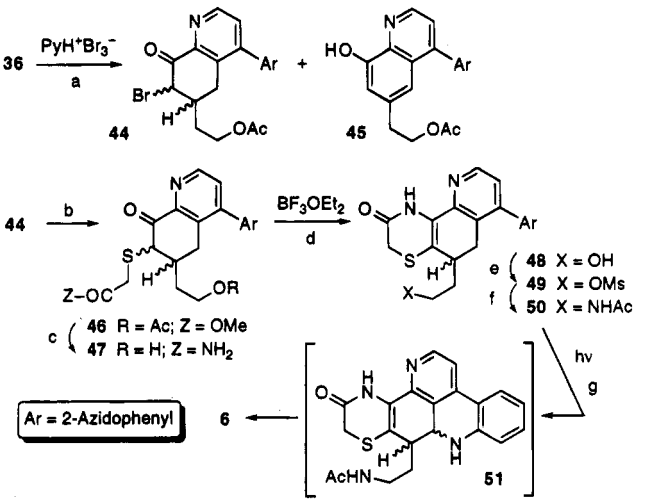


[a] (a) 2-Mercaptoacetamide or methyl 2-mercaptoacetate, 4:1 $CH_2Cl_2$/AcOH; (b) remove volatiles, take up in $CH_2Cl_2$, and titrate with DDQ.

was eluted with 10% MeOH in $CH_2Cl_2$ (94% yield, Scheme 7). We emphasize that the relatively low yield obtained in the photocyclization of **35**, while consistent with earlier observations,[18] appears to be a consequence of lack of substitution at the position adjacent to the ketone carbonyl. Substrates with a substituent at that position, but otherwise identical to **35**, undergo photocyclization in more than double the yield. At this time, we are inclined to attribute the moderate efficiency of this step to a secondary photochemical process that erodes the integrity of **37** and **38**, but the details of such a process elude us, as byproducts formed in this step are exceedingly polar and difficult to identify. Of course, the moderate efficiency of this reaction must be weighed against the fact that completion of the molecular framework in any other manner would have required many more steps. The overall yield of **2** from **26** was 12% over seven steps.

**Total Synthesis of Shermilamine B (6), Kuanoniamine D (7), and Dercitins (8 and 9).** Encouraged by the success of the diplamine synthesis, we embarked in an approach to shermilamine B involving oxidative merger of cystodytin J with α-mercaptoacetamide, an event that would be followed by thiazinone ring formation and adjustment of the oxidation state (Scheme 8). We were dismayed to observe that the seemingly trivial substitution of mercaptoacetic-type thiols for methylmercaptan completely shut down the (formal) conjugate addition pathway *vis a vis* **1**. Both mercaptoacetamide and methyl mercaptoacetate seemingly reduced **1** (development of a purple color, equilibration of a presumed **41** with tautomer **42**), but failed to add to the quinoneimine. Thus, cystodytin J was recovered substantially unchanged after mild oxidation back to the quinone form. The reasons for this behavior remain obscure.

**Scheme 9**[a]



[a] (a) AcOH, 50 °C, 70% crude; (b) $HSCH_2COOMe$, $iPr_2NEt$, EtOH, rt, 10 min, 66% chromatographed from **36**; (c) $NH_3$, MeOH, rt, 12 h and then add $K_2CO_3$, 91%; (d) $CHCl_3$, rt, 90%; (e) MsCl, $CH_2Cl_2$, $Et_3N$, 0 °C to rt, 100%; (f) $AcNH_2$, NaH, DMF, rt, 59%; (g) sunlamp, 10% PhCOMe in PhCl, 110 °C, 67% chromatographed.

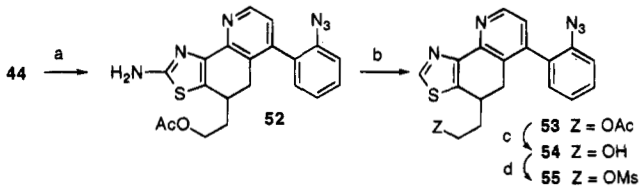
These disappointing results were not regarded as a fatal blow to the original synthetic logic, as a suitable sulfenylated intermediate appeared to be directly available from ketones **35** and **36**, through the sequence depicted in Scheme 9. The well documented α-bromination of tetralones[20] supported the feasibility of these operations. A minor setback was that **35** did not react cleanly with various brominating agents. Seemingly, the acetamide function present in the molecule would suffer conversion to an unstable *N*-bromo derivative, which then rapidly decayed to complex mixtures. No such problems were observed with ketone **36**, wherein the side chain contains an acetate group. This material reacted rapidly with pyridinium tribromide[21] to furnish bromo ketone **44**. However, **44** was always accompanied by small amounts of phenol **45**. The phenol probably forms upon HBr elimination from **44**, a reaction that appeared to be quite facile, that was seemingly promoted by silica gel, and that consequently undermined attempts at purification of **44**. Fortunately, minor quantities of the phenol proved to be perfectly tolerable in the subsequent step.

The bromo ketone reacted smoothly with methyl mercaptoacetate in the presence of Hünig's base, and the resulting **46** underwent facile ammonolysis/deacetylation under the customary conditions. Ketoamide **47** cyclized without incident to thiazinone **48** upon exposure to $BF_3{\cdot}OEt_2$, and the free alcohol in **48** formed the mesylate without disturbance to, or interference from, other functionality present in the molecule. The subsequent displacement of mesylate with *N*-sodioacetamide, a potentially troublesome transformation, also occurred uneventfully. The total synthesis of shermilamine B was completed by thermophotolysis of **50** under true Meth−Cohn conditions (9:1 mixture of chlorobenzene and acetophenone, 110 °C).[15] Acetophenone, the triplet sensitizer, was needed in this case, because the substrate lacks an aromatic ketone chromophore required for internal sensitization. We were pleased to observe that when this reaction is applied to dihydroaromatic substrates such as **50**, *in situ* oxidation of the presumed intermediate **51** follows cyclization to provide shermilamine B (**6**). This will

(20) E.g.: Jung, K.-Y.; Koreeda, M. *J. Org. Chem.* **1989**, *54*, 5667, and references cited therein.

(21) Cf. Kornfeld, E. C.; Fornefeld, E. J.; Kline, B.; Mann, M. J.; Morrison, D. E.; Jones, R. G.; Woodward, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 3087.

**Scheme 10**[a]




[a] (a) Thiourea, EtOH, 35 °C, 15 min, 95%; (b) i-AmONO, DMF, 80 °C, 82%, (c) $K_2CO_3$, MeOH, 94%; (d) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C, 99%.

also be seen later for the kuanoniamine–dercitin group of substances. It is likely that the oxidant is photoexcited acetophenone, the triplet state of which probably abstracts H-atoms from **51**. Close scrutiny of the photolysis step revealed that an initially formed intermediate, observable as an intensely purple spot by TLC, turns into shermilamine (orange spot) during the course of the reaction. By analogy with the case of cystodytins and diplamine, the blue spot is attributed to a tautomer of the primary photoproduct **51**. Fully synthetic **6**, 252–254 °C dec without melting (lit. 254 °C dec without melting), was thus isolated directly from the photolysis mixture in 67% chromatographed yield. As mentioned earlier, it is apparent that photocyclization of substituted azidoketones is considerably more efficient than that of unsubstituted congeners. The yield of **6** from **26** was 8% over 11 steps.

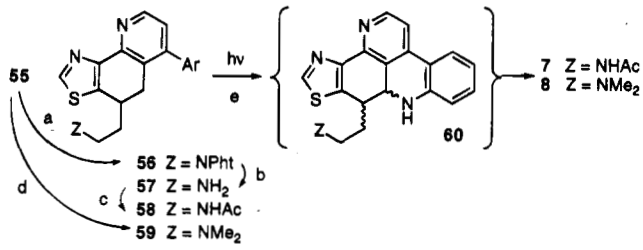
Bromo ketone **44** proved to be an excellent substrate for the venerable Traumann reaction,[22] and as such, it became the starting point in the route to kuanoniamines and dercitins. Thus, reaction of **44** with thiourea in warm ethanol occurred rapidly and exothermically to furnish extremely polar aminothiazole **52**, white powder, in virtually quantitative yield (Scheme 10). Deamination with isoamyl nitrite in hot DMF[23] provided thiazole **53**, white dendrites, mp 164 °C, in excellent yield. This material was safely chromatographed to remove the small amount of contaminating **45**. We presume that a one-step conversion of **44** to **53** should be possible through reaction with thioformamide, but the presence of the extra amino group in **52** may be advantageous for the synthesis of analogues of **7**–**9** and for SAR work. Conversely, attempted one-step aminothiazole formation from **44** under Dodson–King conditions[24] failed.

Installation of the correct side chain groups, as dictated by the structures of the various natural products, was readily effected at the stage of mesylate **55**, at which point the synthetic routes to dercitins and kuanoniamines diverged (Scheme 10).

The synthesis of kuanoniamine D (**7**), an especially bioactive member of the omonimous family, yet weakly active on an absolute scale, required prior formation of acetamide **58**. Mesylate displacement from **55** with *N*-sodioacetamide, under conditions identical to those used for the analogous reaction of **49**, produced only complex mixtures. A remedy for this curious problem emerged in the form of a classical Gabriel sequence, which provided the desired **58** in three steps and in 68% overall yield. The synthesis of **7** was completed by irradiation of a 0.005 M solution of acetamide **58** in 9:1 chlorobenzene–acetophenone. A beautiful emerald green fluorescence appeared at the surface of the solution during photolysis, at the same time that the color of the solution slowly changed to red-purple. As in the case of shermilamine, TLC again revealed the presumed primary photopruduct **60** (Z = NHAc) as a slow-moving, purple intermediate that gradually became oxidized to kuanoniamine

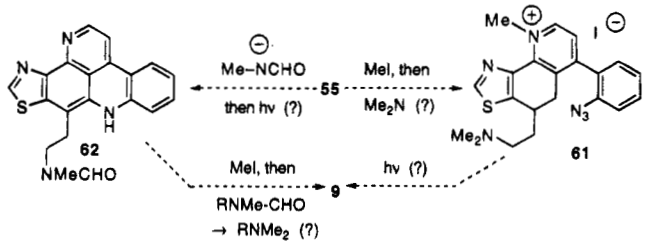
(22) Traumann, V. *Liebigs Ann. Chem.* **1888**, *249*, 31.
(23) Cf. Doyle, M. P.; Dellaria, Jr., J. F.; Siegfried, B.; Bishop, S. W. *J. Org. Chem.* **1977**, *42*, 3494.
(24) Dodson, R. M.; King, L. C. *J. Am. Chem. Soc.* **1945**, *67*, 2242.

**Scheme 11**[a]




[a] (a) PhtNK, DMF, 50 °C, 84%; (b) $N_2H_4$, MeOH, 94%; (c) $Ac_2O$, $Et_3N$, 86%; (d) 40% aqueous $Me_2NH$, DMF, 86%; (e) sunlamp, 9:1 PhCl–PhCOMe, 110 °C, 62% (**1**), 63% (**2**) chromatographed.

**Scheme 12**

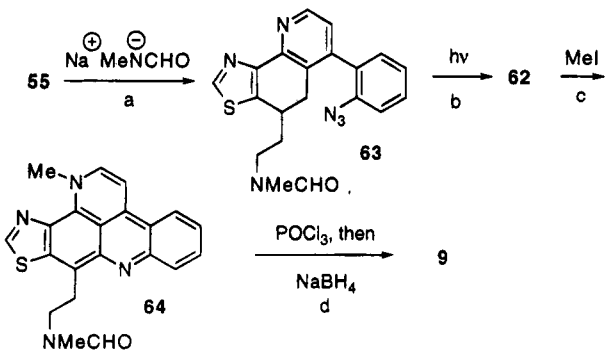



(faster, bright yellow spot). Undoubtedly, the highly conjugated chromophore of **7** was responsible for the fluorescence, while the now familiar tautomer of **60** was imparting a purple color to the solution. Fully synthetic **7**, yellow solid, 260 °C dec without melting (lit. mp > 300 °C), was directly obtained from this photochemical step in 62% chromatographed yield. The overall yield of **7** from **26** was 8% over 13 steps. True to its name, kuanoniamine instantly turned violet upon exposure to acids. Similarly, nordercitin was obtained upon exposure of **55** to 40% aqueous dimethylamine in DMF and photolysis of the resulting **59**, thick oil, under the usual conditions. Totally synthetic **8**, yellow solid, mp 177–179 °C (lit. mp 176 °C), was isolated in 63% chromatographed yield and in 12.5% overall yield from **26** over 11 steps (Scheme 11).

The synthesis of dercitin required selective N-methylation of the pyridine unit at some appropriate stage. This necessitated additional maneuvering, as it was readily recognized that selective N-methylation of the pyridine ring could not be carried out in the presence of the considerably more nucleophilic side chain dimethylamino group. Conversely, the thiazole subunit was not regarded as a likely source of interference during the desired transformation, given its well-established 20-fold lower reactivity toward methyl iodide relative to pyridine.[25] Two possible strategies were formulated, the first one involving N-methylation of **55**, mesylate displacement, and azide photolysis of pyridinium ion **61** (Scheme 12). A troublesome feature of this plan was the well-documented oxidizing ability of photoexcited pyridinium ions,[26] a property that could have serious, possibly fatal, repercussions on the feasibility of the photochemical step. An alternative plan centering on introduction of the side chain amine in latent form appeared to be safer, and compound **62** seemed to be an especially good advanced intermediate. The formamide unit would repress nucleophilic reactivity at the side chain, while being amenable to reduction to the requisite dimethylamino group. The dihydroacridine nitrogen is not a likely source of nucleophilic interference: dihydroacridine is a weaker nucleophile than acridine, which, in turn, is considerably weaker than pyridine. While pyridine reacts vigorously with MeI, N-methylation of acridine occurs

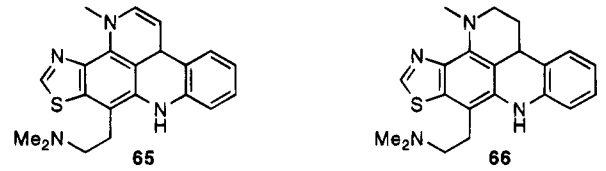
(25) Metzeger, J. V. *Chem. Heterocycl. Compds.* **1979**, *34–1*, 125.
(26) Cf. Bird, C. L.; Kuhn, A. T. *Chem. Soc. Rev.* **1981**, *10*, 49.

**Scheme 13**[a]




[a] (c) MeNHCHO, NaH, DMF, 0 °C to rt, 86%; (b) sunlamp, 9:1 PhCl–PhCOMe, 110 °C, 64%; (c) $K_2CO_3$, refl PhH, 99%; (d) $POCl_3$, THF, cat. pyr, 45 °C and then vacuum-dry, add DME and $NaBH_4$, 0 °C, 87%.

**Scheme 14**




only slowly with methyl tosylate in nitrobenzene at 150 °C.[27] Moreover, the side chain in **62** creates a severe peri interaction around the dihydroacridine nitrogen, further reducing its reactivity. We were not to regret our decision to proceed through **62** *en route* to dercitine.

Amide **63**, mp 168 °C, emerged in excellent yield upon reaction of **55** with the sodium salt of *N*-methylformamide, compounding our disappointment with the earlier failure of mesylate displacement with acetamide anion. Subsequent photolysis/aromatization furnished **62** as a yellow solid, mp 171–172 °C, in 64% chromatographed yield. This heterocycle reacted with MeI/$K_2CO_3$ in refluxing benzene to give exclusively *N*-methylpyridine **64** in 99% yield, as a dark purple solid (cf. chromophore **12**) of mp 170–171 °C. As expected, **64** turned red in acidic solution, but it did not turn yellow under basic conditions, as it cannot attain chromophoric structure **10**. Reduction of **64** to **9** was effected by the Kuehne method.[28] This excellent procedure involves $NaBH_4$ reduction of a chloroiminium ion, formed *in situ* from the formamide and $POCl_3$. Fully synthetic dercitin, deep blue solid, mp 165–167 °C (lit. 168 °C) was thus obtained in 87% yield. The overall yield of **9** was 10% over 13 steps from **26** (Scheme 13).

This final step required us to investigate a number of reductive protocols, as conversion of **64** to **9** was not as straightforward as we had originally thought. Dercitin reportedly undergoes $NaBH_4$ reduction to form a leuco derivative, which we term leucodercitin and for which we postulate structure **65**. Leucodercitin is easily air oxidized back to **9**. Reduction with more vigorous agents delivers a substance that is not air oxidized back to dercitin and that we term apodercitin. We speculate that apodercitin may be structure **66** (Scheme 14).

Undoubtedly, leucodercitin is an intermediate in the conversion of **64** to **9**. The telltale blue color of the natural products began to develop only during workup of the Kuehne step and attendant exposure of the reaction mixture to the atmosphere. Initial attempts at reduction of **64** with diisobutylaluminum hydride (DIBAL) gave a mixture of overreduced products that were not oxidized back to dercitin. Excess DIBAL appeared to reduce even the thiazole ring, as its diagnostic proton was no longer evident at 9.5–10 ppm in the $^1H$ spectra of crude reaction mixtures. Careful titration of **64** with DIBAL solution did not improve things; likewise, no desired **9** was obtained upon attempted reduction with $BH_3$[29] or with $NaBH_4$ under Borch conditions.[30] Fortunately, the Kuehne protocol resolved all such difficulties.

Several structures generated during this research were assayed for anti-AIDS activity under the aegis of the National Institutes of Health. Compounds **7–9** were inactive against HIV, but with the notable exception of weakly cytotoxic kuanoniamine D ($IC_{50} > 10^{-4}$ M), they exhibited comparable toxicity toward the human CEM-SS cell line utilized in the bioassay ($IC_{50} \approx 10^{-6}$–$10^{-5}$ M). Cytotoxicity against healthy cells appears to be much lower than that reported for tumor lines, suggesting that the new substances may indeed represent useful leads for the development of chemotherapeutic resources. This fact underscores the practical importance of a coherent strategy for the chemical synthesis of the major classes of pyridoacridine alkaloids. We believe that this objective has been fully realized through to the chemistry just described.

**Conclusions.** Pyridoacridines are now readily available, despite their natural paucity. While the compact, refractory ring system of the natural products does not seem amenable to facile modification, minor changes in the synthetic plan described here should produce analogues of **1–9** displaying a range of structural variations, both in the ring system and at the side chain. This should greatly facilitate medicinal chemistry and SAR work. From a purely chemical standpoint, this work demonstrates the value of our pyridine-forming reaction and of photochemical transformations of azides in the construction of complex polycyclic heteroaromatic molecules. We remain hopeful that the newly established synthetic routes will promote pyridoacridine alkaloids from the realm of exciting structural curiosities to that of subjects of detailed pharmacological scrutiny.

## Experimental Section

Melting points (uncorrected) were measured on a Fischer-Johns hot stage apparatus. NMR spectra (ppm on the $\delta$ scale) were recorded at room temperature on Bruker AC 250 (250 MHz for $^1H$ and 62.5 MHz for $^{13}C$) or on IBM AF300 (300 MHz for $^1H$ and 75 MHz for $^{13}C$) spectrometers from $CDCl_3$ solutions, unless otherwise indicated. Splitting patterns are described as "s" (singlet), "d", "dd", "ddd", etc. (doublet, doublet of doublets, doublet of doublets of doublets), "t" (triplet), "q" (quartet), "m" (multiplet), and further characterized as "app" (apparent), "br" (broad), or "c" (complex). IR spectra ($cm^{-1}$) were obtained with a Perkin Elmer 1600 FTIR spectrophotometer from films deposited on NaCl plates, unless otherwise indicated. Low resolution mass spectra (*m/e*, solid probe, 70 eV EI) were obtained on a Finnigan 6000 quadrupole instrument. High resolution mass spectra (*m/e*, solid probe, 70 eV EI) were obtained on a Finnigan-MAT 4000 instrument. Analytical and preparative TLC was carried out with Merck silica gel 60 plates with fluorescent indicator. Spots were visualized with UV light or stained with iodine, molybdic acid (solution of 24 g $(NH_4)_6Mo_7O_{24}$ and 0.5 g $Ce(SO_4)_2$ in 500 mL of 10% aqueous $H_2SO_4$) anisaldehyde, or Dragendorff reagents (Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; John Wiley & Sons: New York, 1972; pp 378–379). Chromatographic silica gel was purchased from Jenssen (60–200 mesh) or Merck (230–400) mesh. Chlorobenzene, ethyl acetate, and ethyl vinyl ether were distilled at atmospheric pressure; methanol was dried over 4 Å molecular sieves, dichloromethane was first passed through alumina and then distilled from $CaH_2$; boron trifluoride etherate, 1,2-dichloroethane, *N,N*-diisopropylethylamine, pyridine, toluene, and triethylamine were distilled from $CaH_2$ at atmospheric pressure;

(27) Albert, A.; Ritchie, B. *J. Chem. Soc.* **1943**, 458.
(28) Kuehne, M. E.; Shannon, P. J. *J. Org. Chem.* **1977**, *42*, 2082.
(29) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *Synthesis* **1981**, 996.
(30) Borch, R. F. *Tetrahedron Lett.* **1968**, *9*, 61.

acetophenone and methanesulfonyl chloride were vacuum distilled. All other reagents and solvents were used as received. Photolyses were carried out in degassed solutions (bubbling with Ar for at least 20 min) maintained under Ar atmosphere (balloon) throughout irradiation. The light source was a Sylvania 275 W sunlamp.

**Cycloadduct 32.** Methanesulfonyl chloride (1.36 mL) was added dropwise to a stirred solution of ketone **26** (4.67 g, 11.7 mmol) and $Et_3N$ (2.68 mL, 1.93 g, 19 mmol) in $CH_2Cl_2$ (70 mL), at 0 °C under argon. After 10 min the mixture was warmed to room temperature and sequentially washed with half-saturated brine, deionized water, and saturated aqueous NaCl. Vacuum concentration gave 5.52 g (99%) of **31**, bright yellow solid, mp 74−76.5 °C; $R_f$ = 0.62 (50% EtOAc/hexane). A solution of 5.47 g of **31** and Yb(fod)$_3$ (605 mg 5 mol %) in 47 mL of a 1:1 mixture of 1,2-dichloroethane−ethyl vinyl ether was gently refluxed overnight, cooled, diluted with 35 mL $CH_2Cl_2$, and sequentially washed with saturated aqueous $NaHCO_3$, deionized water, and saturated aqueous NaCl. Vacuum concentration gave **32** as a thick yellow oil in quantitative yield; $R_f$ = 0.78 (50% EtOAc/hexane). $^1$H: 7.33−7.05 (c m, 8H), 7.00 and 6.97 (two br s, 1H total), 5.18−5.09 (c m, 1H), 4.19 (q, 2H, $J$ = 5.9 Hz), 4.15−3.54 (c m, 2H), 2.94 and 2.88 (two s, 3H total), 2.72 (app br d, 1H, $J$ = 14.7 Hz), 2.39−2.24 (c m, 2H), 2.19−1.57 (c m, 6H), 1.31 and 1.22 (two t, 3H total, $J$ = 7.0 Hz). $^{13}$C: 144.8, 144.3, 138.2, 137.9, 137.8, 134.4, 134.0, 132.5, 131.9, 130.5, 130.0, 129.3, 128.0, 127.8, 127.6, 124.9, 124.6, 124.2, 118.3, 118.2, 118.0, 117.9, 117.6, 112.7, 111.8, 99.1, 98.1, 68.0, 67.6, 64.5, 64.0, 37.2, 37.0, 35.1, 34.7, 33.8, 33.2, 33.1, 32.7, 31.0, 30.2, 29.6, 15.3, 15.1. IR: 3065, 3030, 2966, 2931, 2123, 1623, 1588, 1476, 1455, 1356, 1286, 1223, 1166, 1138, 1061, 1040, 963, 801, 759, 674. MS: 522 ($M^+ - N_2$), 494 ($M^+ - 2\,N_2$), 448, 434, 398, 353, 351, 336, 323, 298, 271, 240, 196, 194, 174, 168, 130, 129 (100%); HRMS: calcd for $C_{27}H_{30}N_4O_5S$ ($M^+ - N_2$); 522.1937; obsd 522.1919; calcd for $C_{27}H_{30}N_2O_5S$ ($M^+ - 2\,N_2$); 494.1875; obsd 494.1876.

**Acetamide 33.** A mixture of **32** (6.2 g, 11.3 mmol), NaH (2.7 g, 110 mmol, 10 equiv), acetamide (6.7 g, 110 mmol, 10 equiv) and dry DMF (15 mL), initially chilled to 0 °C, was stirred under argon while being allowed to warm to rt. The reaction completed after 2 h (TLC). The mixture was diluted with 10% aqueous $Na_2CO_3$ and ether, and the organic layer was separated and sequentially washed with deionized water and saturated aqueous NaCl. Concentration yielded **33** as a thick oil in essentially quantitative yield; $R_f$ = 0.53 (10% MeOH/$CHCl_3$). $^1$H: 7.33−7.00 (c m, 8H), 6.95 and 6.93 (two br s, 1H total), 5.44 (br s, 1H), 5.14−5.05 (c m, 1H), 4.12−3.46 (c m, 2H), 3.10 (q, 2H, $J$ = 5.9 Hz), 2.73−2.61 (c m, 1H), 2.27 (m, 2H), 2.13−1.55 (c m, 4H), 1.86 (s, 3H), 1.50−1.35 (c m, 2H), 1.28 and 1.19 (two t, 3H total, $J$ = 7.0 Hz). $^{13}$C: 169.9, 144.3, 138.2, 137.8, 134.5 134.0, 133.0, 132.4, 130.6, 130.5, 129.9, 129.4, 127.9, 127.7, 127.6, 124.9, 124.5, 124.2, 118.3, 118.2, 118.0, 117.6, 117.1, 113.2, 112.2, 109.8, 99.1, 98.0, 64.5, 64.0, 37.5, 37.3, 35.5, 35.0, 34.6, 34.0, 33.6, 33.3, 33.2, 32.3, 31.7, 29.6, 23.1, 15.3, 15.1. IR: 3311, 3072, 2981, 2931, 2133, 1652, 1574, 1546, 1476, 1455, 1377, 1293, 1145, 1047, 970, 948, 878, 759, 674. MS: 513 ($M^+$), 485, 457, 397, 323, 297, 281, 168, 130 (100%), 129, 117, 92. HRMS: calcd for $C_{28}H_{31}N_7O_3$ ($M^+$): 513.2488; obsd 513.2504; calcd for $C_{28}H_{31}N_5O_3$ ($M^+ - N_2$): 485.2427; obsd 485.2425.

NOTE: All the following azido compounds were obtained as a 1:1 mixture of diastereomeric rotamers due to restricted rotation about the biaryl system, hence the doubling of many $^1$H and $^{13}$C NMR lines.

**Pyridine 34.** A mixture of **33** (5.55 g, 10.9 mmol), moist hydroxylamine hydrochloride (3.11 g), and acetonitrile (39 mL) was refluxed for 7 h with vigurous stirring, and then it was cooled and concentrated. The residue was dissolved in $CH_2Cl_2$ and washed with saturated aqueous $NaHCO_3$, and then the organic layer was passed over a short plug of silica gel and evaporated to leave 3.15 g (62% yield) of **34**, mp 60.5−62 °C; $R_f$ = 0.32 (60% EtOAc/hexane). $^1$H: 8.50 (d, 1H, $J$ = 5.1 Hz), 8.00 (br s, 1H), 7.44 (t, 1H, $J$ = 8.1 Hz), 7.34−7.04 (c m, 7H total), 6.94 (t, 1H, $J$ = 4.8 Hz), 5.79 (br s, 1H), 3.09 (c m, 2H), 2.90 (br d, 1H, $J$ = 14.7 Hz), 2.68−2.17 (c m, 4H), 1.81 (s, 3H), 1.46 (c m, 2H). $^{13}$C: 169.9, 152.4 & 152.1, 146.7, 146.6 & 146.5, 138.6, 137.5 & 137.2, 135.9 & 135.8, 130.6 & 130.3, 130.4, 130.2 & 130.1, 130.0, 129.6 & 129.5, 129.3, 128.3, 124.9 & 124.8, 124.2, 123.6 & 123.5, 123.3, 118.5 & 118.3, 118.2, 37.2, 35.0 & 34.8, 33.6 & 33.4, 33.1 & 32.9, 31.3 & 31.2, 22.9. IR: 3283, 3065, 2931, 2123, 1652, 1567, 1546, 1483, 1441, 1398, 1377, 1293, 1138, 1082, 1040, 836, 753, 667. MS: 464 ($M^+$), 436 ($M^+ - N_2$), 394, 348, 336, 322 (100%), 320, 307. HRMS: calcd for $C_{26}H_{24}N_8O$: 464.2073; obsd 464.2073.

**Ketone 35.** Ozonized oxygen was bubbled through a cold (−78 °C) solution of **34** (3.15 g) in 60 mL of 4:1 $CH_2Cl_2$/MeOH until the starting material disappeared (TLC, ≈30 min). Excess $O_3$ was purged by bubbling argon prior to addition of methyl sulfide (5 mL). The resulting solution was stirred at room temperature for 1.5 h, and then it was concentrated. The residue was dissolved in $CH_2Cl_2$ and washed with deionized water. The organic layer was directly applied to a column of 30 g silica gel. Azidobenzaldehyde produced in the reaction was eluted with $CH_2Cl_2$ and recycled. The product, yellow crystals, mp 188−189 °C; $R_f$ = 0.51 (10% MeOH/$CHCl_3$), was eluted with 10% MeOH/$CHCl_3$ (1.60 g; 67% yield). $^1$H: 8.56 (d, 1H, $J$ = 4.4 Hz), 7.42 (t, 1H, $J$ = 7.7 Hz), 7.25−6.86 (c m, 4H), 3.60−2.99 (c m, 2H), 2.86−2.12 (c m, 5H), 1.81 (s, 3H), 1.64−1.37 (c m, 2H). $^{13}$C: 196.3, 196.2, 170.4, 170.3, 147.8, 147.7, 147.3, 138.5, 138.0, 137.4, 136.9, 130.1, 130.0, 128.7, 128.3, 128.1, 127.8, 124.9, 124.7, 118.4, 118.1, 44.7, 44.6, 36.3, 34.7, 34.4, 32.7, 32.4, 31.6, 31.5, 22.6, 15.3. IR: 3304, 3065, 2981, 2931, 2875, 2123, 1708, 1652, 1574, 1483, 1448, 1363, 1300, 1223, 1202, 1138, 1096, 1033, 857, 766, 730, 695. MS: 349 ($M^+$), 321 ($M^+ - N_2$), 320, 308, 296, 280, 262, 250, 249, 235 (100%), 207, 179, 152, 127, 77. HRMS: calcd for $C_{19}H_{19}N_5O_2$: 349.1539; obsd 349.1536.

**Cystodytin J, 1.** A thoroughly degassed chlorobenzene (24 mL) solution of **35** (109 mg) in a common Pyrex flask was maintained at 105−110 °C internal temperature, under Ar, during irradiation with a sunlamp. After ≈8 h the reaction was complete (TLC), and the solution was cooled to rt. The deep purple primary photoproduct was carefully titrated with a $CH_2Cl_2$ solution of DDQ until conversion into bright yellow **1** was complete. The mixture was applied to a column of silica gel (5 g), and chlorobenzene was eluted with 20% EtOAc/hexanes. The product, yellow prisms, mp 196−197 °C dec; $R_f$ = 0.44 (10% MeOH/$CHCl_3$), was recovered with 10% MeOH/$CHCl_3$ (30 mg, 30% yield). $^1$H: 8.98 (d, 1H, $J$ = 4.6 Hz); 8.46 (d, 1H, $J$ = 8 Hz); 8.31 (d, 1H, $J$ = 7.9 Hz); 8.23 (d, 1H, $J$ = 4.9 Hz); 7.96 (app dt, 1H, $J_1$ = 7.3 Hz, $J_2$ = 1.2 Hz); 7.85 (app. dt, 1H, $J_1$ = 7.3 Hz, $J_2$ = 0.9 Hz); 6.87 (s, 1H); 6.62 (br s, 1H); 3.81 (q, 2H, $J$ = 6.4 Hz); 3.27 (t, 2H, $J$ = 6.4 Hz); 2.04 (s, 3H). $^{13}$C: 183.4; 170.4; 152.2; 150.3, 149.8; 146.5; 145.3; 137.0; 132.8; 131.9; 129.9; 122.9; 121.8; 119.1; 117.9; 39.3; 31.7; 23.3. IR: 3311; 3086; 2987; 2938; 1659; 1581; 1553; 1462; 1441; 1377; 1328; 1293; 1173; 1096; 1054; 758; 695. MS: 317 ($M^+$), 315, 272, 243, 218, 205, 190, 152, 115, 77, 43 (100%). HRMS: calcd for $C_{19}H_{15}N_3O_2$: 317.1164; obsd 317.1163.

**Diplamine, 2.** Methyl mercaptan was bubbled for about 5 s through a solution of cystodytin J (15 mg) in 4 mL of $CH_2Cl_2$ and 1 mL of AcOH. The yellow solution immediately turned deep blue, and the solvents were evaporated. The dark blue residue was dissolved in $CH_2Cl_2$ and titrated with a $CH_2Cl_2$ solution of DDQ until the color of the mixture changed to orange-yellow. The solvent was evaporated, and the residue was taken up in 10% MeOH/$CHCl_3$ and filtered through silica gel (1 g) with 10% MeOH/$CHCl_3$. The eluate was concentrated to afford a quantitative yield of **1**, burnt orange crystals, 200−201 °C dec without melting; $R_f$ = 0.54 (10% MeOH/$CHCl_3$). $^1$H: 9.08 (d, 1H, $J$ = 5.5 Hz); 8.49 (dd, 1H, $J_1$ = 7.9 Hz, $J_2$ = 1.2 Hz); 8.36 (d, 1H, $J$ = 5.5 Hz); 8.29 (dd, 1H, $J_1$ = 7.6 Hz, $J_2$ = 0.9 Hz); 7.94 (ddd, 1H, $J_1$ = 7.6 Hz, $J_2$ = 7.6 Hz; $J_3$ = 1.2 Hz); 7.83 (app dt, 1H, $J_1$ = 7.6 Hz, $J_2$ = 7.6 Hz, $J_3$ = 1.5 Hz); 6.50 (br s, 1H); 3.75 (br s, 4H); 2.64 (s, 3H); 1.94 (s, 3H). $^{13}$C: 176.6; 170.3; 151.6; 150.0; 149.8; 146.8; 145.6; 143.4; 137.0; 131.9; 131.8; 129.7; 122.9; 121.5; 119.2; 117.3; 39.9; 29.9; 23.3; 17.9. IR: 3332; 3079; 2924; 1659; 1609; 1539; 1476; 1441; 1377; 1286; 1194; 1152; 1089; 878; 773; 730. MS: 363 ($M^+$), 348, 315, 300, 285, 247, 231, 230, 215, 169, 131, 119, 117 (100%), 91, 69. HRMS: calcd for $C_{20}H_{17}N_3O_2S$: 363.1041; obsd 363.1040.

**Bromo Ketone 44.** Pyridinium tribromide (2.1 g, 6.6 mmol, 1.25 equiv) was added in three equal portions over 5 min to a warm (50 °C) solution of ketone **36** (1.85 g, 5.3 mmol) in glacial AcOH (60 mL), under Ar. The reaction was stirred for 2 h at 50 °C and then cooled to room temperature and vacuum concentrated. The residue was taken up in $CH_2Cl_2$ and sequentially washed with 10% aqueous $NaHCO_3$, deionized water, and saturated aqueous NaCl. The organic layer was dried ($Na_2SO_4$) and concentrated to give crude **44** as an orange oil, $R_f$ = 0.62 (100% EtOAc), in nearly quantitative yield. Spectral

analysis indicated contamination by phenol **45**, but due to the labile nature of **44**, crude material was taken directly into the next reaction. $^1$H: 8.87 (d, 1H, $J$ = 4.9 Hz), 7.18−7.62 (c m, 5H), 4.31 & 4.30 (2 app t, 1 H total, $J$ = 6.8 Hz), 4.14 (m, 2H), 3.21 (app t, 1 H, $J$ = 7.9 Hz), 2.43−2.98 (c m, 2 H), 1.6−2.1 (c m, 2H), 1.96 and 1.94 (two s, 3 H total). IR: 3061, 2962, 2124, 1738, 1721, 1585, 1495, 1297, 1235, 1048, 759. MS: 428/426 (M − 2), 400/398, 340/338, 327/325, 313/311, 258, 179, 43 (100%). HRMS: calcd for $C_{19}H_{17}{}^{79}BrN_4O_3 - H_2$: 428.0484; obsd 428.0476.

**Sulfenylated Ketone 46.** A mixture of crude **44** (0.56 g, 1.3 mmol), methyl thioglycolate (0.15 mL; 1.25 equiv), and diisopropylethylamine (Hunig's base; 0.29 mL; 1.25 equiv) in dry ethanol (4 mL) was stirred at room temperature for 10 min. The solvent was evaporated, and the residue was taken up in $CH_2Cl_2$. The solution was washed with deionized water and evaporated. Chromatography of the residue afforded **46** (0.391 g, 66% yield for two steps) as a thick yellow oil, $R_f$ = 0.73 (100% EtOAc). $^1$H: 8.77 (t, 1H, $J$ = 4.8 Hz), 7.51 (br t, 1H, $J$ = 7.4 Hz), 7.33−7.20 (c m, 3H), 7.19−7.11 (c m, 1H), 4.18 (m, 2H), 3.94−3.22 (c m, 4H), 3.76 and 3.75 (two s, 3H total), 3.07−2.39 (c m, 2H), 2.1−1.6 (c m, 2H), 2.00, 1.98, 1.97 and 1.95 (four s, 3H total). $^{13}$C: 189.2, 189.1, 189.0, 170.2, 169.8, 169.5, 169.4, 148.5, 148.4, 146.8, 146.3, 146.1, 145.6, 144.7, 137.5, 136.8, 136.6, 136.4, 134.8, 129.9, 129.8, 129.6, 128.6, 128.1, 127.9, 127.4, 124.7, 124.6, 118.2, 118.1, 118.0, 117.9, 61.8, 61.7, 61.1, 61.0, 60.8, 60.7, 52.1, 51.8, 51.7, 34.1, 33.3, 33.2, 31.6 30.6, 30.4, 29.1, 28.5, 20.3. IR: 3374, 2952, 2123, 1743, 1694, 1581, 1497, 1441, 1363, 1286, 1244, 1152, 1033, 766. MS: 454 ($M^+$), 422, 421 (100%), 350, 293, 260, 235, 234, 233, 205, 179, 90. HRMS: calcd for $C_{22}H_{22}N_4O_5S$: 454.1311; obsd 454.1312.

**Amide 47.** A solution of **46** (0.38 g) in dry MeOH (10 mL) was saturated with ammonia gas and stirred at room temperature overnight. Solid $K_2CO_3$ (100 mg) was added, and stirring was continued for another 10 min. The solvent was evaporated, and the residue was taken up in $CH_2Cl_2$ and washed with deionized water. Evaporation left **47** (0.30 g, 91% yield) as a thick oil, $R_f$ = 0.28 (10% MeOH/$CHCl_3$). $^1$H: 8.42 (d, 1H, $J$ = 5.2 Hz), 7.47 (br t, 1H, $J$ = 7.9 Hz), 7.34−6.71 (c m, 3H), 7.02 (d, 1H, $J$ = 4.6 Hz), 5.10 (br s, 1H), 3.93−3.29 (c m, 4H), 2.98 (dd, 1H, $J_1$ = 16.2 Hz, $J_2$ = 4.0 Hz), 2.83−2.64 (c m, 2H), 2.54 (br t, 1H, $J$ = 16.5 Hz), 1.63 (c m, 2H). $^{13}$C: 195.0, 172.5, 147.9, 147.8, 147.7, 145.6, 145.5, 145.4, 142.7, 142.5, 137.9, 137.7, 136.9, 131.1, 130.4, 130.0, 129.8, 129.6, 128.8, 124.7, 124.5, 124.1, 123.9, 118.4, 118.3, 118.1, 105.6, 59.6, 59.4, 36.9, 35.5, 35.4, 33.3, 33.2, 33.0, 29.7, 29.4. IR: 3360, 3065, 2917, 2130, 1680, 1623, 1609, 1588, 1490, 1427, 1300, 1138, 1047, 850, 766. MS: 379 ($M^+ - H_2O$), 353, 321, 308, 294, 293, 279, 262, 246, 233, 219, 205, 192, 181, 160, 128, 116, 104, 98, 96, 91 (100%), 64, 60. HRMS: calcd for $C_{19}H_{17}N_5O_2S$ ($M^+ - H_2O$): 379, 1103; obsd 379.1107.

**Thiazinone 48.** A solution of amide **47** (0.29 g) and $BF_3$·$OEt_2$ (0.18 mL, 2 equiv) in $CHCl_3$ (1.5 mL) was stirred at room temperature, under argon, for 10 min and then washed with deionized water and evaporated. Compound **48** (0.22 g, 90%) was obtained as yellow crystals, mp 101−103 °C. $^1$H: 8.84 (br s, 1H), 8.35 (d, 1H, $J$ = 6.0 Hz), 7.48 (dt, 1H, $J_1$ = 8.0 Hz, $J_2$ = 1.5 Hz), 7.35−6.96 (c m, 4H), 3.78−3.50 (m, 2H), 3.50 (s, 2H), 3.07 and 2.85 (two dd, 1H total, $J_1$ = 16.0 Hz, $J_2$ = 8.0 Hz), 2.63 (m, 2H), 2.55 (m, 1H), 1.92−1.46 (c m, 2H). $^{13}$C: 162.2, 145.6, 145.5, 145.3, 145.2, 137.5, 136.9, 130.2, 129.9, 129.6, 129.3, 129.2, 127.4, 126.7, 126.6, 124.7, 123.7, 123.5, 118.2, 118.1, 118.0, 59.3, 59.2, 35.3, 35.2, 33.1, 32.9, 29.5, 29.3, 28.8, 28.6. IR: 3353, 2924, 2123, 1666, 1609, 1588, 1546, 1490, 1469, 1448, 1391, 1286, 1152, 1054, 843, 752. MS: 380 (M + H)$^+$, 379 ($M^+$), 320, 306, 264, 260 (100%), 246, 232, 205, 179, 152, 139, 101, 63. HRMS: calcd for $C_{19}H_{17}N_5O_2S$: 379.1103; obsd 379.1105.

**Mesylate 49.** The same procedure described above for mesylation of ketone **26** was applied to **48** to give **49**, mp 166 °C dec, in quantitative yield. $^1$H: 8.80 (br s, 1H), 8.37 (d, 1H, $J$ = 6.0 Hz), 7.50 (dd, 1H, $J_1$ = 8.0 Hz, $J_2$ = 1.5 Hz), 7.40−6.97 (c m, 4H), 4.30−4.10 (m, 2H), 3.50 (s, 2H), 3.51−2.47 (c m, 3H), 2.98 and 2.92 (two s, 3H total), 2.10−1.65 (c m, 2H). $^{13}$C: 161.9, 145.8, 145.7, 145.1, 144.9, 137.6, 136.9, 130.2, 129.9, 129.8, 129.1, 129.0, 128.0, 126.1, 124.9, 124.8, 124.0, 123.8, 118.4, 118.2, 115.5, 67.2, 67.1, 37.0, 33.1, 33.0, 32.3, 32.2, 29.5, 29.3, 28.9, 28.8. IR: 3346, 2938, 2137, 1687, 1609, 1588, 1539, 1497, 1469, 1441, 1406, 1356, 1293, 1265, 1223, 1180, 1033, 962, 948, 913, 829, 808, 752, 738. MS: 458 (M + H)$^+$, 457 ($M^+$; 100%), 334, 261, 260, 216. HRMS: calcd for $C_{20}H_{19}N_5O_4S_2$: 457.0878; obsd 457.0882.

**Amide 50.** A mixture of **49** (0.24 g), NaH (63 mg, 5 equiv), acetamide (157 mg, 5 equiv), and dry DMF (1 mL), initially chilled to 0 °C, was stirred under argon while being allowed to warm to rt. The reaction completed after 2 h (TLC). The mixture was diluted with 10% aqueous $Na_2CO_3$ and $CH_2Cl_2$, and the organic layer was separated and washed with deionized water followed by saturated aqueous NaCl. Concentration and chromatography yielded **50** as a thick oil (0.13 g, 59%); $R_f$ = 0.53 (10% MeOH/$CHCl_3$). $^1$H: 8.80 (br s, 1H), 8.33 (d, 1H, $J$ = 6.0 Hz), 7.48 (dt, 1H, $J_1$ = 8.0 Hz, $J_2$ = 1.5 Hz), 7.33−7.07 (c m, 3H), 6.99 (t, 1H, $J$ = 4.5 Hz), 5.78 (br s, 1H), 3.47 (s, 2H), 3.4−2.4 (c m, 5H), 1.93 and 1.92 (two s, 3H total), 1.78−1.48 (c m, 2H). $^{13}$C: 170.1, 170.0, 162.2, 146.0, 145.9, 145.8, 145.4, 145.3, 137.8, 137.2, 130.4, 130.2, 130.0, 129.5, 129.4, 128.0, 126.8, 126.7, 125.2, 125.0, 124.1, 124.0, 118.7, 118.4, 116.7, 116.6, 37.2, 34.5, 34.4, 33.0, 32.9, 29.8, 29.2, 29.0, 23.2. IR: 3332, 3079, 2938, 2116, 1673, 1609, 1574, 1553, 1497, 1455, 1434, 1406, 1356, 1286, 1230, 1181, 1152, 1103, 1054, 927, 843, 766, 738. MS: 421 ($M^+$ + H), 420 ($M^+$), 393, 333, 306 (100%), 260. HRMS: calcd for $C_{21}H_{20}N_6O_2S$: 420.1368; obsd 420.1369.

**Shermilamine B, 6.** A thoroughly degassed (bubbling with Ar for 20 min) solution of **50** (23 mg; 0.054 mmol) and acetophenone (1.5 mL) in 13.5 mL of chlorobenzene was maintained at an internal temperature of 110 °C during irradiation with a sunlamp, with good stirring under Ar. The reaction completed in ≈3 h (TLC). The solution was cooled and applied to a short plug of silica gel. Elution with 20% EtOAc/hexane removed acetophenone and chlorobenzene. Crude product (19 mg) was eluted with 10% MeOH/$CHCl_3$. Preparative TLC purification provided **6** (14 mg; 67%) as orange crystals, 252−254 °C dec without melting. $^1$H (DMSO-$d_6$) 10.24 (br s, 1H); 9.24 (br s, 1H); 8.54 (br t, 1H, $J$ = 5.1 Hz); 8.49 (d, 1H, $J$ = 4.9 Hz); 8.00 (d, 1H, $J_1$ = 7.9 Hz); 7.49 (d, 1H, $J_1$ = 5.1 Hz); 7.43−7.35 (c m, 2H, overlapping resonances of an aromatic H and one of the NH's); 7.01 (br dt, app. $J_1$ = 5.6 Hz; $J_2$ = 1.3 Hz); 3.32 (s, 2H); 3.12−3.07 (br m, 2H); 2.95−2.92 (br m, 2H); 1.93 (s, 3H). $^{13}$C NMR (DMSO-$d_6$): 171.5; 163.6; 150.8; 140.0; 139.5; 136.9; 132.0; 131.2; 124.0; 121.6; 121.5; 120.9; 116.6; 116.4; 115.4; 108.8; 107.2; 37.1; 29.3; 27.7; 22.4. IR: 3339; 3283; 3212; 3072; 2966; 2931; 2861; 1637; 1602; 1588; 1553; 1497; 1441; 1377; 1335; 1300; 1251; 1202; 1152; 1117; 1068; 1040; 998; 941; 913; 829; 794; 738. MS: 391 ($M^+$ + 1, 100%), 390 ($M^+$), 319, 276, 121, 105, 77. HRMS: calcd for $C_{21}H_{18}N4O_2S$: 390.1150; obsd 390.1151.

**Aminothiazole 52.** A solution of crude **44** (2.20 g, 5.13 mmol) and thiourea (0.8 g, 10.5 mmol) in absolute ethanol (120 mL) was gently heated to effect dissolution and then stirred for 15 min at room temperature. The solvent was evaporated, and the residue was taken up in $CH_2Cl_2$. The resulting solution was sequentially washed wtih 10% aqueous $NaHCO_3$, water, saturated aqueous NaCl, and then it was dried ($Na_2SO_4$) and concentrated to yield **52** in quantitative crude yield. This material was clearly contaminated with **45** ($^1$H NMR), due to the nature of the starting **44**; but it was advanced to the next step without purification, because of its polarity. $R_f$ (1:9 MeOH/$CHCl_3$): 0.48. $^1$H: 8.49 (d, 1 H, $J$ = 5.0 Hz), 7.49 and 7.48 (2 app dt, 1 H total, $J_1$ = 7.6, $J_2$ = 1.9 Hz), 7.17−7.31 (c m, 3 H), 6.94 and 6.93 (two d, 1 H total, $J$ = 5.0 Hz), 5.06 (br s, 2 H), 4.00−4.11 (c m, 2 H), 2.88−3.19 (c m, 2 H), 2.49−2.75 (m, 1 H), 2.00 and 1.98 (two s, 3 H total), 1.65−2.05 (c m, 2 H). IR: 3278, 3173, 3065, 2956, 2929, 2127, 1731, 1370, 1297, 1231, 1039, 759. MS: 406 ($M^+$), 378, 363, 348, 338, 320, 276, 176 (100%). HRMS: calcd for $C_{20}H_{18}N_6O_2S$: 406.1212; obsd 406.1202.

**Thiazole 53.** Isoamyl nitrite (2.5 mL, excess) was added dropwise to a DMF (15 mL) solution of aminothiazole **52** (1.97 g, 4.85 mmol) maintained at 80 °C under Ar. Gas was evolved, and the solution gradually turned from orange to dark red. After addition, stirring was continued for 25 min. The solution was then cooled and all volatiles were vacuum-removed. The residue was chromatographed to yield 1.03 g of **53** (54% yield over three steps from **44**, 81.4% avg yield/step) as white crystals, mp 164 °C. $R_f$ (100% EtOAc): 0.39. $^1$H: 8.76 (s, 1H), 8.56 (d, 1H, $J$ = 4.7 Hz), 7.45 (app. dt, 1H, $J_1$ = 7.6, $J_2$ = 1.9 Hz), 7.12−7.27 (c m, 3H), 6.99 and 6.98 (two d, $J$ = 4.7 Hz), 3.95−

4.10 (c m, 2H), 2.56−3.41 (c m, 3H), 1.95 and 1.93 (two s, 3H total), 1.70−1.97 (c m, 2H). $^{13}$C: 170.7, 151.5, 149.1, 147.5, 145.9 & 145.79, 138.5 & 138.5, 137.7 & 137.4, 130.5 & 130.3, 130.1, 129.9, 127.6 & 127.5, 125.1 & 125.0, 123.8 & 123.7, 118.4, 61.7 & 61.5, 33.8 & 33.7, 31.5, 30.1, 20.7. IR: 3056, 2957, 2127, 1736, 1576, 1437, 1291, 1231, 1038, 759. MS: 391 ($M^+$), 363, 302, 290, 288, 276 (100%), 244, 205. HRMS calcd for $C_{20}H_{17}N_3O_2S$ (M − $N_2$) 363.1041; obsd 363.1041.

**Alcohol 54.** A mixture of **53** (650 mg, 1.66 mmol), methanol (70 mL), and $K_2CO_3$ (200 mg) was stirred at room temperature, under Ar, for 15 min. The volatiles were vacuum-removed and the residue was partitioned between $CH_2Cl_2$/deionized water. The organic layer was washed with deionized water and with saturated aqueous NaCl, dried ($Na_2SO_4$) and concentrated to yield 542 mg of pale yellow **54** (93% yield), mp 87−89 °C. $R_f$ (100% EtOAc): 0.13. $^1$H: 8.73 (s, 1H), 8.54 (d, 1H, $J$ = 4.8 Hz), 7.47 (app dt, 1H, $J_1$ = 7.5, $J_2$ = 1.7 Hz), 7.14−7.28, (c m, 3H), 6.99 and 6.98 (two d, 1H total, $J$ = 4.8 Hz), 3.67 and 3.60 (two t, 2H total, $J$ = 6.1 Hz), 3.42 (m, 1H), 3.29 (br s, 1H), 2.58−3.16 (c m, 2H), 1.64−1.94 (c m, 2H). $^{13}$C: 151.4, 150.3, 149.3, 147.4, 145.8 & 145.7, 139.7 & 139.4, 137.8 & 137.4, 130.4, 130.4 & 130.3, 129.8, 127.9, 127.7, 125.0 & 124.9, 123.8 & 123.7, 118.4, 59.6 & 59.5, 37.5 & 37.3, 31.4, 29.4 & 29.3. IR: 3376 (br), 3050, 2938, 2877, 2127, 1576, 1443, 1291, 1065, 759. MS: 349 ($M^+$), 321, 302, 291, 288, 278, 276 (100%), 244. HRMS calcd for $C_{18}H_{15}N_5$-OS 349.0997; obsd 349.0998.

**Mesylate 55.** Methanesulfonyl chloride (142 μL, 210 mg, 1.84 mmol, 1.2 equiv) was slowly added to a $CH_2Cl_2$ (50 mL) solution of alcohol **54** (535 mg, 1.53 mmol) and $Et_3N$ (284 μL, 202 mg, 2.00 mmol, 1.3 equiv) maintained at 0 °C under Ar. After 10 min, the mixture was partitioned between half-saturated aqueous NaCl and $CH_2Cl_2$. The combined organic extracts were washed with water and saturated aqueous NaCl and then evaporated to yield 648 mg of **55** (99%) as a thick oil. $R_f$ (100% EtOAc): 0.31. $^1$H: 8.79 (s, 1H), 8.59 (d, 1H, $J$ = 5.0 Hz), 7.48 (app dt, 1H, $J_1$ = 7.6 Hz, $J_2$ = 1.7 Hz), 7.30−7.14 (m, 3H), 7.03 and 7.01 (two d, 1H total, $J$ = 5.0 Hz), 4.29−4.08 (m, 2H), 3.48−2.48 (m, 3H), 2.93 and 2.91 (two s, 3H total), 2.13−1.81 (m, 2H). $^{13}$C: 151.75, 150.6 & 150.5, 149.0 & 148.9, 147.57, 146.02, 137.8 & 137.5, 137.4 & 137.2, 130.5, 130.2, 129.9, 127.8 & 127.2, 125.1, 124.0 & 123.8, 118.5, 66.8 & 66.5, 37.3, 34.1, 31.2, 29.3. IR: 3064, 2931, 2858, 2129, 1553, 1450, 1363, 1288, 1201, 1174, 1044, 968, 930, 761. MS: 427 ($M^+$), 399, 367, 329, 320, 302, 288, 276 (100%), 244, 96. HRMS: calcd for $C_{19}H_{17}N_5O_3S_2$ 427.0773; obsd 427.0777.

**Phthalimide 56.** A solution of mesylate **55** (160 mg 0.37 mmol) and potassium phthalimide (83 mg, 0.46 mmol, 1.25 equiv) in 5 mL of *N*,*N*-dimethylformamide was stirred at 50 °C for 8 h, under argon. The cooled mixture was diluted with 40 mL of ethyl acetate and sequentially washed with 10% aqueous $Na_2CO_3$, water, and saturated aqueous NaCl solution. The organic phase was dried ($Na_2SO_4$) and evaporated to dryness to afford 150 mg of **56** (84%) as a white solid, 83 °C dec, $R_f$ (100% ethyl acetate): 0.47. $^1$H: 8.79 (s, 1H), 8.59 (d, 1H, $J$ = 5.0 Hz), 7.80 (m, 2H), 7.69 (m, 2H), 7.48 (m, 1H), 7.36−7.17 (m, 3H), 7.02 (br d, $J$ = 5.0 Hz), 3.72 and 3.65 (two t, 2H total, $J$ = 7.0 Hz), 3.35−2.67 (m, 3H), 2.09−1.80 (m, 2H). $^{13}$C: 168.0, 151.6, 150.2, 148.9, 147.1, 146.0, 138.8, 137.6 & 137.4, 133.9, 131.7, 130.4 & 130.3, 130.0 & 129.9, 129.8, 127.9, 124.9 & 124.8, 123.7, 123.1, 118.4 & 118.3, 35.3, 34.2 & 34.0, 31.2 & 31.1, 30.9 & 30.8. IR: 3050, 2944, 2858, 2127, 1709, 1576, 1443, 1397, 1290, 912, 720. MS: 450 ($M^+$ − 28), 304, 302, 290, 288, 276 (100%), 244, 160. HRMS: calcd for $C_{26}H_{18}N_6O_2S$ 450.1150, obsd 450.1147.

**Amine 57.** A mixture of phthalimide **56** (76 mg, 0.16 mmol) and hydrazine hydrate (200 μL, excess) in 2.5 mL of methanol and 0.5 mL of tetrahydrofuran was stirred at room temperature for 30 min. The solvents were removed *in vacuo*, the residue was taken up in dichloromethane, and the resulting solution was washed quickly with 10% aqueous sodium hydroxide followed by slightly basified water. The organic phase was dried ($Na_2SO_4$) and evaporated to give 52 mg (94%) of **57** as a beige solid, mp 176−177 °C, $R_f$ (20% methanol/80% chloroform): 0.10. $^1$H: 8.69 (s, 1H), 8.50 (d, 1H, $J$ = 5.0 Hz), 7.43 (app dt, 1H, $J_1$ = 7.4 Hz, $J_2$ = 1.9 Hz), 7.32−7.11 (m, 3H), 6.95 and 6.94 (two d, 1H total, $J$ = 4.9 Hz), 3.31−3.02 (m, 2H), 2.83−2.55 (m, 3H), 1.99−1.57 (m, 4H; the $NH_2$ protons are part of this multiplet). $^{13}$C: 151.2, 150.2, 149.3, 147.3, 145.5 & 145.4, 139.45 & 139.40, 137.6 & 137.4, 130.4 & 130.3, 130.2, 129.7, 127.9 & 127.7, 124.9, 123.6 & 123.5, 118.3, 39.3, 38.8 & 38.5, 31.5, 30.5. IR: 3303 (br), 3057, 2931, 2864, 2134, 1576, 1556, 1502, 1450, 1291, 766. MS: 348 ($M^+$), 346, 302, 290, 288, 278, 276 (100%), 244, 190. HRMS: calcd for $C_{18}H_{16}N_6S$ (M − $N_2$) 320.1095, obsd 320.1097.

**Acetamide 58.** A cold (0 °C) mixture of amine **57** (150 mg, 0.43 mmol), triethylamine (209 μL, 153 mg, 1.5 mmol, 3.5 equiv), and acetic anhydride (122 μL, 132 mg, 1.29 mmol, 3 equiv) in 5 mL of tetrahydrofuran was allowed to warm to room temperature with good stirring, and then all volatiles were removed in vacuo. The residue was taken up in chloroform and sequentially washed with deionized water and with saturated aqueous NaCl. Evaporation of the solvents and chromatography of the residue left 145 mg (86%) of **58** as a white solid, 154 °C dec, $R_f$ (1:9 MeOH/$CHCl_3$): 0.36. $^1$H: 8.64 (s, 1H), 8.45 (d, 1H, $J$ = 4.9 Hz), 7.40 (app dt, 1H, $J_1$ = 7.6, $J_2$ = 1.5 Hz), 7.06−7.23 (c m, 3H), 6.92 and 6.91 (two d, 1H total, $J$ = 4.9 Hz), 5.86 (br s, 1H), 3.05−3.22 (c m, 2H), 2.46−3.10 (c m, 3H), 1.88 and 1.86 (two s, 3H total), 1.54−1.85 (c m, 2H). $^{13}$C: 170.3, 151.5 & 151.4, 150.4, 149.2, 147.4, 145.8 & 145.2, 138.9, 137.7 & 137.4, 130.4 & 130.3, 130.1 & 129.9, 128.2, 127.9 & 127.7, 125.0, 123.8, 118.5, 37.2 & 37.1, 35.1 & 35.0, 30.9 & 30.8, 23.14. IR: 3276, 3065, 2924, 2127, 1653, 1582, 1559, 1434, 1282, 929, 759, 732. MS: 361 (M − 28), 302, 290, 288, 278, 276 (100%), 244, 205. HRMS: calcd for $C_{20}H_{18}N_6OS$: 389.1184, obsd 389.1177.

**Kuanoniamine D, 7.** A degassed (Ar bubbling for 25 min) solution of **58** (72 mg, 0.18 mmol) in chlorobenzene (45 mL) and acetophenone (5 mL) was heated in a sand bath, under an argon atmosphere, to an internal temperature of 110 °C. The mixture was irradiated with a Sylvania 275 W sunlamp while the internal temperature was carefully maintained at 110 °C ± 5 °C. The solution gradually changed from yellow to a purple-brown, with a green fluorescence at the edges. After 2.75 h, the sunlamp was turned off, the solution was cooled to room temperature, and most of the PhCl and PhCOMe was removed in a high-vacuum rotary evaporator. The residue was chromatographed to yield **7** (41 mg, 62%), yellow solid, mp > 300 °C. $R_f$ (10% MeOH/$CHCl_3$): 0.24. $^1$H (DMSO-$d_6$): 9.91 (br s, 1H), 8.80 (d, 1H, $J$ = 4.9 Hz), 8.77 (s, 1H), 7.51 (d, 1H, $J$ = 4.9 Hz), 7.44 (app t, 1H, $J$ = 6.3 Hz), 7.42 (d, 1H, $J$ = 5.8 Hz), 7.06 (app t, 1H, $J$ = 6.7 Hz), 6.32 (br m, 1H), 3.43 (c m, 2H), 3.15 (c m, 2H), 2.17 (s, 3H). $^{13}$C (DMSO-$d_6$): 171.01, 150.92, 149.05, 140.70, 139.78, 139.55, 139.27, 133.44, 131.88, 123.94, 121.04, 117.68, 116.25, 115.77, 108.53, 104.48, 36.74, 31.04, 22.49. IR: 3281, 3064, 2925, 2858, 1645, 1570, 1550, 1452, 1374, 1286, 1270, 755. MS: 360 ($M^+$), 300, 288, 275, 231, 189 (100%), 171, 144. HRMS calcd for $C_{20}H_{16}N_4OS$: 360.1045; obsd 360.1049.

**Dimethylamine 59.** Aqueous 40% dimethylamine solution (0.5 mL, excess) was added to a DMF (1 mL) solution of **55** (30 mg, 0.07 mmol), and the mixture was heated to 50 °C for 1 h. The cooled mixture was partitioned between $CH_2Cl_2$ and deionized water. The combined organic extracts were washed with water and saturated aqueous NaCl, dried ($Na_2SO_4$), and evaporated to yield **59** (20.8 mg, 86%), white solid, mp 167−168 °C. $R_f$ (100% EtOAc): 0.14. $^1$H: 8.76 (s, 1 H), 8.56 (d, 1 H, $J$ = 4.9 Hz), 7.48 & 7.47 (two app dt, 1 H total, $J_1$ = 1.9, $J_2$ = 7.6 Hz), 7.14−7.30 (c m, 3 H), 7.00 & 6.99 (two d, 1 H total, $J$ = 5.0 Hz), 2.20−3.37 (c m, 5 H), 2.26 & 2.21 (2 s, 6 H), 1.6−1.88 (c m, 2H). $^{13}$C: 151.6 & 151.5, 150.5, 149.4, 147.5, 145.7, 138.9 & 138.6, 137.9 & 137.4, 130.6 & 130.4, 130.3 & 130.2, 129.8, 127.7, 125.0, 123.8 & 123.6, 118.5 & 118.4, 56.3 & 56.2, 44.8 & 44.7, 32.0 & 31.9, 31.7 & 31.5, 30.7 & 29.6. IR: 3057, 2930, 2861, 2127, 1576, 1490, 1443, 1297, 759. MS: 376 ($M^+$), 346, 304 (100%), 290, 288, 276, 243, 58. HRMS calcd for $C_{20}H_{20}N_6S$: 376.1470; obsd 376.1467.

**Nordercitin, 8.** A solution of **59** (240 mg, 0.64 mmol) in chlorobenzene (90 mL) and acetophenone (10 mL) was treated as described above for **58**. Chromatography afforded **8** (140 mg, 63%), yellow solid, mp 177−179 °C. $R_f$ (10% MeOH/$CHCl_3$): 0.19. This compound became red upon dissolution in trifluoroacetic acid-*d*. $^1$H (TFA-*d*): 9.58 (s, 1H), 8.56 (d, 1H, $J$ = 6.7 Hz), 8.29 (d, 1H, $J$ = 8.4 Hz), 8.02 (d, 1H, $J$ = 6.9 Hz), 7.89 (app t, 1H, $J$ = 7.7 Hz), 7.69 (d, 1H, $J$ = 8.4 Hz), 7.53 (app t, 1H, $J$ = 7.7 Hz), 3.87 (m, 2H), 3.65 (m, 2H), 3.21 (s, 6H). Note: the acridine NH protons signal either overlaps with the TFA resonance at 10.8 ppm, or it is too broad to be seen. $^{13}$C (TFA-*d*): 158.4, 153.4, 145.1, 143.7, 142.1, 139.6, 137.0, 134.3, 131.0, 127.7, 127.1, 121.4, 120.1, 117.1, 111.0, 106.4, 56.8, 45.3, 28.1. IR: 3043, 2957, 1676, 1603, 1477, 1417, 1198, 1138, 720. MS: 346 ($M^+$),

299, 291, 288, 278 (100%), 276, 244, 58. HRMS calcd for $C_{20}H_{18}N_4S$: 346.1252; obsd 346.1254.

**Formamide 63.** A solution of **55** (80 mg, 0.19 mmol) in *N*-methylformamide (3 mL) was added dropwise to a cold (0 °C) white slurry of *N*-methyl-*N*-sodioformamide prepared by slow addition of *N*-methylformamide (3 mL) to a cold (0 °C) suspension of NaH (45 mg, 2.0 mmol) in THF (1 mL) in a flame-dried flask, under Ar (**CAUTION**: vigorous gas evolution). The white slurry turned into a red solution, which was warmed to room temperature and stirred for 3 h. The reaction mixture was diluted with $CH_2Cl_2$ and washed with water and saturated aqueous NaCl. The organic layer was dried ($Na_2SO_4$) and evaporated to yield **63** (56 mg, 77%), white solid, mp 168 °C. $R_f$ (10% MeOH/$CHCl_3$): 0.31. $^1$H: 8.80 & 8.78 (two s, 1 H total), 8.59 & 8.58 (two d, 1 H total, $J$ = 4.9 Hz), 7.96, 7.94, 7.93 & 7.89 (four s, 1 H total), 7.45−7.52 (c m, 1 H), 7.15−7.31 (c m, 3 H), 7.01−7.04 (c m, 1 H), 3.12−3.38 (c m, 3 H), 2.86, 2.83, 2.80 & 2.75 (four s, 3 H total), 2.58−3.02 (c m, 2 H), 1.58−2.00 (c m, 2 H). $^{13}$C: 162.6 & 162.5 & 162.4 & 162.3, 151.6, 149.2 & 149.1 & 149.0, 147.7 & 147.7 & 147.3, 146.0 & 145.9 & 145.8, 138.9 & 138.8, 137.9 & 137.8 & 137.4, 130.5, 130.3 & 130.2, 130.1 & 130.0 & 129.9, 127.8 & 127.7 & 127.3 & 127.1, 125.2 & 125.1 & 125.05 & 125.0, 124.1 & 124.0 & 123.8, 118.6, 46.9 & 46.8, 41.9, 34.4 & 34.3, 33.5 & 33.4 & 32.2 & 31.9, 31.4 & 31.0 & 30.3 & 29.4. IR: 3058, 2930, 2861, 2127, 1672, 1578, 1441, 1292, 759. MS: 362 (M − 28), 360, 319, 304, 301, 288, 278, 276 (100%), 244. HRMS: calcd for $C_{20}H_{18}N_6OS$ (M − $N_2$): 362.1201; obsd 362.1199.

**Pentacyclic Intermediate 62.** A solution of **63** (30 mg, 0.08 mmol) in chlorobenzene (9 mL) and acetophenone (1 mL) was treated as described above for **58**. Chromatography afforded **62** (18 mg, 63%), yellow solid, mp 171−172 °C. $R_f$ (10% MeOH/$CHCl_3$): 0.28. This compound became red upon dissolution in trifluoroacetic acid-*d*. $^1$H NMR (1:9 TFA-*d*/$CDCl_3$): 9.37 (s, 1 H), 8.49 (d, 1 H, $J$ = 6.7), 8.35 (s, 1 H), 8.23 (d, 1 H, $J$ = 7.9 Hz), 7.90 (app t, 1 H, $J$ = 7.0 Hz), 7.87 (d, 1 H, $J$ = 6.7 Hz), 7.68 (d, 1 H, $J$ = 8.4 Hz), 7.52 (app t, 1 H, $J$ = 7.7 Hz), 3.68 (m, 2 H), 3.46 (m, 2 H), 3.34 (s, 3 H). $^{13}$C NMR (in 10% TFA-*d*, 90% $CDCl_3$): 166.4, 155.8, 150.7, 143.3, 141.3, 140.3, 140.2, 137.3, 134.0, 131.7, 129.9, 125.1, 119.1, 118.2, 114.8, 108.1, 107.1, 43.2, 37.2, 28.2. IR: 2996, 2958, 1682, 1461, 1419, 1199, 1131, 839, 799, 720. MS: 360 ($M^+$), 314, 300, 288 (100%), 278, 276, 244, 217. HRMS: calcd for $C_{20}H_{16}N_4OS$: 360.1045; obsd 360.1043.

***N*-Methylpyridine 64.** A mixture of **62** (73.5 mg, 0.20 mmol) and methyl iodide (250 μL, excess) in 10 mL of 1:1 $CH_2Cl_2$−benzene containing suspended $K_2CO_3$ (200 mg, excess) was heated to reflux. The solution soon began to turn purple. Additional methyl iodide (100 μL) was necessary to complete the reaction. After 3 h, the cooled deep purple solution was evaporated to dryness. The residue was taken up in $CH_2Cl_2$ and washed with water and saturated aqueous NaCl. The organic phase was dried ($Na_2SO_4$) and evaporated to give **64** (76 mg, 99%), dark purple solid, mp 170−171 °C. $R_f$ (10% MeOH/$CHCl_3$): 0.13. This material produced a burgundy solution when dissolved in TFA-*d*. $^1$H (1:9 TFA-*d*/$CDCl_3$): 9.08 (s, 1H), 8.38 (s, 1H), 8.29 (d, 1H, $J$ = 6.9 Hz), 8.18 (d, 1H, $J$ = 8.4 Hz), 7.84 (dd, 1H, $J_1$ = 7.1 Hz, $J_2$ = 8.4 Hz), 7.78 (d, 1H, 6.9 Hz), 7.61 (d, 1H, $J$ = 8.0 Hz), 7.46 (dd, 1H, $J_1$ = 7.1 Hz, $J_2$ = 8.0 Hz), 4.84 (s, 3H), 3.67 (m, 2H), 3.46 (m, 2H), 3.36 (s, 3H). $^{13}$C (1:9 TFA-*d*/$CDCl_3$): 166.5, 149.9, 149.1, 147.1, 146.5, 139.6, 136.8, 134.2, 134.1, 133.4, 125.0, 124.9, 121.1, 120.3, 117.6, 107.9, 107.5, 50.2, 43.3, 37.3, 28.9. IR: 2937, 2858, 1656, 1576, 1311, 1198, 1158, 1131, 759, 720. MS: 374 ($M^+$), 319, 302 (100%), 288, 278, 276, 243, 216. HRMS: calcd for $C_{21}H_{18}N_4OS$: 374.1201; obsd 374.1199.

**Dercitin, 9.** A mixture of **64** (50 mg, 0.13 mmol), $POCl_3$ (4 mL), THF (1 mL), and pyridine (2 drops) was heated to 45 °C for 2 h, and then all volatiles were vacuum-removed. The residue was taken up in 1,2-diethoxyethane and cooled to 0 °C. Ethanolic $NaBH_4$ was added dropwise, just a few drops past the point where the solution color dissipated. The mixtue was stirred at 0 °C for 20 min, and then the solvents were reduced to a small volume. 2 N HCl was added (**CAUTION**: vigorous hydrogen evolution), and the solution was heated at 100 °C for 1 h, open to the atmosphere, whereupon it turned bright reddish-purple. After cooling, the solution was adjusted to pH 10 (aqueous NaOH), causing a color change to a deep purple. The product was extracted with dichloromethane. The organic extracts were washed with water and saturated aqueous NaCl, dried ($Na_2SO_4$), and evaporated to give **9** (41.5 mg, 87%), dark deep purple powder, mp 165−167 °C. $R_f$ (10% MeOH/$CHCl_3$): 0.26. This material formed a burgundy solution when dissolved in TFA-*d*. $^1$H (TFA-*d*): 9.50 (s, 1 H), 8.70 (d, 1 H, $J$ = 7.0 Hz), 8.57 (d, 1 H, $J$ = 8.4 Hz), 8.22 (d, 1 H, $J$ = 7.0 Hz), 8.18 (app t, 1 H, $J$ = 7.4 Hz), 8.08 (d, 1 H, $J$ = 8.4 Hz), 7.81 (app t, 1 H, $J$ = 7.7 Hz), 5.22 (s, 3 H), 4.21 (m, 2H), 3.97 (m, 2H), 3.56 (s, 6 H). $^{13}$C (TFA-*d*): 151.4, 151.1, 148.9, 148.02, 141.0, 138.3, 136.5, 135.8, 135.6, 126.5, 126.2, 122.0, 119.1, 116.3, 109.8, 106.7, 56.4, 51.1, 44.9, 28.5. IR: 2924, 2858, 2778, 1629, 1576, 1530, 1463, 1323, 1198, 1145, 1045, 1012, 748. MS: 360 ($M^+$), 314, 302 (100%), 288, 286, 278, 260, 243, 216. HRMS: calcd for $C_{21}H_{20}N_4S$: 360.1408; obsd 360.1403.

**Acknowledgment.** We are deeply grateful to the National Institutes of Health (CA-55268), the National Science Foundation (CHE 91-16820), the Robert A. Welch Foundation (C-1007), and the Donors of the Petroleum Research Fund, administered by the American Chemical Society (AC-20399) for support of our research. M.A.C. is an Alfred P. Sloan Fellow (1994−96). M.J.B. (current address: Glaxo-Wellcome Co., Research Triangle Park, NC) gratefully acknowledges support through the Robert A. Welch Predoctoral Program (1989−90) and Wray−Todd (1990−91) and Schlumberger (1991−92) Fellowships.

JA953119U