# Trapping of the Putative Cationic Intermediate in the Morin Rearrangement with Carbon Nucleophiles†

John D. Freed, David J. Hart,* and Nabi A. Magomedov

*Department of Chemistry, The Ohio State University, 100 W. 18th Avenue, Columbus, Ohio 43210*

*hart.10@osu.edu*

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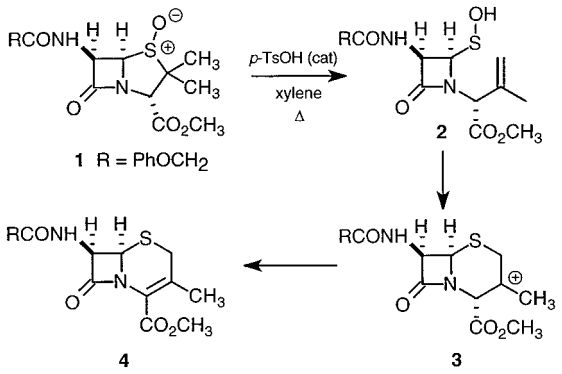
This paper presents reactions in which the putative cationic intermediate in the Morin rearrangement is trapped by aromatic carbon nucleophiles (indoles and furans). For example, reaction of sulfoxide **27** with trifluoroacetic acid in chloroform provides, among other products, indole **29** and indoline **30**. The indoline was shown to be in equilibrium with the nine-membered ring bridged indole **31**. Other examples of Morin rearrangement−trapping reactions are presented, and mechanisms for these transformations are proposed.

## Introduction

In 1963 researchers at Eli Lilly Laboratories reported the conversion of penicillin sulfoxides to cephalosporins.[1] This process involves a sequence of reactions including elimination of the starting sulfoxide to provide an olefinic sulfenic acid (**1** → **2**), addition of the sulfenic acid to the olefin (**2** → **3**), and proton loss to provide the product sulfide (**3** → **4**). Although the intimate details of this process may vary from one substrate, and/or acid catalyst, to another, this rearrangement has been extended to a variety of starting heterocyclic sulfoxides and appears to be a somewhat general process.[2,3] This paper describes our investigations of this process within the context of synthetic studies directed toward the natural product spiroquinazoline (**9**)[4] and presents the first examples of trapping of the putative cationic intermediate in carbon−carbon bond-forming reactions.[5]




The goal of our studies in this area was to develop a process for converting thiazolidine **5** to spiroquinazoline (**9**). It was hoped that ionization of **5**, or a derivative thereof, might afford an *N*-acyliminium ion (**6**) that might be captured by the pendant indole to afford an iminium ion (**7**) that might cyclize to afford a viable spiroquinazoline precursor (**8**). The nature of the $N^*$-substituent in **8** would be a function of the method used to ionize thiazolidine **5**. The first objective of this research, therefore, became the synthesis of **5**.

**Synthesis of Thiazolidine 5.** The synthesis of **5** was accomplished as shown in Scheme 1. Treatment of anthranilamide (**10**) with pyruvoyl chloride[6] in the presence of triethylamine gave the known amide **11** in 48−67% yields.[7] The yield of this transformation improved to 78% under Schotten−Baumann conditions ($CH_2Cl_2$, $NaHCO_3$, $H_2O$), but this procedure was less practical as a 6−8-fold excess of the easily hydrolyzable pyruvoyl chloride was required to drive the acylation to completion. When a suspension of **11** was warmed in aqueous ethanol in the presence of potassium carbonate, a mixture of 2-acetyl-4(3*H*)-quinazolinone[8a] and a more polar compound was obtained. Pure 2-acetyl-4(3*H*)-quinazolinone could be isolated by suspending the mixture of products in dichloromethane, filtration, and recrystallization of the dichloromethane-soluble materials. On the other hand, it was more practical to allow the entire product mixture to react directly with 2-mercaptoethanolamine hydrochloride in the presence of triethylamine to afford crystalline **12** in 86% overall yield from **10**.[8b] Acylation of **12**

† This paper is dedicated to the memory of Dr. Kurt Loening (1924-2000) who provided assistance with nomenclature for this paper and many others published by faculty at OSU. His dedication to advancing the field of organic nomenclature, and his kindness, will be missed.

(1) Morin, R. B.; Jackson, B. G.; Mueller, R. A.; Lavagnino, E. R.; Scanlon, W. B.; Andrews, S. L. *J. Am. Chem. Soc.* **1963**, *85*, 1896.

(2) (a) Morin, R. B.; Jackson, B. G.; Mueller, R. A.; Lavagnino, E. R.; Scanlon, W. B.; Andrews, S. L. *J. Am. Chem. Soc.* **1969**, *91*, 1401. (b) Morin, R. B.; Spry, D. O. *J. Chem. Soc., Chem. Commun.* **1970**, 335.

(3) (a) Gottstein, W. J.; Misco, P. F.; Cheney, L. C. *J. Org. Chem.* **1972**, *17*, 2765. (b) Enebaeck, C. *Finn. Chem. Lett.* **1982**, 19. (c) Farina, V.; Kant, J. *Synlett* **1994**, 565. (d) Chiocccara, F.; Oliva, L.; Prota, G.; Novellino, E. *Synthesis* **1978**, 744. (e) Chioccara, F.; Prota, G. *Synthesis* **1977**, 876. (f) Mah, H. D.; Lee, W. S. *J. Heterocycl. Chem.* **1989**, *26*, 1447. (g) Mah, H.; Nam, K. D.; Hahn, H.-G. *Heterocycles* **1997**, *45*, 1999. (h) Chen, C. H. *Tetrahedron Lett.* **1976**, *17*, 25. (i) Ueda, N.; Shimizu, H.; Kataoka, T.; Hori, M. *Tetrahedron Lett.* **1984**, *25*, 757. (j) Lee, W. H.; Lee, K.; Nam, K. D.; Kim, Y. J. *Tetrahedron* **1991**, *38*, 8091. (k) Chen, C. H.; Donatelli, B. A. *J. Org. Chem.* **1976**, *41*, 3053. (l) Nickon, A.; Rodriguez, A.; Shirhatti, V.; Ganguly, R. *J. Org. Chem.* **1985**, *50*, 4218. (m) Wilson, G. E. *J. Am. Chem. Soc.* **1965**, *87*, 3785. (n) Yoshino, H.; Kawazoe, Y.; Taguchi, T. *Synthesis* **1974**, 713.

(4) Barrow, C. J.; Sun, H. H. *J. Nat. Prod.* **1994**, *57*, 471.

(5) (a) For a communication that describes a portion of this research, see Hart, D. J.; Magomedov, N. A. *J. Org. Chem.* **1999**, *64*, 2990. (b) This article is abstracted in part from the Ph.D. Thesis of Magomedov, N. A. The Ohio State University, 2000. (c) This article is abstracted in part from the Honors Thesis of Freed, J. D. The Ohio State University, 2000.

(6) Ottenheijm, H. C. J.; de Man, J. H. M. *Synthesis* **1975**, 163.

(7) Wegfahrt, P. F.; Rapoport H. *J. Org. Chem.* **1969**, *34*, 3035.

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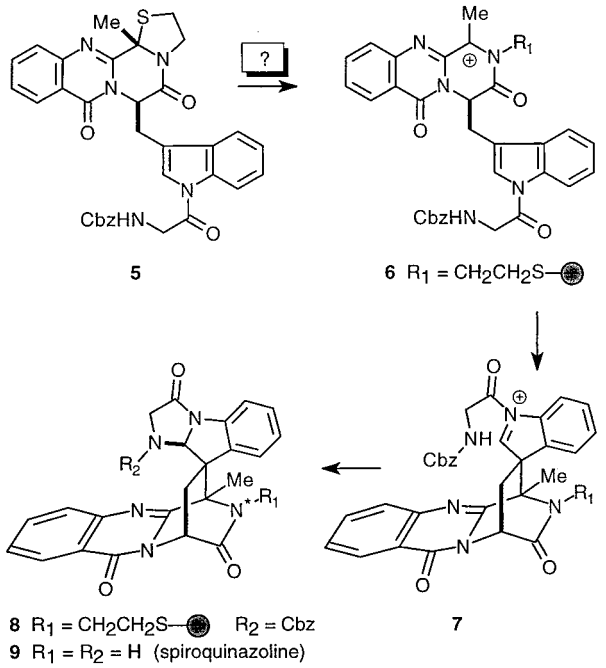



**Figure 1.**

with α-bromoacetyl bromide, using triethylamine as a base, gave a 75% yield of highly insoluble amide **13** along with 8% of 2-acetyl-4(3*H*)-quinazolinone. Treatment of **13** with DBU in tetrahydrofuran furnished a 94% yield of tetracyclic thiazolidine **14**. A more convenient one-pot conversion of **12** to **14** was accomplished by Schotten−Baumann acylation of **12**, followed by addition of trimethylhexadodecylammonium bromide directly to the reaction mixture. This procedure provided tetracycle **14** in 85% yield from **12**.

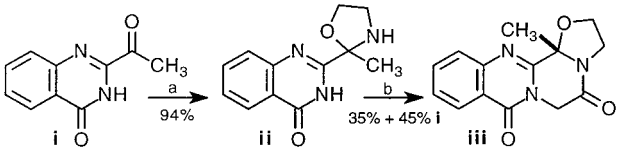
Two procedures were used to introduce a 3-indolylmethyl group into **14**. The first involved adaptation of a procedure developed by Kametani for introduction of this group onto the methylene group of diketopiperazines.[9] Thus, deprotonation of **14** with *n*-butyllithium and quenching the resulting anion with methyl chloroformate gave a 70% yield of **15** along with 23% of recovered starting material. Rapid addition of an excess of the acylating agent was necessary to minimize proton transfer from the more acidic **15** to the anion derived from **14**. It is notable that **15** was obtained as a single diastereomer with a pseudoaxially disposed carbomethoxy group. The stereochemical course of this acylation is likely due to a thermodynamic preference for a pseudoaxial carbomethoxy group to minimize allylic strain with the quinazolinone carbonyl group.[10] Tributylphosphine-mediated Kametani condensation of **15** with gramine in acetonitrile under reflux furnished indoles **16** (84%) and **17** (9%) after separation by column chromatography. The stereochemistry of **16** and **17** was apparent from the chemical shift of the $C_{13b}$ methyl groups, which appear at $\delta$ 1.90 and 0.65 in **16** and **17**, respectively. The upfield value of this signal in **17** indicates a *cis*-relationship between the methyl group and indolylmethyl group, resulting in shielding of the methyl group. The $^1$H NMR spectrum of **16** also provided evidence for folding of the indole over the thiazolidine ring, as the methylene protons in the α-position relative to sulfur were separated by more than 1 ppm ($\delta$ 1.42 for $H_{2\alpha}$ and $\delta$ 2.54 for $H_{2\beta}$ in $CDCl_3$). These protons appear as a two-proton multiplet ($\delta$ 2.96−3.07) in the $^1$H NMR spectrum of **17**. It is also notable that the carbomethoxy group in **16** appeared as a sharp singlet ($\delta$ 3.97 in $CDCl_3$ at room temperature) as did the methyl ester in **15**. On the other hand, the $^1$H NMR spectrum of **17** displayed the carbomethoxy group as a broad singlet ($\delta$ 3.82 in $CDCl_3$ at room temperature) that sharpened as the temperature was increased. This observation suggests that rotation around the $C_6-CO_2$-Me bond is slow due to steric interactions with the quinazolinone carbonyl group. Treatment of a mixture of **16** and **17** with anhydrous lithium chloride in HMPA containing 1.5 equiv of water provided **18** (12%) and **19** (80%) after separation by chromatography over either alumina or silica gel.[11] The stereochemistry of these isomers was initially assigned using $^1$H NMR arguments similar to those used with **16** and **17**, and was ultimately confirmed by X-ray crystallographic analysis of **19**.[12] In the solid state, as in solution, the C-ring adopts a boatlike conformation with the 3-indolylmethyl and methyl groups occupying pseudoaxial positions. It is notable that the indolyl group projects away from the quinazolinone ring, as in spiroquinazoline.[4]

The second method for introduction of the 3-indolylmethyl group involved direct copper-promoted alkylation of the lithium enolate of **14**.[13] Thus, treatment of **14** with lithium diisopropylamide (2.2 equiv) and $Li_2CuCl_4$ (0.1 equiv), followed by addition of solid gramine methosulfate, provided **18** (11%) and **19** (54%).

The synthesis of **5** was completed from **19** following a protocol originally described by Klausner and Chorev for *N*-acylation of indoles.[14] Thus, treatment of a DMF solution of **19** with *p*-nitrophenyl *N*-Cbz-glycinate in the presence of KF, 18-C-6, and Hunig's base gave an 85% yield of **5** along with 13% of recovered starting material. The structure of **5** was confirmed by X-ray crystallography.[12] It is notable that in the solid phase, the acylated indole group is still folded over the tetracyclic backbone, but the indole now projects toward the quinazolinone ring.

**Morin Rearrangement of Sulfoxide 20 and Related Compounds.** Although our original plan called for

(8) (a) Bergman, J.; Brynolf, A. *Tetrahedron* **1990**, *46*, 1295. (b) The more polar compound that accompanied 2-(acetyl)-4(3*H*)-quinazolinone was a mixture of diastereomeric dimers based on $^1$H, $^{13}$C, and MS data. The precise structure of the dimeric material was not determined. This material was formed from 2-(acetyl)-4(3*H*)-quinazolinone upon warming with $K_2CO_3$ in ethanol. (c) The oxygen analogue of **14** was also prepared in a similar manner. Experimental procedures are provided in the Supporting Information.




(a) $HOCH_2CH_2NH_2$, PhH, Δ (b) $BrCH_2COBr$, $K_2CO_3$, THF; *n*-$Bu_4OH$, $H_2O$

(9) Kametani, T.; Kanaya, N.; Ihara, M. *J. Am. Chem. Soc.* **1980**, *102*, 3974.

(10) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. (b) Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841.

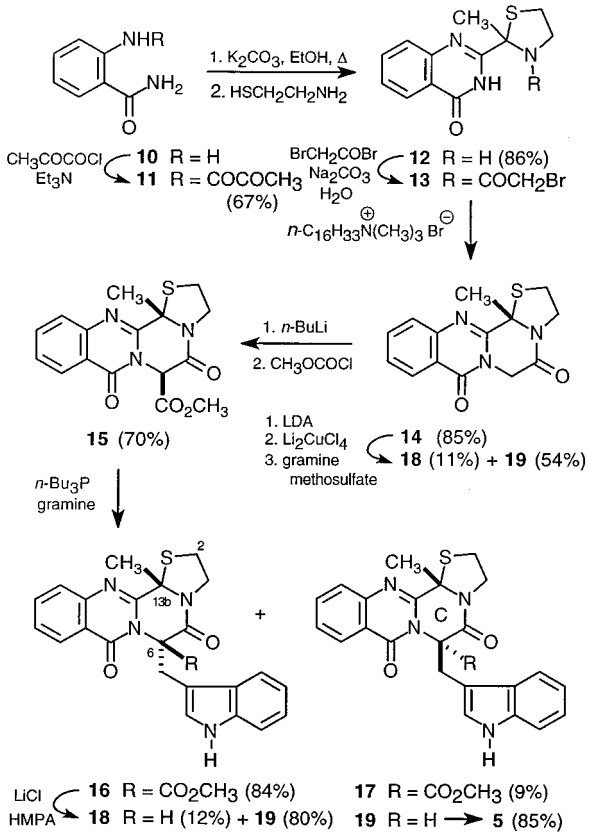
(11) Asaoka, M.; Miyake, K.; Takei, H. *Chem. Lett.* **1975**, 1149.

(12) We thank Dr. Judith C. Gallucci for X-ray crystallographic determination of the structures of **5**, **19,** and **31** at the OSU Department of Chemistry Crystallographic Facility.

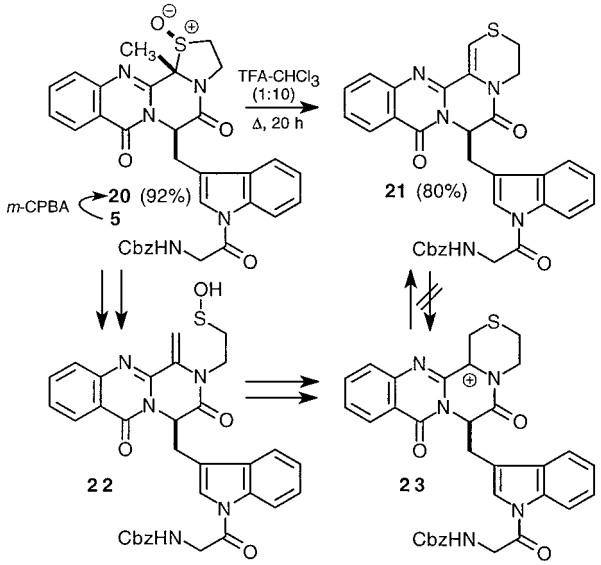
(13) Gelin, J.; Mortier, J.; Moyroud, J.; Chene, A. *J. Org. Chem.* **1993**, *58*, 3473.

(14) Klausner, Y. S.; Chorev, M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 627.

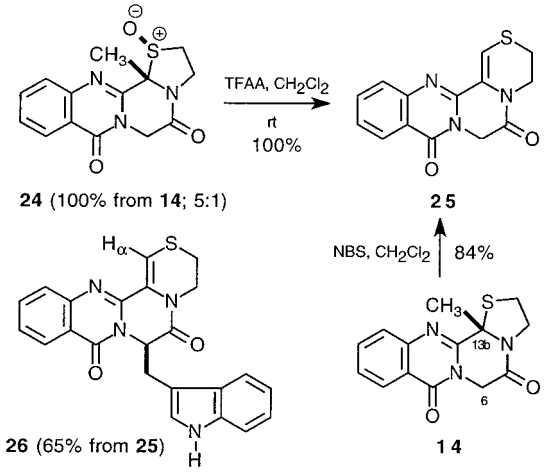
**Scheme 1**




**Scheme 2**




**Scheme 3**




electrophile-initiated ionization of **5** (Figure 1), preliminary results (vide infra) quickly led us to examine the chemistry of sulfoxide **20**, prepared in 92% yield by oxidation of **5** with *m*-chloroperoxybenzoic acid. The stereochemical assignment for **20** is tentative and was based only on the expected direction of approach of the peroxyacid to the sulfide. Treatment of **20** with 8 equiv of trifluoroacetic anhydride in dichloromethane at room temperature gave vinyl sulfide **21** in 80% yield. A similar result was obtained when **20** was warmed under reflux in a 10:1 mixture of chloroform and trifluoroacetic acid. The structure of **20** was based largely on spectroscopic data, including disappearance of the methyl singlet and appearance of a new vinyl proton at $\delta$ 6.89. It is probable that **21** was formed by some variation of the mechanism depicted in Scheme 2. Thus, elimination of **20** could provide enamide-sulfenic acid **22**. Electrophilic addition of the sulfenic acid to the enamide, probably promoted by acid, would provide *N*-acyliminium ion **23**, and proton loss would then afford **21**. This process is strictly analogous to the Morin rearrangement.

The results with **20** were not too surprising based on preliminary experiments performed with sulfide **14** (Scheme 3). It had been hoped that alkylation of the sulfur in **14** would provide a site-selective manner for the generation of an iminium ion at $C_{13b}$. Attempted alkylation of **14** with iodomethane, however, left starting material unchanged. Alkylations under more forcing conditions, such as iodomethane−silver tetrafluoroborate−dichloromethane, methyl triflate−dichloromethane, or *p*-methoxybenzyl chloride−silver tetrafluoroborate−acetonitrile, were not promising and provided complex mixtures of heterogeneous solid materials. It was at this point that sulfoxides **24** (5:1 mixture of diastereomers), prepared in quantitative yield by oxidation of **14** with *m*-chloroperoxybenzoic acid, were examined (Scheme 3).[15] It was imagined that reaction of **24** with electrophilic reagents would result in heterolytic ring-opening of the thiazolidine ring. In the event, warming a benzene solution of **24** under reflux with a catalytic amount of *p*-toluenesulfonic acid for 35 h gave **25** in 50% yield. The structure of **25** was based on spectroscopic data. The relatively simple $^1$H NMR spectrum of **25** showed that this product had a higher degree of symmetry than the starting tetracycle **24**. For example, the $C_6$-methylene protons on the C-ring appeared as a singlet ($\delta$ 4.64 in DMSO) in **25** whereas they were diastereotopic in **24**. In addition, spectroscopic data indicated that **25** lacked the methyl group present in the starting material. Finally, the $^1$H NMR spectrum of **25** displayed an additional downfield singlet at $\delta$ 7.40, assigned to the new vinylic proton at $C_1$ adjacent to sulfur, in addition to the expected four aromatic protons.

Other electrophiles promoted the rearrangement of sulfoxides **24**. For example, a dichloromethane suspension of **24** gave **25** in quantitative yield upon treatment

(15) The stereochemical assignment for the major diastereomer is tentative and based on expected attack of the peracid on the sterically most accessible $\beta$-face lone pair on sulfur.

with an excess of trifluoroacetic anhydride at room temperature for 30 min. Rearrangement with trifluoroacetic acid and chloroform at reflux also provided **25** (79%). Tetracyclic sulfide **14** was also transformed into **25** in 84% yield when treated with 1 equiv of NBS in dichloromethane for 15 min at room temperature. In this case, the NBS likely behaves as a mild thiophilic electrophile capable of activating the C−S bond for heterolysis. It is probable that cyclization of an intermediate enamide-sulfenyl bromide then furnishes **25**.

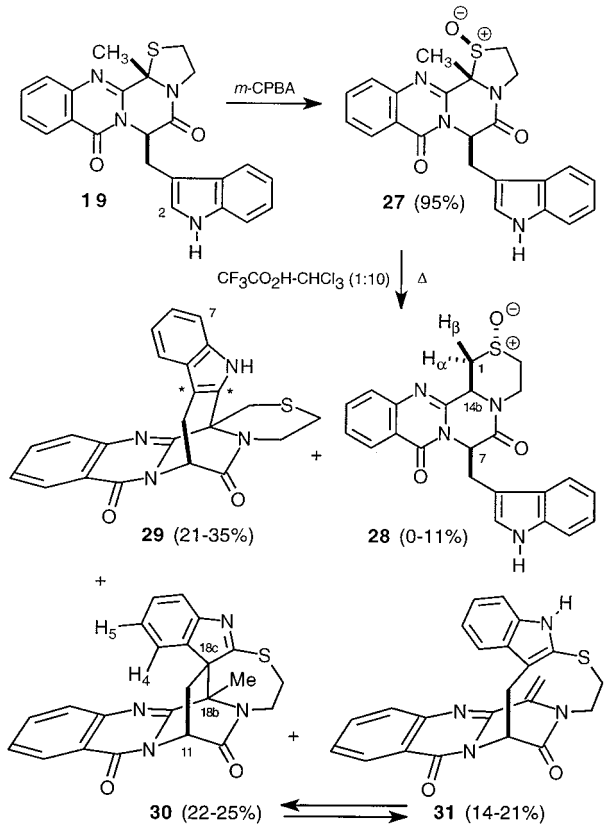
In another mechanistically meaningful experiment, it was shown that **26**, prepared in 65% yield by alkylation of **25** with gramine methosulfate, did not undergo exchange of the vinylic proton ($H_\alpha$) upon treatment with $CF_3CO_2D$ in chloroform at reflux. This experiment suggests that if the rearrangement of **20** proceeds through *N*-acyliminium ion **23** (Scheme 2) proton loss to provide **21** is irreversible.

Whereas the experiments described in Schemes 2 and 3 did not provide the desired rearrangement−cyclization products (Figure 1), they did suggest that an *N*-acylated indole was not a wise choice for a nucleophile to capture *N*-acyliminium ions of type **23**, or perhaps even of type **6**. The next logical step was to investigate sulfoxides derived from **19** in which the indole side chain would be expected to be a better nucleophile.

**Morin Rearrangement-Trapping with Sulfoxide 27.** Sulfoxide **27** was prepared as a single diastereomer in 95% yield by oxidation of **19** using *m*-chloroperoxybenzoic acid. Once again the stereochemical assignment is merely based on the expected attack of the peracid on the more accessible lone pair of the sulfur. Treatment of **27** with trifluoroacetic anhydride gave a very complex, intractable mixture of products. Reaction of **27** with chloroform−trifluoroacetic acid (10:1) under reflux also gave a complex but reasonably clean mixture of products (Scheme 4). A combination of fractional crystallization and chromatography allowed separation of four products, which accounted for all the peaks seen in the $^1$H NMR spectrum of the crude reaction mixture. These products included sulfoxide **28** (0−11%), bridged indole **29** (21−35%), spirothioimidate **30** (22−25%), and enamide **31** (14−21%). The yield ranges are based on several runs.

The most polar product (**28**) was an isomer of **27** based on HREIMS. The mass spectrum of **28** showed a peak at *m*/*z* 416, corresponding to loss of an oxygen atom from the molecular ion, a fragmentation characteristic of sulfoxides. In addition, the base peak corresponded to the 3-indolylmethyl cation (*m*/*z* 130). The $^1$H NMR spectrum of **28** also revealed the presence of the indolylmethyl group, the absence of the methyl group ($\delta$ 0.35 in $CDCl_3$ in **27**), and the presence of a new $CHCH_2$ spin system, in addition to the expected tryptophan-derived $CHCH_2$ and thiazolidine-derived $CH_2CH_2$ spin systems. The $^{13}$C and DEPT spectra indicated that the aliphatic carbons of **28** were represented by four methylenes and two methines. This information, along with selected decoupling experiments, was enough to establish the structure of **28** with unspecified stereochemistry. The stereochemical assignments at $C_7$ and $C_{14b}$ rest largely on the upfield appearance of $H_{1\beta}$ as a doublet of doublets at $\delta$ 0.02 with geminal and vicinal (anti) coupling constants of 13.7 and 12.2 Hz, respectively. Its geminal partner ($H_{1\alpha}$) appeared as a doublet of triplets at $\delta$ 2.82 with a geminal coupling constant of 13.7 Hz and vicinal (gauche) and W-couplings of 2.5 Hz. The upfield chemical shift of $H_{1\beta}$ indicates that

**Scheme 4**




it is shielded by the tryptophan ring. This kind of shielding effect is known in the diketopiperazine literature.[16] The extreme upfield shift observed in **28** may be due to a strong attraction between the positive end of the S−O dipole and the aromatic $\pi$-system and hence stronger shielding by the aromatic ring than is normally observed in such systems.[17] This argument is only valid if the sulfoxide stereochemistry is as indicated in structure **28**. A possible mechanism for the formation of **28** is shown in Scheme 5. Thus, the expected elimination reaction would transform **27** into enamide-sulfenic acid **32**. *Syn*-addition of the sulfenic acid to the olefin, with reverse orientation of the elimination, would provide **28**. Finally, it was noted that the shorter the reaction time, the greater the yield of **28** relative to other products. This suggests that the conversion **28** and **27** (or **32**) may be reversible.[18,19] Compounds **29**−**31** were isomers with molecular formulas $C_{23}H_{18}N_4O_2S$ based on HREIMS and, hence, were formal products of dehydration of sulfoxide **27**. The EIMS spectra of **29**−**31** displayed intense molecular ions, and no peaks corresponding to the 3-indolylmethyl cation were detected. These data implied that the indole groups in **29**−**31** were not just connected to the rest of the molecule by a methylene group, but were probably incorporated in polycyclic structures. The $^1$H NMR spectrum of **29** showed the presence of an indole

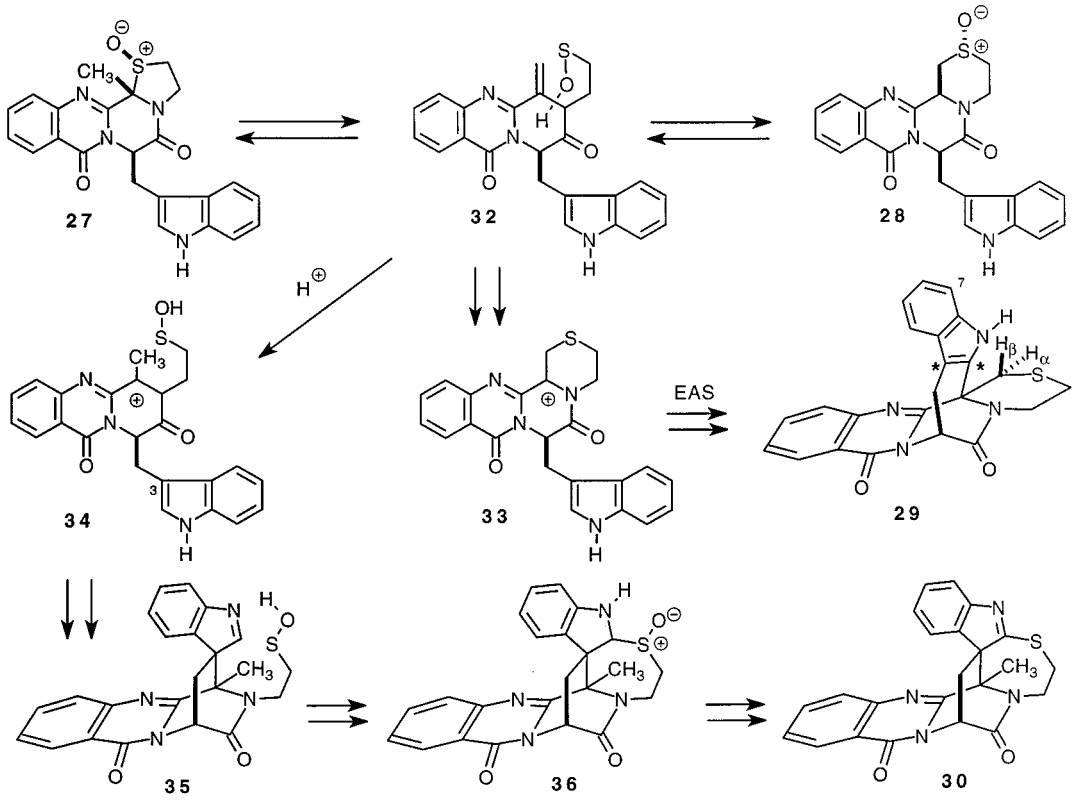
(16) Anteunis, M. J. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 627.

(17) Cooper, R. D. G.; DeMarco, P. V.; Cheng, J. C.; Jones, N. D. *J. Am. Chem. Soc.* **1969**, *91*, 1408.

(18) Braverman, S. In *The Chemistry of Sulphenic Acids and Their Derivatives*; Patai, S., Ed.; Academic Press: Chichester, 1990; p 312.

(19) It is notable that the coupling constants between the tryptophan-derived methine ($H_7$) and methylene protons were small ($J$ = 4.1 and 3.1 Hz). This is consistent with a $C_7$-$CH_2$ conformation in which $H_7$ and the 3-indolyl group have an *anti*-relationship, placing the indole group in close proximity to the sulfoxide and $C_1$.

**Scheme 5**




NH ($\delta$ 11.3 in DMSO-$d_6$) and eight aromatic protons. The spectrum showed an absence of the methyl group and the characteristic aromatic signal due to $H_2$ of the indole ($\delta$ 6.60 in **27**). The aliphatic region of the $^1$H NMR spectrum of **29** revealed that in addition to tryptophan-derived $CHCH_2$ and thiazolidine-derived $CH_2CH_2$ patterns, there was a new AB-system. These two protons were coupled only to one another and were fairly downfield ($\delta$ 3.93 and 4.09 with $J = 14.7$ Hz). These and other data suggested structure **29**, a logical product resulting from the Morin rearrangement (**27** → **32** → **33** in Scheme 5), followed by an electrophilic aromatic substitution reaction.[20] As electrophilic reactions of 3-substituted indoles can occur through intermediate spiroindolines, the orientation of the indole in **29** could not be taken for granted.[21] Difference NOE experiments helped rule out an alternative, mechanistically reasonable structure in which the indole is transposed at the carbons marked with an asterisk. Thus, irradiation of the indole NH resulted in a 4% enhancement of the signal due to $H_\beta$ adjacent to sulfur ($\delta$ 4.09) in addition to a 3% enhancement of $H_7$ of the indole substructure. Alternatively, irradiation of $H_\beta$ resulted in a 5% enhancement of the indole NH in addition to a 7% enhancement of $H_\alpha$ ($\delta$ 3.93) adjacent to sulfur.

The structure of spiroindoline **30** was assigned on the basis of spectral data and chemical correlation with enamide **31** (vide infra). The $^1$H NMR spectrum revealed a singlet due to the $C_{18b}$ methyl group ($\delta$ 1.20), eight aromatic protons, tryptophan-derived $CHCH_2$, and thiazolidine-derived $CH_2CH_2$ spin systems. Notably, **30** lacked an NH as well as the $C_2$ proton of the indole. The methylene protons of the tryptophan-derived $CHCH_2$ spin system were significantly more upfield ($\delta$ 1.74 and 2.29) than in **28**, **29**, and **31**, suggesting that they were no longer pseudo-benzylic and that the aromaticity of the five-membered ring of the indole was disrupted. It was also surprising that two of the eight aromatic protons of **30** (doublet at $\delta$ 5.93 and triplet at $\delta$ 6.51) were significantly upfield relative to the typical chemical shifts observed in **27**. One of these was even more upfield than the $C_{11}$ methine, which appeared at $\delta$ 6.06. $^{13}$C and DEPT experiments revealed one methyl group, three methylenes, one methine, and two quaternary carbons in the $sp^3$-carbon region. The methyl group, $CHCH_2$ and $CH_2$-$CH_2$ subunits accounted for five of these carbons. One of the quaternary carbons was thought to be derived from the methyl-bearing carbon ($C_{18b}$). The other quaternary carbon was thought to come from addition of an electrophile to $C_3$ of the original indole. This would disrupt aromaticity, resulting in the observed upfield shift of the tryptophan-derived methylene. All this information resulted in the deduction of structure **30** as a candidate for this product. The structure readily explains the anomalous upfield chemical shifts of the two aromatic protons, as $H_4$ and $H_5$ are clearly in the shielding cone of the quinazolinone ring. One mechanism for the formation of **30** is proposed in Scheme 5. Protonation of **32** followed by capture of the resulting *N*-acyliminium ion **34** with $C_3$ of the indole would give indoline **35**. Trapping of the indoline by the sulfenic acid (protonation of nitrogen followed by capture of the resulting iminium ion by sulfur) would afford amino sulfoxide **36**. Protonation of the sulfoxide, loss of water, and finally loss of a proton from nitrogen would accomplish the internal redox

(20) For cyclizations of some relevance in the diketopiperazine literature see: Ottenheijm, H. C. J.; Plate, R.; Noordik, J. H.; Herscheid, J. D. M. *J. Org. Chem.* **1982**, *47*, 2147.

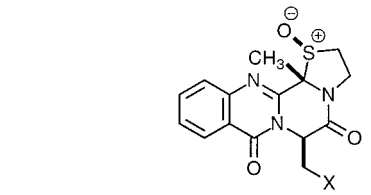
(21) (a) Jackson, A. H.; Naidoo, B.; Smith, P. *Tetrahedron* **1968**, *24*, 6119. (b) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper Collins Publishers: New York, 1987; p 444.

chemistry (Pummerer) needed to transform **36** into **30**. An alternate mechanism for formation of **30** will be suggested later (vide infra).

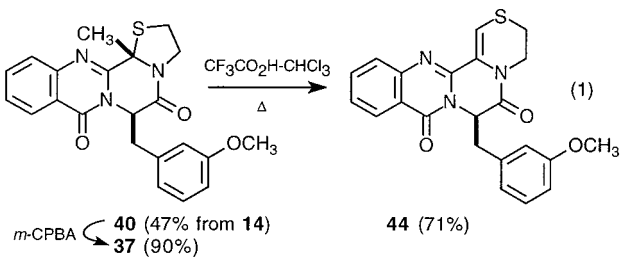
The structure of **31** was also deduced using spectroscopic data and confirmed by X-ray crystallography.[12] It was also observed that **30** and **31** were in equilibrium in the presence of traces of acid. This was discovered when NMR solutions of pure **30** or **31** in $CDCl_3$ began to show cross contamination upon standing at room temperature for several hours. Independent treatment of either **30** or **31** with a 10:1 mixture of chloroform and trifluoroacetic acid at reflux for 30 min provided a 2:1 mixture of **30** and **31**, respectively. A reasonable mechanism for the conversion of **30** to **31** involves sequential protonation of the indoline nitrogen, breaking of the $C_{18b}-C_{18c}$ bond with formation of the indole and an *N*-acyliminium ion, and loss of a proton from the methyl group to provide **31**. It seems reasonable that this process would be reversible as observed.

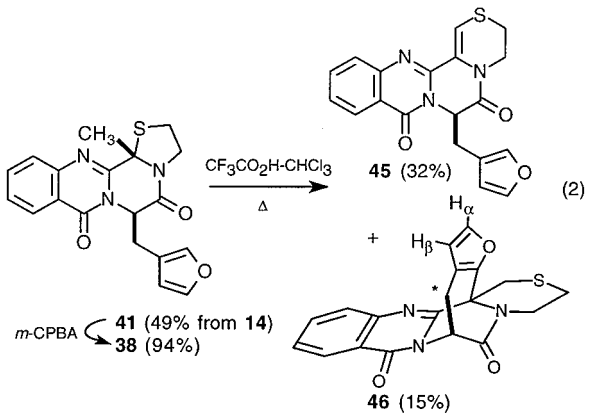
**Extensions of the Morin Rearrangement−Trapping Reaction.** The generality of Morin rearrangement−trapping reactions was briefly investigated.[5c] It was decided to hold the rearrangement part of the system constant and vary the trap by examining the behavior of sulfoxides **37**−**39**. The sulfoxides were prepared as shown in eqs 1−3. Thus, tetracycle **14** was deprotonated with lithium diisopropylamide and treated with several electrophiles in the presence of $Li_2CuCl_4$. Use of *m*-methoxybenzyl bromide,[22] 3-bromomethylfuran,[23] and *N*-Boc-2-bromomethylindole[24] gave **40**, **41**, and **42** in 47%, 49%, and 57% yields, respectively. The Boc-group was removed from **42** in high yield upon warming at 200 °C for 1−2 min to provide **43**.[25] The sulfides (**40**, **41**, **43**) were converted to the corresponding sulfoxides (**37**−**39**) using *m*-chloroperoxybenzoic acid as the oxidant in 90%, 94%, and 98% yields, respectively. In each case the sulfoxides appeared to be single isomers by NMR.

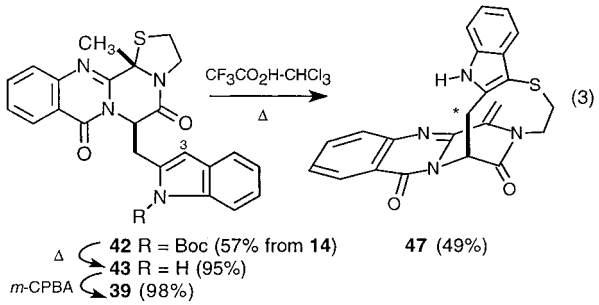
Treatment of **37** with chloroform−trifluoroacetic acid (10:1) at reflux provided a 71% yield of Morin rearrangement product **44**. Furan **38** gave a separable mixture of rearrangement product **45** (32%) and rearrangement−trapping product **46** (15%) under the same reaction conditions. Finally, indole **39** gave a single isolable product in 49% yield, assigned structure **47**. The structure assignments of **44** and **45** were straightforward based on spectroscopic evidence. The structure of **46** was also deduced on the basis of spectroscopic evidence. Key points included the appearance of an AB quartet at $\delta$ 3.94 due to the isolated $CH_2S$ spin system, disappearance of the singlet corresponding to the 2-furyl proton in the starting material, and the appearance of a new quaternary carbon at $\delta$ 59.8 in the $^{13}C$ NMR spectrum of **46**. In addition, observation of an NOE at each of the C* methylene protons upon irradiation of $H_\beta$ (and the absence of such an NOE upon irradiation of $H_\alpha$) established the regiochemistry of the cyclization. The structure of **47** was also based on spectroscopic evidence using $^1H$ and $^{13}C$ NMR spectroscopy in tandem with $^1H-^1H$ and $^1H-^{13}C$ COSY data. The presence of the enamide methylidene was evident from signals in the $^1H$ NMR spectrum at $\delta$ 4.36 and 5.25 and a triplet at $\delta$ 97.7 in the $^{13}C$ NMR spectrum. The orientation of the indole was based on an NOE observed at the indole NH upon irradiation of one ($\delta$ 4.04) of the diastereotopic C* methylene protons. There seem to be two reasonable mechanisms that could account for the formation of **47** (Scheme 6). One mechanism, related to that proposed in Scheme 5 for formation of **31**, would involve conversion of **39** to **48**, protonation of the enamide to provide **49**, an electrophilic aromatic substitution reaction to provide **50**, electrophilic attack of the protonated sulfenic acid on $C_3$ of the indole to provide iminium ion **51**, and fragmentation to give **47**.



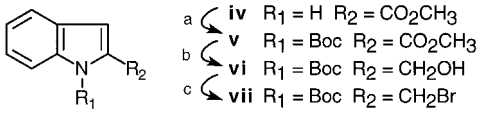
**37** X = 3-methoxyphenyl
**38** X = 3-furyl
**39** X = 2-indolyl



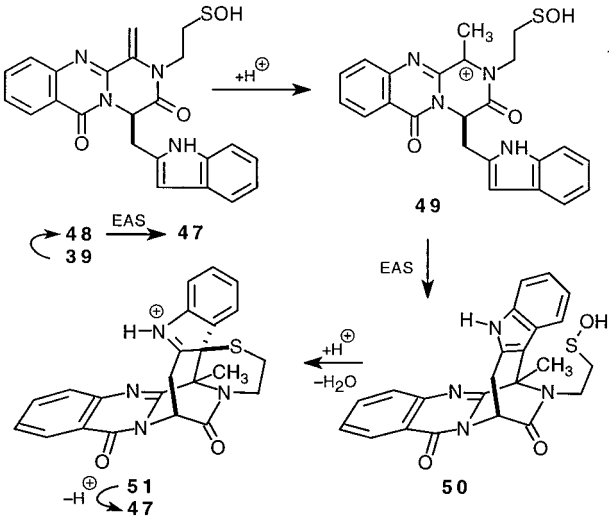




(22) Commercially available.
(23) Wang, E. S. *Tetrahedron* **1996**, *52*, 12137.
(24) The 2-bromomethyl-1-(*tert*-butoxycarbonyl)indole was prepared from methyl indole-2-carboxylate as indicated below [(a) $(t\text{-BuOCO})_2O$, 4-DMAP, $CH_3CN$ (99%) (b) *i*-$Bu_2AlH$, toluene (67%) (c) LiBr, $CH_2Cl_2$, $CH_3SO_2Cl$; LiBr, $CH_3CN$ (63%)]. Experimental procedures and relevent references are provided in the supporting material.




(25) Rawal, V. H.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 6141.

**Scheme 6**




An alternative mechanism would involve direct cyclization of sulfenic acid **48** to **47** via an electrophilic aromatic substitution reaction. This result also suggested an alternative mechanism to that proposed in Scheme 5 for the formation of **30** and **31** from **27**. Thus, sulfoxide elimination (**27** → **32**) followed by a direct electrophilic aromatic substitution at $C_2$ of the indole, would provide **31**, which is in equilibrium with **30** as described above.

The studies described above indicate that the degree of trapping of the putative cationic intermediate in the Morin rearrangement is clearly a function of the nucleophilicity of the trapping group (indole > furan > anisole).

## Summary and Conclusions

From the standpoint of developing a synthesis of spiroquinazoline, the studies described above are both discouraging and encouraging. It seems clear that a Morin rearrangement−cyclization−trapping approach is not viable. An *N*-acylated indole is not electrophilic enough to trap the Morin intermediate, and the Morin rearrangement product (at least in the case of **26**) is not a good precursor to the required *N*-acyliminium ion. On the other hand, the interconversion of **31** and **30** indicates that protonation of an enamide will provide a viable entry to *N*-acyliminium ions of type **6**. In addition, if the mechanism for formation of **30** shown in Scheme 5 is operative, the reactions of **27** can be regarded as proof-of-principle for an *N*-acyliminium ion-trapping sequence for the formation of the spirocyclic substructure of the natural product.[26]

From the standpoint of fundamental chemistry, the reactions of **27** and **38** provide clear examples in which the putative cationic intermediate in a Morin rearrangement has been trapped by a carbon nucleophile. The reactions of **27** and **39** provide examples in which (1) protonation of an intermediate enamide initiates a reasonable cascade of cyclization and fragmentation reactions or (2) the sulfenic acid intermediate in the Morin rearrangement is captured in an intramolecular electrophilic aromatic substitution reaction involving formation of a nine-membered ring.

(26) For the synthesis of a structural relative of spiroquinazoline, see Hart, D. J.; Magomedov, N. A. *Tetrahedron Lett.* **1999**, *40*, 5429.

## Experimental Section[27]

***o*-Pyruvamidobenzamide (11).** To a stirred solution of 27.2 g (0.20 mol) of anthranilamide (**10**) in 1.2 L of dichloromethane was added 83.5 mL of triethylamine in one portion. The mixture was cooled in ice−water bath, and freshly prepared pyruvoyl chloride (32.0 g, 0.3 mol) was added dropwise over a period of 15 min. After the addition was over, the reaction mixture was left to stir at room temperature for 2 h, and then sequentially washed with 100 mL of water, 100 mL of 1 N aqueous HCl, 100 mL of 10% aqueous $NaHCO_3$, and 100 mL of water. The organic solution was dried ($MgSO_4$) and concentrated in vacuo, and the residue was recrystallized from ethyl acetate to provide 28.0 g (67%) of amide **11** as a white crystalline solid: mp 199.0−200.5 °C (EtOAc); lit.[7] mp 180−182 °C ($CH_2Cl_2$/pentane); $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 2.42 (s, 3H), 7.20 (ddd, $J$ = 7.9 Hz, 7.5 Hz, 1.1 Hz, 1H), 7.56 (ddd, $J$ = 8.3 Hz, 7.5 Hz, 1.4 Hz, 1H), 7.75 (bs, 1H), 7.85 (dd, $J$ = 7.9 Hz, 1.4 Hz, 1H), 8.29 (bs, 1H), 8.59 (dd, $J$ = 8.3 Hz, 1.1 Hz, 1H), 12.65 (bs, 1H).

**(±)-2-(2-Methyl-2-thiazolidinyl)-4(3*H*)-quinazolinone (12).** A suspension of 9.75 g of diamide **11** in 700 mL of $K_2CO_3$ in aqueous ethanol (4:3) (pH 9) was heated to 70 °C. After the solid dissolved, the reaction mixture was stirred for 1 h 20 min, cooled in an ice−water bath, acidified with 3 N HCl to pH 2, and concentrated on a rotary evaporator to a volume of 200 mL. A significant amount of precipitate formed at this point, and the suspension was placed in a freezer for 2 h. The precipitate was collected, washed with water, and dried in air to give 8.2 g (92%) of material. This product is a mixture of two compounds, the desired 2-acylquinazolinone and a significantly more polar substance of unidentified structure. No separation is necessary before the next step because both compounds provide a desired *N*,*S*-acetal upon reaction with 2-mercaptoethylamine. If necessary, the difference in solubility allows easy separation of two compounds. The quinazolinone is soluble in dichloromethane, whereas the more polar compound is soluble only in dipolar aprotic solvents such as DMSO and DMF. Concentration of the dichloromethane solution followed by recrystallization provides 2-acetylquinazolinone as white needles: mp 203−204 °C (EtOAc), lit.[8a] mp 200−201 °C (MeCN); $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.76 (s, 3H), 7.62 (ddd, $J$ = 7.9 Hz, 6.6 Hz, 1.6 Hz, 1H), 7.81−7.90 (m, 2H), 8.36 (ddd, $J$ = 7.9 Hz, 1.2 Hz, 0.5 Hz, 1H), 9.95 (bs, 1H).

To a suspension of 7.5 g (0.04 mol) of the aforementioned crude material in 350 mL of absolute ethanol in a 1-L round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser, fitted with a $CaCl_2$-tube, was added 11.2 g (0.113 mol) of 2-mercaptoethylamine hydrochloride followed by 16.2 mL (0.113 mol) of triethylamine. The reaction mixture was refluxed for 2 h, cooled to room temperature, and concentrated in vacuo to provide a pinkish solid. The solid was partitioned between 800 mL of EtOAc and 100 mL of water. The organic layer was separated, washed with three 100-mL portions of water, dried ($Na_2SO_4$), and concentrated in vacuo to furnish 9.5 g (93%) of *N*,*S*-acetal **12** as a yellowish white crystalline solid. This material was used directly in the next reaction. An analytically pure sample was obtained as a white crystalline solid by recrystallization from ethyl acetate: mp 177−178 °C; IR (KBr) 3448, 3363, 3189, 3133, 3069, 3000, 2938, 1666, 1607, 1471 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 1.87 (s, 3H), 2.86−2.98 (m, 2H), 3.14−3.22 (m, 1H), 3.32−3.40 (m, 1H), 3.92 (bs, 1H), 7.48 (ddd, $J$ = 7.9 Hz, 7.3 Hz, 0.9 Hz, 1H), 7.63 (ddd, $J$ = 8.2 Hz, 0.9 Hz, 0.6 Hz, 1H), 7.79 (ddd, $J$ = 8.2 Hz, 7.3 Hz, 1.4 Hz, 1H), 8.10 (ddd, $J$ = 7.9 Hz, 1.4 Hz, 0.6 Hz, 1H), 11.53 (bs, 1H); $^{13}$C NMR (DMSO-$d_6$, 75.5 MHz) $\delta$ 28.7 (q), 37.1 (t), 52.5 (t), 78.0 (s), 120.7 (s), 125.8 (d), 126.4 (d), 126.9 (bd), 134.5 (d), 148.1 (bs), 159.6 (bs), 161.4 (bs); mass-spectrum (EI), *m*/*z* (relative intensity) 247 ($M^+$, 13), 232 (12), 214 (87), 200 (100), 173 (73), 147 (19), 146 (18), 119 (28), 102 (72), 90 (56), 61 (52), 42 (74); exact mass calcd for $C_{12}H_{13}N_3OS$ *m*/*z* 247.0779, found *m*/*z* 247.0780. Anal. Calcd for $C_{12}H_{13}N_3OS$: C, 58.28; H, 5.30. Found: C, 58.39; H, 5.36.

(27) See Supporting Information for general experimental procedures.

**(±)-2,3-Dihydro-13b-methylthiazolo[2′,3′:3,4]pyrazino-[2,1-*b*]quinazoline-5,8(6*H*,13b*H*)-dione (14).** To a vigorously stirred two-phase system consisting of 500 mg (1.95 mmol) of **12** in 100 mL of $CH_2Cl_2$ and 10 mL of 1 M aqueous $Na_2CO_3$, was added dropwise at room temperature a solution of 470 mg (2.34 mmol) of α-bromoacetyl bromide in 5 mL of $CH_2Cl_2$. After 30 min, TLC (EtOAc, silica gel) indicated complete consumption of starting material. Solid $Me(CH_2)_{13}NMe_3Br$ (32 mg, 5 mol %) was added to the reaction mixture and stirring was continued for 3 h. The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo to provide the crude product as an off-white foam. Purification by flash chromatography over 50 g of silica gel (eluted with EtOAc:hexane, 2:1) gave 561 mg (85%) of the tetracycle **14** as a white crystalline solid: mp 208.5−209.0 °C ($CHCl_3$/hexane); IR (KBr) 3099, 2947, 1670, 1604, 1467, 1433 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 2.01 (s, 3H), 3.16 (ddd, $J$ = 11.6 Hz, 7.4 Hz, 4.8 Hz, 1H), 3.30 (ddd, $J$ = 11.6 Hz, 7.4 Hz, 7.4 Hz, 1H), 3.97 (ddd, $J$ = 12.2 Hz, 7.4 Hz, 4.8 Hz, 1H), 4.27 (d, $J$ = 18.3 Hz, 1H), 4.36 (ddd, $J$ = 12.2 Hz, 7.4 Hz, 7.4 Hz, 1H), 5.34 (d, $J$ = 18.3 Hz, 1H), 7.51 (ddd, $J$ = 8.0 Hz, 6.6 Hz, 1.8 Hz, 1H), 7.72−7.81 (m, 2H), 8.28 (ddd, $J$ = 8.0 Hz, 1.5 Hz, 0.6 Hz, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75.5 MHz) $\delta$ 28.4 (t), 30.6 (q), 45.8 (t), 48.9 (t), 73.2 (s), 120.3 (s), 127.0 (d), 127.7 (d), 127.7 (d), 135.0 (d), 147.2 (s), 152.6 (s), 160.3 (s), 160.8 (s); mass-spectrum (EI), *m*/*z* (relative intensity) 287 ($M^+$, 97), 272 (100), 244 (61), 199 (29), 102 (20); exact mass calcd for $C_{14}H_{13}N_3O_2S$ *m*/*z* 287.0728, found *m*/*z* 287.0737. Anal. Calcd for $C_{14}H_{13}N_3O_2S$: C, 58.58; H, 4.56. Found: C, 58.58; H, 4.58. If no phase-transfer catalyst is added to the system, the intramolecular alkylation reaction is slow and it is possible to isolate compound **13**, which has very poor solubility in most of organic solvents, as a white powder: $^1H$ NMR (DMSO-$d_6$, 300 MHz) $\delta$ 2.00 (s, 3H), 3.18−3.38 (m, 2H), 3.88−4.02 (m, 1H), 4.11 (d, $J$ = 15.0 Hz, 1H), 4.29−4.43 (m, 1H), 4.37 (d, $J$ = 15.0 Hz, 1H), 7. 50 (t, $J$ = 8.1 Hz, 1H), 7.61 (d, $J$ = 8.2 Hz, 1H), 7.82 (t, $J$ = 8.2 Hz, 1H), 8.09 (d, $J$ = 8.1 Hz, 1H), 11.90 (bs, 1H); mass-spectrum (EI), *m*/*z* (relative intensity) 369 ($M^+$, 0.6), 287 (100), 286 (18), 272 (90), 244 (49), 199 (21), 185 (17), 132 (39), 82 (31), 80 (33).

**Methyl (±)-(6*R**,13b*R**)-2,3,5,6,8,13b-Hexahydro-13b-methyl-5,8-dioxothiazolo-[2′,3′:3,4]-pyrazino[2,1-*b*]quinazoline-6-carboxylate (15).** To a stirred solution of 2.07 g (7.2 mmol) of tetracycle **14** in 100 mL of dry THF, cooled to −78 °C, was added dropwise 6.0 mL of 1.31 M *n*-BuLi in hexanes over a period of 10 min under an argon atmosphere. The reaction mixture was stirred at −78 °C for 20 min, and 2.8 mL (36.0 mmol) of freshly distilled methyl chloroformate was added in one portion. The reaction mixture was stirred at −78 °C for 20 min and then at room temperature for 1 h. The mixture was concentrated in vacuo, and the residue was partitioned between 250 mL of dichloromethane and 100 mL of water. Organic layer was separated, washed with water (100 mL), dried ($MgSO_4$), and concentrated in vacuo to give an orange foam. The foam was flash chromatographed over 250 g of silica gel (EtOAc:hexanes, 7:3) to give crude methyl ester as a yellow foam. Continued elution provided 470 mg (23%) of starting material (**14**). The crude product was recrystallized from a mixture of chloroform and hexanes to furnish 1.7 g (70%) of pure ester **15** as a white crystalline solid: mp 216−217 °C ($CHCl_3$/hexane); IR (KBr) 2955, 1738, 1698, 1677, 1600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 2.09 (s, 3H), 3.16 (ddd, $J$ = 11.4 Hz, 7.7 Hz, 5.4 Hz, 1H), 3.30 (ddd, $J$ = 11.4 Hz, 7.3 Hz, 6.8 Hz, 1H), 3.87 (ddd, $J$ = 12.5 Hz, 7.3 Hz, 5.4 Hz, 1H), 3.90 (s, 3H), 4.58 (ddd, $J$ = 12.5 Hz, 7.7 Hz, 6.8 Hz, 1H), 6.00 (s, 1H), 7.51 (ddd, $J$ = 8.0 Hz, 6.6 Hz, 1.7 Hz, 1H), 7.75−7.84 (m, 2H), 8.25 (ddd, $J$ = 8.0 Hz, 1.7 Hz, 0.5 Hz, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75.5 MHz) $\delta$ 28.1 (t), 31.9 (q), 49.1 (t), 54.3 (q), 60.0 (d), 73.3 (s), 120.0 (s), 127.1 (d), 127.8 (d), 127.8 (d), 135.3 (d), 147.3 (s), 151.9 (s), 156.5 (s), 160.2 (s), 165.7 (s); mass-spectrum (EI), *m*/*z* (relative intensity) 345 ($M^+$, 78), 330 (29), 298 (100), 286 (28), 198 (27), 130 (39), 102 (36), 69 (20); exact mass calcd for $C_{16}H_{15}N_3O_4S$ *m*/*z* 345.0783, found *m*/*z* 345.0798. Anal. Calcd for $C_{16}H_{15}N_3O_4S$: C, 55.69; H, 4.38. Found: C, 55.73; H, 4.43.

**Methyl (±)-(6*R**,13b*S**)-2,3,5,6,8,13b-Hexahydro-6-(indol-3-ylmethyl)-13b-methyl-5,8-dioxothiazolo[2′,3′:3,4]-pyrazino[2,1-*b*]quinazoline-6-carboxylate (17); Methyl (±)-(6*R**,13b*R**)-2,3,5,6,8,13b-Hexahydro-6-(indol-3-ylmethyl)-13b-methyl-5,8-dioxothiazolo-[2′,3′:3,4]-pyrazino[2,1-*b*]quinazoline-6-carboxylate (16).** To a stirred solution of 0.95 g (2.76 mmol) of methyl ester **15** and 0.53 g (3.04 mmol) of gramine in 50 mL of acetonitrile was added dropwise 0.28 mL (1.10 mmol) of *n*-$Bu_3P$ over a period of 2 min at room temperature. The reaction mixture was brought to gentle reflux for 3 h, cooled to room temperature, passed through a 1-cm pad of silica gel, and concentrated in vacuo to provide an off-white crystalline solid which consisted of a 9:1 mixture of two diastereomeric products and traces of starting material, as indicated by $^1H$ NMR. Separation of this mixture by flash chromatography over 25 g silica gel (EtOAc:hexanes, 2:1) gave 1.10 g (84%) of pure **16** and 112 mg (9%) of **17**. Compound **17** was obtained as a white amorphous solid: IR (KBr) 3372, 3047, 2950, 1763, 1684, 1609, 1593, 1458, 1439, 1375, 1239 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.65 (s, 3H), 2.96−3.07 (m, 2H), 3.19 (ddd, $J$ = 12.5 Hz, 8.4 Hz, 7.3 Hz, 1H), 3.82 (bs, 3H), 4.17 (d, $J$ = 15.1 Hz, 1H), 4.23 (d, $J$ = 15.1 Hz, 1H), 4.90 (ddd, $J$ = 12.5 Hz, 7.5 Hz, 4.5 Hz, 1H), 6.63 (d, $J$ = 2.4, 1H), 6.89 (ddd, $J$ = 8.1 Hz, 7.1 Hz, 0.9 Hz, 1H), 7.08 (ddd, $J$ = 8.1 Hz, 7.1 Hz, 1.0 Hz, 1H), 7.25 (dm, $J$ = 8.1 Hz, 1H), 7.34 (d, $J$ = 8.1 Hz, 1H), 7.53 (ddd, $J$ = 8.1 Hz, 7.2 Hz, 1.2 Hz, 1H), 7.63 (ddd, $J$ = 8.4 Hz, 1.2 Hz, 0.5 Hz, 1H), 7.79 (ddd, $J$ = 8.4 Hz, 7.2 Hz, 1.5 Hz, 1H), 8.12 (bs, 1H), 8.34 (ddd, $J$ = 8.1 Hz, 1.5 Hz, 0.5 Hz, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75.5 MHz) $\delta$ 27.3 (t), 29.0 (t), 29.5 (q), 46.4 (t), 53.2 (q), 70.7 (s), 70.9 (bs), 106.1 (s), 111.6 (d), 117.4 (d), 118.7 (d), 119.5 (s), 121.5 (d), 124.8 (d), 126.7 (d), 126.8 (d), 127.4 (s), 127.9 (d), 135.7 (d), 135.8 (s), 146.1 (s), 151.1 (s), 159.7 (bs), 160.2 (s), 166.3 (bs); mass-spectrum (EI), *m*/*z* (relative intensity) 474 ($M^+$, 8), 345 (10), 313 (6), 228 (10), 130 (100), 102 (8), 43 (16); exact mass calcd for $C_{25}H_{22}N_4O_4S$ *m*/*z* 474.1362, found *m*/*z* 474.1324. Anal. Calcd for $C_{25}H_{22}N_4O_4S$: C, 63.33; H, 4.68. Found: C, 63.21; H, 4.68. Compound **16**: white crystalline solid, mp 156 °C ($CHCl_3$/hexane), morphological changes occur upon melting; IR (KBr) 3404, 3055, 2952, 1765, 1738, 1668, 1596, 1457, 1440, 1374, 1239 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.42 (ddd, $J$ = 10.0 Hz, 9.2 Hz, 8.1 Hz, 1H), 1.90 (s, 3H), 2.54 (ddd, $J$ = 10.0 Hz, 7.6 Hz, 2.5 Hz, 1H), 3.36 (ddd, $J$ = 12.3 Hz, 9.2 Hz, 7.6 Hz, 1H), 3.89 (s, 3H), 4.05 (d, $J$ = 14.8, 1H), 4.30 (d, $J$ = 14.8 Hz, 1H), 4.41 (ddd, $J$ = 12.3 Hz, 8.1 Hz, 2.5 Hz, 1H), 6.17 (d, $J$ = 2.4 Hz, 1H), 6.94 (ddd, $J$ = 7.9 Hz, 7.0 Hz, 0.9 Hz, 1H), 7.07 (ddd, $J$ = 8.1 Hz, 7.0 Hz, 1.0 Hz, 1H), 7.22 (d, $J$ = 8.1 Hz, 1H), 7.54 (ddd, $J$ = 7.9 Hz, 7.2 Hz, 1.2 Hz, 1H), 7.55 (d, $J$ = 7.9 Hz, 1H), 7.66 (ddd, $J$ = 8.3 Hz, 1.2 Hz, 0.5 Hz, 1H), 7.80 (ddd, $J$ = 8.3 Hz, 7.2 Hz, 1.6 Hz, 1H), 8.06 (bs, 1H), 8.33 (ddd, $J$ = 7.9 Hz, 1.6 Hz, 0.5 Hz, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75.5 MHz) $\delta$ 27.5 (t), 30.1 (t), 35.5 (q), 47.6 (t), 53.8 (q), 70.6 (s), 71.4 (s), 108.1 (s), 111.2 (d), 119.5 (d), 119.5 (d), 120.7 (s), 122.3 (d), 123.5 (d), 127.1 (d), 127.4 (d), 127.4 (s), 127.6 (d), 135.3 (d), 136.1 (s), 146.8 (s), 152.4 (s), 160.0 (s), 160.8 (s), 167.2 (s); mass-spectrum (EI), *m*/*z* (relative intensity) 474 ($M^+$, 30), 345 (20), 313 (10), 228 (17), 130 (100); exact mass calcd for $C_{25}H_{22}N_4O_4S$ *m*/*z* 474.1362, found *m*/*z* 474.1373. Anal. Calcd for $C_{25}H_{22}N_4O_4S$: C, 63.33; H, 4.68. Found: C, 63.21; H, 4.66.

**(±)-(6*R**,13b*R**)-2,3-Dihydro-6-(indol-3-ylmethyl)-13b-methylthiazolo[2′,3′:3,4]-pyrazino-[2,1-*b*]quinazoline-5,8(6*H*,13b*H*)dione (18) and (±)-(6*R**,13b*S**)-2,3-Dihydro-6-(indol-3-ylmethyl)-13b-methylthiazolo[2′,3′:3,4]pyrazino-[2,1-*b*]quinazoline-5,8-(6*H*,13b*H*)dione (19).** From methyl esters **16** and **17**: To a solution of 2.49 g (5.25 mmol) of the mixture of **17** and **16** (1:9) in 20 mL of dry HMPA were added 1.10 g (26.23 mmol) of anhydrous LiCl and 0.15 mL (7.88 mmol) of water. The stirred reaction mixture was heated at 100 °C for 14 h after which time the TLC (silica gel, EtOAc) indicated complete consumption of starting material. The reaction mixture was cooled to room temperature and partitioned between 400 mL of a mixture of ethyl acetate and hexane (1:1) and 100 mL of water. The organic layer was washed with three 100-mL portions of water, dried ($MgSO_4$), and concentrated in vacuo to give a white solid representing, by $^1H$ NMR, a clean mixture of **18** and **19** (1:7). This mixture was separated by chromatography over 200 g of flash silica

gel (EtOAc/hexanes, 2:1) to give 260 mg (12%) of **18** and 1.75 g (80%) of **19**. From tetracycle **14**: To a stirred solution of 1.01 mL (7.26 mmol) of *i*-$Pr_2NH$ in 40 mL of dry THF was added dropwise 5.6 mL of a 1.6 M solution of *n*-BuLi in hexanes over a period of 5 min under an argon atmosphere. After 10 min at −78 °C, a solution of 946 mg (3.30 mmol) of tetracycle **14** in 60 mL of dry THF was added dropwise over a period of 10 min. After 30 min, to the resulting red solution was added via cannula 3.3 mL (10 mol %) of a 0.1 M solution of $Li_2CuCl_4$ in THF followed by addition of 1.18 g (3.96 mmol) of solid gramine methosulfate over a period of 10 min. The reaction mixture was warmed to room temperature, stirred for 4 h, quenched with 10 mL of saturated aqueous ammonium chloride, and partitioned between 200 mL of EtOAc and 100 mL of 1 N HCl. The organic layer was separated, washed with water (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography over 150 g of silica gel (EtOAc:hexanes, 2:1) to provide 740 mg (54%) of compound **19** as a white crystalline solid and 150 mg (11%) of its $C_6$ epimer (**18**). Compound **19**: mp 261−262 °C ($CHCl_3$); IR (KBr) 3376, 2935, 1666, 1587, 1396 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.86 (s, 3H), 2.98−3.06 (m, 2H), 3.25 (ddd, $J$ = 12.5 Hz, 7.8 Hz, 7.8 Hz, 1H), 3.72 (dd, $J$ = 15.1 Hz, 3.3 Hz, 1H), 3.82 (dd, $J$ = 15.1 Hz, 5.4 Hz, 1H), 4.89 (ddd, $J$ = 12.5 Hz, 6.7 Hz, 5.7 Hz, 1H), 5.64 (dd, $J$ = 5.4 Hz, 3.3 Hz, 1H), 6.69 (d, $J$ = 2.4, 1H), 6.94 (ddd, $J$ = 8.0 Hz, 7.1 Hz, 1.1 Hz, 1H), 7.11 (ddd, $J$ = 8.0 Hz, 7.1 Hz, 1.0 Hz, 1H), 7.26 (dm, $J$ = 8.0 Hz, 1H), 7.39 (dm, $J$ = 8.0 Hz, 1H), 7.54 (ddd, $J$ = 8.0 Hz, 7.1 Hz, 1.3 Hz, 1H), 7.66 (ddd, $J$ = 8.3 Hz, 1.3 Hz, 0.5 Hz, 1H), 7.79 (ddd, $J$ = 8.3 Hz, 7.1 Hz, 1.6 Hz, 1H), 8.00 (bs, 1H), 8.37 (ddd, $J$ = 8.0 Hz, 1.6 Hz, 0.5 Hz, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75.5 MHz) $\delta$ 27.3 (t), 27.6 (t), 30.4 (q), 46.3 (t), 57.8 (d), 71.9 (s), 107.6 (s), 111.4 (d), 117.9 (d), 118.6 (d), 119.8 (s), 121.2 (d), 124.4 (d), 126.3 (d), 126.7 (d), 127.2 (d), 127.4 (s), 135.0 (d), 135.9 (s), 146.6 (s), 152.4 (s), 159.6 (s), 161.9 (s); mass-spectrum (EI), *m*/*z* (relative intensity) 416 ($M^+$, 5), 199 (5), 170 (5), 131 (7), 130 (100), 103 (7), 77 (8); exact mass calcd for $C_{23}H_{20}N_4O_2S$ *m*/*z* 416.1307, found *m*/*z* 416.1262. Anal. Calcd for $C_{23}H_{20}N_4O_2S$: C, 66.39; H, 4.84. Found: C, 66.21; H, 4.77. The minor diastereomer **18**: mp 265−266 °C ($CHCl_3$/hexane); IR (KBr) 3417, 3055, 2945, 1684, 1658, 1590, 1568, 1404 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.21 (ddd, $J$ = 9.9 Hz, 9.1 Hz, 8.0 Hz, 1H), 1.83 (s, 3H), 2.49 (ddd, $J$ = 9.9 Hz, 8.0 Hz, 2.1 Hz, 1H), 3.26 (dddd, $J$ = 12.3 Hz, 9.1 Hz, 8.0 Hz, 0.8 Hz, 1H), 3.73 (dd, $J$ = 14.9 Hz, 4.4 Hz, 1H), 3.84 (dd, $J$ = 14.9 Hz, 2.9 Hz, 1H), 4.51 (ddd, $J$ = 12.3 Hz, 8.3 Hz, 2.1 Hz, 1H), 5.59 (ddd, $J$ = 4.4 Hz, 2.9 Hz, 0.8 Hz, 1H), 6.12 (d, $J$ = 2.4, 1H), 6.98 (ddd, $J$ = 8.1 Hz, 7.1 Hz, 1.1 Hz, 1H), 7.10 (ddd, $J$ = 8.0 Hz, 7.0 Hz, 1.2 Hz, 1H), 7.23 (dm, $J$ = 8.1 Hz, 1H), 7.55 (dm, $J$ = 8.1 Hz, 1H), 7.56 (ddd, $J$ = 8.2 Hz, 7.2 Hz, 1.2 Hz, 1H), 7.70 (ddd, $J$ = 8.3 Hz, 1.2 Hz, 0.5 Hz, 1H), 7.81 (ddd, $J$ = 8.3 Hz, 7.2 Hz, 1.6 Hz, 1H), 7.92 (bs, 1H), 8.39 (ddd, $J$ = 8.2 Hz, 1.6 Hz, 0.5 Hz, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75.5 MHz) $\delta$ 27.0 (t), 27.2 (t), 34.6 (q), 45.9 (t), 57.2 (d), 70.3 (s), 106.5 (s), 111.1 (d), 117.9 (d), 118.1 (d), 120.1 (s), 120.8 (d), 123.6 (d), 126.3 (d), 126.7 (d), 127.1 (d), 127.3 (s), 134.9 (d), 136.0 (s), 146.4 (s), 152.3 (s), 159.8 (s), 162.3 (s); mass-spectrum (EI), *m*/*z* (relative intensity) 416 ($M^+$, 6), 198 (5), 170 (8), 130 (100), 102 (18), 77 (20); exact mass calcd for $C_{23}H_{20}N_4O_2S$ *m*/*z* 416.1307, found *m*/*z* 416.1295. Anal. Calcd for $C_{23}H_{20}N_4O_2S$: C, 66.39; H, 4.84. Found: C, 66.15; H, 4.76.

**Benzyl (±)-[[[3-[[(±)-(6*R**,13b*S**)-2,3,5,6,8,13b-Hexahydro-13b-methyl-5,8-dioxothiazolo-[2′,3′:3,4]pyrazino[2,1-*b*]quinazolin-6-yl]methyl]indol-1-yl]carbonyl]methyl]carbamate (5).** To a solution of 430 mg (1.03 mmol) of **19**, 514 mg (1.55 mmol) of *p*-nitrophenyl *N*-Cbz-glycinate, and 273 mg (1.03 mmol) of 18-crown-6 in 2 mL of DMF was introduced 124 mg (2.06 mmol) of anhydrous KF in one portion followed by addition of 198 $\mu$L (1.24 mmol) of *i*-$Pr_2NEt$. The reaction mixture was sonicated for 30 min and then stirred at room temperature for 24 h. To the reaction mixture was then added 100 mL of EtOAc followed by filtration through a pad of Celite. The Celite was washed with two 30-mL portions of EtOAc, the combined organic extracts were concentrated in vacuo, and the residue was flash chromatographed over 80 g of silica gel (EtOAc:hexanes, 2:1) to provide 531 mg (85%) of compound **5** as a white amorphous solid together with 57 mg (13%) of recovered starting material (**19**). Crystallization of **5** from chloroform provided a white crystalline solid which, even after an extensive drying, contained traces of solvent of crystallization: mp 132−134 °C ($CHCl_3$/hexane); IR (KBr) 3422, 2944, 1713, 1674, 1594, 1454, 1398, 1218 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz, 75 °C) $\delta$ 1.70 (s, 3H), 3.09 (ddd, $J$ = 10.9 Hz, 8.0 Hz, 6.5 Hz, 1H), 3.21 (ddd, $J$ = 10.9 Hz, 7.7 Hz, 5.3 Hz, 1H), 3.39−3.50 (m, 2H), 3.58 (ddd, $J$ = 12.5 Hz, 7.7 Hz, 6.5 Hz, 1H), 4.34 (dd, $J$ = 17.5 Hz, 6.1 Hz, 1H), 4.40 (dd, $J$ = 17.5 Hz, 6.1 Hz, 1H), 4.56 (ddd, $J$ = 12.5 Hz, 8.0 Hz, 5.3 Hz, 1H), 5.10 (s, 2H), 5.50 (dd, $J$ = 6.6 Hz, 5.6 Hz, 1H), 7.19 (tm, $J$ = 7.9, 1H), 7.29−7.39 (m, 6H), 7.46 (bs, 1H), 7.57−7.67 (m, 4H), 7.87 (ddd, $J$ = 8.2 Hz, 7.2 Hz, 1.6 Hz, 1H), 8.23 (ddd, $J$ = 7.8 Hz, 1.6 Hz, 0.5 Hz, 1H), 8.28 (dm, $J$ = 8.2 Hz, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75.5 MHz) $\delta$ 27.5 (t), 28.1 (t), 31.6 (q), 44.0 (t), 47.3 (t), 56.5 (d), 65.7 (t), 72.4 (s), 79.1 (s), 115.8 (d), 116.6 (s), 119.0 (d), 119.9 (s), 123.5 (d), 124.1 (d), 125.1 (d), 126.4 (d), 126.8 (d), 127.3 (d), 127.7 (d), 127.7 (d), 127.8 (d), 128.3 (d), 129.9 (s), 135.0 (d), 135.1 (s), 136.9 (s), 146.6 (s), 152.5 (s), 156.7 (s), 159.6 (s), 161.2 (s), 168.1 (s); mass-spectrum (EI), *m*/*z* (relative intensity) ($M^+$, 0.3), 213 (24), 151 (15), 130 (100), 113 (15), 79 (14); exact mass calcd for $C_{33}H_{29}N_5O_5S$ *m*/*z* 607.1889, found *m*/*z* 607.1845.

**Benzyl (±)-[[[3-[[(±)-(6*R**,13b*S**)-2,3,5,6,8,13b-Hexahydro-13b-methyl-5,8-dioxothiazolo-[2′,3′:3,4]pyrazino[2,1-*b*]quinazolin-6-yl]methyl]indol-1-yl]carbonyl]methyl]carbamate, *S*-Oxide (20).** To a solution of 111 mg (0.183 mmol) of **5** in 10 mL of $CH_2Cl_2$, cooled to −78 °C, was added 43 mg (0.220 mmol) of 80% *m*-CPBA in 5 mL of $CH_2Cl_2$ in one portion. The reaction mixture was stirred for 30 min at dry ice bath temperature, after which time TLC (EtOAc:hexane, 2:1, silica gel) indicated complete consumption of starting material. The reaction mixture was poured into a separatory funnel charged with 30 mL of saturated aqueous $Na_2SO_3$ and extracted with two 60-mL portions of EtOAc. The combined extracts were washed sequentially with 1 M $Na_2CO_3$ (20 mL) and water (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was flash chromatographed over 12 g of silica gel ($CH_2Cl_2$:MeCN, 1:1) to furnish 104 mg (92%) of sulfoxide **20** as a white amorphous solid: IR (KBr) 3059, 2942, 1713, 1684, 1594, 1567, 1455, 1402, 1374, 1315, 1216 $cm^{-1}$; $^1H$ NMR (acetone-$d_6$, 300 MHz) $\delta$ 0.95 (s, 3H), 2.92 (ddd, $J$ = 14.5 Hz, 9.2 Hz, 3.3 Hz, 1H), 3.30 (ddd, $J$ = 14.5 Hz, 9.7 Hz, 6.7 Hz, 1H), 3.48−3.57 (m, 1H), 3.58 (dd, $J$ = 14.8 Hz, 3.4 Hz, 1H), 3.71 (dd, $J$ = 14.8 Hz, 5.8 Hz, 1H), 4.33 (dd, $J$ = 17.5 Hz, 6.0 Hz, 1H), 4.52 (dd, $J$ = 17.5 Hz, 6.0 Hz, 1H), 4.96 (ddd, $J$ = 12.7 Hz, 9.2 Hz, 6.7 Hz, 1H), 5.12 (s, 2H), 5.59 (dd, $J$ = 5.8 Hz, 3.4 Hz, 1H), 6.72 (bt, $J$ = 6.0 Hz, 1H), 7.12 (tm, $J$ = 7.8 Hz, 1H), 7.29−7.42 (m, 7H), 7.56 (s, 1H), 7.61−7.67 (m, 2H), 7.89 (ddd, $J$ = 8.3 Hz, 7.1 Hz, 1.6 Hz, 1H), 8.32 (dm, $J$ = 7.9 Hz, 1H), 8.36 (d, $J$ = 8.3 Hz, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75.5 MHz) $\delta$ 20.7 (q), 28.7 (t), 44.4 (t), 45.1 (t), 47.2 (t), 57.5 (d), 67.1 (t), 88.1 (s), 117.1 (s), 117.1 (d), 119.8 (d), 121.3 (s), 124.6 (d), 125.0 (d), 126.3 (d), 127.5 (d), 128.1 (d), 128.5 (d), 128.7 (d), 129.3 (d), 131.2 (s), 136.0 (d), 136.6 (s), 138.1 (s), 147.9 (s), 149.4 (s), 157.6 (s), 160.8 (s), 165.5 (s), 168.8 (s), one singlet was not seen due to overlap of signals; mass-spectrum (EI), *m*/*z* (relative intensity) 605 (1), 497 (14), 245 (18), 213 (27), 162 (12), 131 (10), 130 (100), 113 (10), 108 (17), 107 (12), 91 (15), 79 (20), 77 (17), 56 (16), no molecular ion peak was detected; mass-spectrum (FAB), *m*/*z* 624 ($M + 1^+$). Anal. Calcd for $C_{33}H_{29}N_5O_6S$: C, 63.60; H, 4.69. Found C, 63.21; H, 4.83.

**Benzyl (±)-[[[3-[(3,4,6,7-Tetrahydro-6,9-dioxo-9*H*-[1,4]-thiazino[3′,4′:3,4]pyrazino-[2,1-*b*]-quinazolin-7-yl)methyl]indol-1-yl]carbonyl]methyl]carbamate (21).** To a solution of 336 mg (0.54 mmol) of sulfoxide **20** in 40 mL of ethanol-free chloroform was added 4 mL of $CF_3COOH$ in one portion at room temperature. The reaction mixture was refluxed for 20 h, cooled in an ice−water bath, and neutralized with saturated aqueous $Na_2CO_3$. Organic layer was dried ($MgSO_4$) and concentrated in vacuo, and the residue was flash chromatographed over 40 g of silica gel (EtOAc:hexane, 2:1) to give 261 mg (80%) of **21** as a white foam: IR (KBr) 3422, 3063,

2932, 1732, 1674, 1607, 1573, 1550, 1472, 1454, 1400, 1331, 1215 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz, 70 °C) $\delta$ 1.59 (ddd, $J$ = 13.3 Hz, 11.1 Hz, 3.0 Hz, 1H), 2.56 (dddd, $J$ = 13.3 Hz, 3.4 Hz, 2.2 Hz, 1.6 Hz, 1H), 2.80 (ddd, $J$ = 13.3 Hz, 11.1 Hz, 2.2 Hz, 1H), 3.41 (dd, $J$ = 14.8 Hz, 4.7 Hz, 1H), 3.58 (dd, $J$ = 14.8 Hz, 3.6 Hz, 1H), 4.20 (dd, $J$ = 17.6 Hz, 4.9 Hz, 1H), 4.30 (dd, $J$ = 17.6 Hz, 5.2 Hz, 1H), 4.84 (ddd, $J$ = 13.3 Hz, 3.4 Hz, 3.0 Hz, 1H), 5.17 (s, 2H), 5.51 (bs, 1H), 5.87 (dd, $J$ = 4.7 Hz, 3.6 Hz, 1H), 6.64 (s, 1H), 6.89 (d, $J$ = 1.6 Hz, 1H), 7.17 (ddd, $J$ = 8.0 Hz, 7.1 Hz, 0.9 Hz, 1H), 7.30−7.38 (m, 7H), 7.47 (ddd, $J$ = 8.1 Hz, 7.2 Hz, 1.2 Hz, 1H), 7.61 (d, $J$ = 8.0 Hz, 1H), 7.75 (ddd, $J$ = 8.0 Hz, 7.2 Hz, 1.6 Hz, 1H), 8.29 (dm, $J$ = 8.0 Hz, 1H), 8.33 (ddd, $J$ = 8.1 Hz, 1.6 Hz, 0.5 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz) $\delta$ 24.1 (t), 27.5 (t), 37.6 (t), 44.3 (t), 55.0 (d), 67.3 (t), 112.5 (d), 116.7 (d), 119.1 (d), 119.8 (s), 122.7 (d), 122.8 (s), 124.3 (d), 126.2 (d), 126.8 (d), 127.0 (d), 127.5 (d), 128.2 (d), 128.3 (d), 128.5 (d), 128.7 (d), 130.2 (s), 135.3 (d), 135.6 (s), 136.3 (s), 144.6 (s), 147.6 (s), 156.3 (s), 160.4 (s), 163.0 (s), 166.7 (s); mass-spectrum (EI), $m/z$ (relative intensity) 605 ($M^+$, 0.2), 497 (9), 285 (17), 245 (19), 213 (19), 181 (37), 130 (100), 113 (19), 100 (22), 51 (32); exact mass calcd for $C_{33}H_{27}N_5O_5S$ $m/z$ 605.1733, found $m/z$ 605.1750.

**(±)-2,3-Dihydro-13b-methylthiazolo[2′,3′:3,4]pyrazino-[2,1-*b*]quinazoline-5,8(6*H*,13b*H*)-dione, 1-Oxide (24).** To a solution of 1.1 g (3.83 mmol) of **14** in 50 mL of $CH_2Cl_2$ was added 390 mg (4.6 mmol) of solid sodium bicarbonate. The resulting suspension was cooled in a dry ice−acetone bath, and 850 mg (3.85 mmol) of solid 80% *m*-chloroperoxybenzoic acid was added in one portion. The mixture was stirred for 60 min and then quenched by addition of saturated aqueous sodium carbonate. The organic phase was washed with aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated in vacuo to give 1.1 g of a mixture of sulfoxides **24** as a white solid, suitable for use in subsequent reactions. Extraction of the crude solid with dichloromethane followed by removal of solvent gave a white solid that was the pure major diastereomer: mp 206−207 °C (dec); IR (KBr) 1673, 1600, 1066 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz) $\delta$ 1.83 (s, 3H), 3.20 (ddd, $J$ = 14.6, 8.4, 2.3 Hz, 1H), 3.50 (ddd, $J$ = 14.6, 9.8, 8.4 Hz, 1H), 3.95 (ddd, $J$ = 12.3, 9.8, 2.3 Hz, 1H), 4.62 (d, $J$ = 18.2 Hz, 1H), 4.65 (ddd, $J$ = 12.3, 8.4, 8.4 Hz, 1H), 4.82 (d, $J$ = 18.2 Hz, 1H), 7.62 (tm, $J$ = 7.9 Hz, 1H), 7.76 (d, $J$ = 8.1 Hz, 1H), 7.91 (tm, $J$ = 8.1 Hz, 1H), 8.18 (ddd, $J$ = 7.9 Hz, 1.4, 0.7 Hz, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75 MHz) $\delta$ 21.7, 44.2, 45.2, 45.6, 87.2, 119.6, 126.2, 127.0, 127.7, 135.1, 146.5, 148.7, 159.5, 162.2; exact mass calcd for $C_{14}H_{13}N_3O_3S$ $m/z$ 303.0653, found $m/z$ 303.0663. The presence of a minor diastereomeric sulfoxide in the crude product, used in subsequent reactions was suspected based on the appearance of signals in the $^1H$ NMR spectrum, for example a singlet at $\delta$ 1.73 ($CH_3$) and additional downfield signals.

**3,4-Dihydro-9*H*-[1,4]thiazino[3′,4′:3,4]pyrazino[2,1-*b*]-quinazoline-6,9(7*H*)-dione (25).** From tetracycle **14**: To a stirred solution of 144 mg (0.5 mmol) of tetracycle **14** in 10 mL of dichloromethane was added 107 mg (0.6 mmol) of NBS as a solid in one portion at room temperature. The reaction mixture turned bright yellow and was stirred at room temperature for 15 min, after which time TLC (silica gel, EtOAc) indicated complete consumption of starting material. Reaction mixture was partitioned between 10 mL of dichloromethane and 5 mL of saturated aqueous $Na_2SO_3$. The organic layer was separated, washed with 5 mL of water, dried ($MgSO_4$), and concentrated in vacuo to give 160 mg of yellow solid. The solid was recrystallized from a mixture of DMF and water to furnish 120 mg (84%) of **25** as a white solid.

From sulfoxides **24**: To a suspension of 100 mg of a mixture of sulfoxides **24** (5:1) in 9 mL of ethanol-free chloroform was added 1 mL of TFAA in one portion at room temperature. The reaction mixture immediately turned yellow and gradually became homogeneous. After the reaction mixture was stirred for 30 min, TLC (silica gel, EtOAc) demonstrated that the starting material had disappeared. The reaction mixture was partitioned between 20 mL of dichloromethane and 10 mL of saturated aqueous $NaHCO_3$. The organic layer was separated, washed with two 8-mL portions of water, dried ($MgSO_4$), and concentrated in vacuo to give 94 mg (100%) of the crude **25** as a yellowish-white solid which was pure enough for subsequent transformations. An analytically pure sample was obtained as a light green crystalline solid after recrystallization from chloroform/hexanes mixture (80−85% recovery): mp 244−245 °C ($CHCl_3$/hexane); IR (KBr) 3068, 3006, 2928, 1668, 1603, 1569, 1546, 1472, 1401 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz) $\delta$ 3.15−3.18 (m, 2H), 4.07−4.10 (m, 2H), 4.64 (s, 2H), 7.40 (s, 1H), 7.48 (ddd, $J$ = 8.1 Hz, 7.1 Hz, 1.1 Hz, 1H), 7.63 (dm, $J$ = 8.4 Hz, 1H), 7.82 (ddd, $J$ = 8.4 Hz, 7.1 Hz, 1.4 Hz, 1H), 8.09 (dd, $J$ = 8.1 Hz, 1.4 Hz, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75.5 MHz, 72 °C) $\delta$ 24.2 (t), 38.0 (t), 44.3 (t), 111.6 (d), 119.0 (s), 123.9 (s), 125.7 (d), 125.8 (d), 126.6 (d), 134.3 (d), 143.5 (s), 147.0 (s), 159.4 (s), 160.2 (s); mass-spectrum (EI), $m/z$ (relative intensity) 285 ($M^+$, 100), 256 (11), 252 (10), 224 (11), 211 (13), 202 (15), 130 (11), 119 (40), 102 (24), 76 (24), 51 (33); exact mass calcd for $C_{14}H_{11}N_3O_2S$ $m/z$ 285.0572, found $m/z$ 285.0569. Anal. Calcd for $C_{14}H_{11}N_3O_2S$: C, 58.99; H, 3.89. Found: C, 58.82, 58.72; H, 3.91, 3.92.

**(±)-3,4-Dihydro-7-(indol-3-ylmethyl)-9*H*-[1,4]thiazino-[3′,4′:3,4]pyrazino[2,1-*b*]quinazoline-6,9(7*H*)-dione (26).** A 100-mL flame-dried, two-necked, round-bottomed flask equipped with a magnetic stirring bar, solid compound addition funnel fitted with gramine methosulfate, and a wired septum was charged with a suspension of 160 mg (0.56 mmol) of heterocycle **25** in 25 mL of dry THF. To this suspension, cooled to −78 °C, was added a solution of 1.12 mmol of LDA (freshly prepared by dropwise addition of 0.95 mL (1.23 mmol) of a 1.6 M solution of *n*-BuLi in hexanes to a solution of 157 $\mu$L (1.12 mmol) of *i*-$Pr_2NEt$ in 10 mL of dry THF at −78 °C over a period of 3 min) via a cannula over a period of 5 min at −78 °C under an argon atmosphere. The deep red reaction mixture was stirred at dry ice bath temperature for 50 min and 0.56 mL (0.056 mmol) of 0.1 M solution of $Li_2CuCl_4$ in THF was added via cannula followed by addition of 0.20 g (0.67 mmol) of solid gramine methosulfate. The reaction mixture was stirred at dry ice bath temperature for 30 min and left to warm to room temperature. Then 5 mL of water was added to the reaction mixture, and it was concentrated in vacuo to a volume of 5−8 mL. The residue was partitioned between 100 mL of EtOAc and 40 mL of 1 N HCl. The organic layer was separated, washed with 40 mL of water, dried ($MgSO_4$), and concentrated in vacuo to give 250 mg of yellow foam. The foam was flash chromatographed over 40 g of silica gel (EtOAc:hexanes, 1:1) to provide 151 mg (65%) of compound **26** as an off-white foam. An analytically pure sample was obtained as a white crystalline solid after recrystallization from chloroform/hexane: mp 227.5−228.5 °C ($CHCl_3$/hexane); IR (KBr) 3306, 3061, 2990, 2925, 1682, 1659, 1607, 1572, 1550, 1473, 1406 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.25 (ddd, $J$ = 13.2 Hz, 11.5 Hz, 3.0 Hz, 1H), 2.42 (dddd, $J$ = 13.2 Hz, 3.4 Hz, 2.1 Hz, 1.9 Hz, 1H), 2.65 (ddd, $J$ = 13.4 Hz, 11.5 Hz, 2.1 Hz, 1H), 3.43 (dd, $J$ = 15.0 Hz, 4.3 Hz, 1H), 3.71 (dd, $J$ = 15.0 Hz, 3.2 Hz, 1H), 4.85 (ddd, $J$ = 13.4 Hz, 3.4 Hz, 3.0 Hz, 1H), 5.86 (dd, $J$ = 4.3 Hz, 3.2 Hz, 1H), 6.35 (d, $J$ = 2.4 Hz, 1H), 6.75 (d, $J$ = 1.9 Hz, 1H), 7.04 (ddd, $J$ = 8.0 Hz, 7.1 Hz, 1.0 Hz, 1H), 7.18 (ddd, $J$ = 8.0 Hz, 7.1 Hz, 1.1 Hz, 1H), 7.30 (dm, $J$ = 8.0 Hz, 1H), 7.42 (dm, $J$ = 8.0 Hz, 1H), 7.47 (ddd, $J$ = 8.1 Hz, 7.1 Hz, 1.2 Hz, 1H), 7.60 (dm, $J$ = 8.3 Hz, 1H), 7.56 (ddd, $J$ = 8.3 Hz, 7.1 Hz, 1.6 Hz, 1H), 8.05 (bs, 1H), 8.33 (ddd, $J$ = 8.1 Hz, 1.6 Hz, 0.5 Hz, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75.5 MHz) $\delta$ 22.8 (t), 27.3 (t), 37.5 (t), 55.5 (d), 106.4 (s), 110.3 (d), 111.5 (d), 117.6 (d), 118.4 (d), 119.3 (s), 121.0 (d), 122.6 (s), 124.9 (d), 126.0 (d), 126.3 (d), 126.8 (d), 127.4 (s), 134.7 (d), 136.0 (s), 144.1 (s), 147.2 (s), 159.6 (s), 162.6 (s); mass-spectrum (EI), $m/z$ (relative intensity) 414 ($M^+$, 14), 285 (23), 245 (11), 170 (7), 131 (10), 130 (100), 129 (8), 103 (6), 77 (5); exact mass calcd for $C_{23}H_{18}N_4O_2S$ $m/z$ 414.1150, found $m/z$ 414.1148. Anal. Calcd for $C_{23}H_{18}N_4O_2S$: C, 66.71; H, 4.38. Found: C, 66.43; H, 4.34.

**(±)-(1*R**,6*S**,13b*S**)-2,3-Dihydro-6-(indol-3-ylmethyl)-13b-methylthiazolo[2′,3′:3,4]pyrazino[2,1-*b*]quinazoline-5,8(6*H*,13b*H*)-dione, 1-Oxide (27).** To a solution of 208 mg (0.5 mmol) of **19** in 60 mL of EtOAc and 10 mL of DMF, cooled to −78 °C, was added dropwise a solution of 98 mg (0.5 mmol) of 80% MCPBA in 5 mL of EtOAc over a period of 5 min. The

reaction mixture was stirred at bath temperature until the starting material was completely consumed (30 min) as determined by TLC (EtOAc, silica gel). The reaction mixture was washed sequentially with saturated aqueous $Na_2SO_3$ (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and four 15-mL portions of water, dried ($MgSO_4$), and concentrated in vacuo to provide 205 mg (95%) of **27** as a white crystalline solid, of sufficient purity for further transformation: mp 169−170 °C decomposition ($CHCl_3$/hexane); IR (KBr) 3257, 1659, 1592, 1407, 1044, 748 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.35 (s, 3H), 2.83−2.93 (m, 2H), 3.25 (ddd, $J$ = 13.1 Hz, 7.8 Hz, 5.8 Hz, 1H), 3.83 (dd, $J$ = 15.1 Hz, 4.9 Hz, 1H), 4.73 (dd, $J$ = 15.1 Hz, 2.9 Hz, 1H), 5.05 (ddd, $J$ = 13.1 Hz, 8.6 Hz, 7.4 Hz, 1H), 5.69 (dd, $J$ = 4.9 Hz, 2.9 Hz, 1H), 6.60 (d, $J$ = 2.3 Hz, 1H), 6.99 (tm, $J$ = 8.0 Hz, 1H); 7.13 (tm, $J$ = 8.0 Hz, 1H), 7.27 (d, $J$ = 8.0 Hz, 1H), 7.42 (d, $J$ = 8.0 Hz, 1H), 7.56 (ddd, $J$ = 7.9 Hz, 7.1 Hz, 1.1 Hz, 1H), 7.66 (ddd, $J$ = 8.2 Hz, 1.1 Hz, 0.6 Hz, 1H), 7.79 (ddd, $J$ = 8.2 Hz, 7.1 Hz, 1.6 Hz, 1H), 8.04 (bs, 1H), 8.37 (ddd, $J$ = 7.9 Hz, 1.6 Hz, 0.6 Hz, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75.5 MHz) 18.7 (q), 27.5 (t), 43.1 (t), 45.8 (t), 56.9 (d), 86.8 (s), 106.7 (s), 111.6 (d), 117.7 (d), 118.8 (d), 119.7 (s), 121.4 (d), 124.8 (d), 126.5 (d), 126.9 (d), 127.5 (s), 127.8 (d), 135.3 (s), 135.9 (d), 146.4 (s), 148.3 (s), 159.4 (s), 164.5 (s); mass-spectrum (EI), *m/z* (relative intensity) 432 ($M^+$, 0.1), 414 (1), 285 (6), 169 (13), 162 (8), 130 (100), 113 (9), 103 (8), 100 (12), 77 (21); mass-spectrum (FAB), 433 ($M + 1^+$); exact mass calcd for $C_{23}H_{20}N_4O_3S$ *m/z* 432.1256, found *m/z* 432.1228.

**(±)-(2*R**,7*R**,14b*S**)-3,4-Dihydro-7-(indol-3-ylmethyl)-1*H*-[1,4]thiazino[3′,4′:3,4]-pyrazino[2,1-*b*]quinazoline-6,9(7*H*,14b*H*)-dione 2-oxide (28); (±)-(6*R**,14*S**) −14,15-Dihydro-12*H*-17,6-(ethanothiomethano)-6,14-(iminomethano)-5*H*-indolo[2′,3:4,5]azepino-[2,1-*b*]quinazoline-12,16-dione (29); (±)-(11*R**,18b*R**,18c*S**)-7,8-Dihydro-18b-methyl-11,18c-methano-18c*H*-indolo-[3″,2″:6′,7′][1,4]-thiazepino[5′,4′:3,4]pyrazino[2,1-*b*]quinazoline-10,13(11*H*,-18b*H*)-dione (30); (±)-7,8,18,19-Tetrahydro-10-methylene-9,18-methano-5*H*,9*H*-indolo[3′,2′:10,11[1,4,7]thiadiaza-cycloundecino[6,7-*b*]quinazoline-16,20(10*H*)-dione (31).** To a solution of 432 mg of sulfoxide **27** in 125 mL of ethanol-free $CHCl_3$ was added 12.5 mL of $CF_3COOH$. The reaction mixture was refluxed for 48 h, diluted with 100 mL of $CH_2Cl_2$, cooled in an ice−water bath, and quenched with 150 mL of saturated aqueous $NaHCO_3$. The organic solution was separated, and the aqueous phase was extracted with four 50-mL portions of $CH_2Cl_2$. The combined organic solutions were dried ($MgSO_4$) and concentrated in vacuo to provide 433 mg of light brown foam. Chromatographic separation over 100 g of flash silica gel (gradient elution with EtOAc:hexane, 2:1, followed by neat EtOAc) provided 153 mg (37%) of **29** followed by a more polar mixture of **30** and **31**. Careful separation of the mixture of **30** and **31** by preparative TLC (EtOAc, silica gel) gave 88 mg (21%) of bridged indole **31** and 104 mg (25%) of spiroindoline **30**. Compound **29**: mp >300 °C (DMF/$H_2O$); IR (KBr) 3446, 3250, 3060, 2974, 2900, 1681, 1657, 1618, 1606 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz) $\delta$ 2.75−2.90 (m, 2H), 3.22−3.44 (m, 2H), 3.41 (dd, $J$ = 17.6 Hz, 2.8 Hz, 1H), 3.93 (d, $J$ = 14.7 Hz, 1H), 4.09 (d, $J$ = 14.7 Hz, 1H), 4.35 (ddd, $J$ = 14.0 Hz, 4.8 Hz, 3.3 Hz, 1H), 5.83 (dd, $J$ = 4.1 Hz, 2.8 Hz, 1H), 6.98 (t, $J$ = 7.8 Hz, 1H), 7.13 (tm, $J$ = 7.8 Hz, 1H), 7.37−7.41 (m, 2H), 7.51 (tm, $J$ = 8.0 Hz, 1H), 7.63 (d, $J$ = 7.9 Hz, 1H), 7.79 (tm, $J$ = 8.3 Hz, 1H), 8.12 (dd, $J$ = 8.0 Hz, 1.2 Hz, 1H), 11.31 (bs, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75.5 MHz) $\delta$ 24.6 (t), 26.0 (t), 26.8 (t), 37.6 (t), 52.9 (d), 59.4 (s), 106.6 (s), 111.7 (d), 118.3 (d), 119.4 (d), 120.1 (s), 122.6 (d), 126.3 (d), 127.0 (s), 127.4 (d), 127.4 (d), 130.7 (s), 134.9 (d), 135.2 (s), 146.5 (s), 152.2 (s), 159.0 (s), 168.2 (s); mass-spectrum (EI), *m/z* (relative intensity) 414 ($M^+$, 100), 327 (10), 313 (15), 312 (29), 298 (10), 287 (22), 286 (96), 285 (17), 269 (12), 267 (11), 255 (25), 241 (15), 231 (22), 219 (14), 217 (10), 181 (15), 169 (31), 151 (20), 102 (23), 77 (23); exact mass calcd for $C_{23}H_{18}N_4O_2S$ *m/z* 414.1150, found *m/z* 414.1131. Compound **30**: mp 245−7 °C (DMSO) decomp.; IR (KBr) 3041, 2937, 1704, 1622, 1609, 1470, 1386, 1378 $cm^{-1}$; $^1H$ NMR ($C_6D_6$, 300 MHz, 75 °C) $\delta$ 1.20 (s, 3H), 1.74 (dd, $J$ = 14.6 Hz, 3.5 Hz, 1H), 2.29 (dd, $J$ = 14.6 Hz, 2.1 Hz, 1H), 2.28−2.38 (m, 1H), 2.64−2.76 (m, 2H), 4.33−4.43 (m, 1H), 5.93 (dm, $J$ = 7.6 Hz, 1H), 6.06 (dd, $J$ = 3.5 Hz, 2.1 Hz, 1H), 6.51 (ddd, $J$ = 7.6 Hz, 7.6 Hz, 1.1 Hz, 1H), 6.89 (ddd, $J$ = 7.6 Hz, 7.6 Hz, 1.2 Hz, 1H), 7.09 (ddd, $J$ = 7.8 Hz, 7.3 Hz, 1.3 Hz, 1H), 7.29 (ddd, $J$ = 8.2 Hz, 7.3 Hz, 1.6 Hz, 1H), 7.41 (dm, $J$ = 7.6 Hz, 1H), 7.58 (ddd, $J$ = 8.2 Hz, 1.3 Hz, 0.5 Hz, 1H), 8.41 (ddd, $J$ = 7.8 Hz, 1.6 Hz, 0.5 Hz, 1H); $^{13}C$ NMR ($C_6D_6$, 75.5 MHz, 75 °C) $\delta$ 13.3 (q), 30.7 (t), 34.9 (t), 42.4 (t), 52.6 (d), 64.3 (s), 68.7 (s), 121.7 (d), 122.0 (d), 122.2 (s), 127.2 (d), 129.6 (d), 134.8 (d), 140.4 (s), 148.0 (s), 152.8 (s), 155.9 (s), 158.7 (s), 169.5 (s), 181.7 (s), three doublets were not detected due to overlap with solvent peaks; mass-spectrum (EI), *m/z* (relative intensity) 414 ($M^+$, 57), 312 (18), 286 (7), 272 (7), 271 (34), 267 (5), 254 (19), 253 (100), 231 (13), 226 (5), 224 (24), 219 (10), 212 (6), 198 (21), 197 (49), 188 (31), 184 (11), 181 (16), 174 (12), 173 (15), 171 (11), 170 (22), 169 (19), 162 (20), 161 (70), 160 (43), 155 (19), 154 (11), 151 (12), 143 (10), 142 (22), 131 (46), 130 (70), 129 (30), 128 (27), 117 (78), 102 (58), 76 (42); exact mass calcd for $C_{23}H_{18}N_4O_2S$ *m/z* 414.1150, found *m/z* 414.1167. Compound **31**: mp 252−253 °C (benzene); IR (KBr) 3312, 3031, 2932, 1668, 1619, 1560, 1404 $cm^{-1}$; $^1H$ NMR (MeCN-$d^3$, 300 MHz) $\delta$ 3.00 (ddd, $J$ = 14.9 Hz, 4.6 Hz, 0.6 Hz, 1H), 3.50−3.59 (m, 2H), 3.75−3.85 (m, 2H), 4.67 (d, $J$ = 1.6 Hz, 1H), 5.15 (ddd, $J$ = 13.5 Hz, 13.5 Hz, 5.4 Hz, 1H), 5.23 (d, $J$ = 1.6 Hz, 1H), 5.58 (dd, $J$ = 5.4 Hz, 1.8 Hz, 1H), 6.29 (tm, $J$ = 8.0 Hz, 1H), 6.63 (d, $J$ = 8.0 Hz, 1H), 6.86 (ddd, $J$ = 8.2 Hz, 7.2 Hz, 1.0 Hz, 1H), 7.20 (d, $J$ = 8.2 Hz, 1H), 7.31 (d, $J$ = 8.2 Hz, 1H), 7.53 (ddd, $J$ = 8.1 Hz, 7.2 Hz, 1.1 Hz, 1H), 7.72 (ddd, $J$ = 8.2 Hz, 7.2 Hz, 1.5 Hz, 1H), 8.29 (dd, $J$ = 8.1 Hz, 1.5 Hz, 1H), 9.61 (bs, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75.5 MHz) $\delta$ 27.2 (t), 32.7 (t), 42.5 (t), 53.0 (d), 96.3 (t), 110.4 (d), 112.3 (s), 115.8 (d), 118.1 (d), 119.4 (s), 121.5 (d), 125.4 (d), 126.2 (d), 126.6 (d), 127.7 (s), 127.8 (s), 133.9 (d), 134.3 (s), 136.0 (s), 143.0 (s), 146.4 (s), 159.5 (s), 165.2 (s); mass-spectrum (EI), *m/z* (relative intensity) 415 ($M + 1^+$, 14), 414 ($M^+$, 45), 312 (18), 271 (40), 267 (18), 253 (100), 225 (37), 197 (30), 169 (22), 162 (15), 161 (15), 151 (19), 142 (18), 130(18), 129 (17), 119 (56), 117 (21), 113 (22), 111 (18), 100 (24), 77 (15), 51 (22), 41 (17); exact mass calcd for $C_{23}H_{18}N_4O_2S$ *m/z* 414.1150, found *m/z* 414.1144. When the reaction mixture was refluxed for a shorter time period, the highly polar sulfoxide **28** could be isolated by column chromatography (EtOAc:MeOH, 95:5). In one experiment, conducted on the same scale, after 40 h of reflux, 46 mg (11%) of **28** was isolated as a white crystalline solid: mp 203−4 °C (DMSO/$H_2O$); IR (KBr) 3348, 3413, 3056, 2936, 1657, 1594, 1475, 1416, 1337, 1165, 1038, 1013 $cm^{-1}$; $^1H$ NMR ($CD_2Cl_2$, 300 MHz) $\delta$ 0.02 (dd, $J$ = 13.7 Hz, 12.2 Hz, 1H), 1.17 (ddd, $J$ = 14.2 Hz, 13.0 Hz, 3.9 Hz, 1H), 2.38 (dddd, $J$ = 14.2 Hz, 2.5 Hz, 2.5 Hz, 2.5 Hz, 1H), 2.82 (ddd, $J$ = 13.7 H, 2.5 Hz, 2.5 Hz, 1H), 3.38 (m, 1H), 3.69 (dd, $J$ = 15.0 Hz, 4.1 Hz, 1H), 3.80 (dd, $J$ = 15.0 Hz, 3.1 Hz, 1H), 4.67 (dm, $J$ = 14.1 Hz, 1H), 5.08 (dd, $J$ = 11.9 Hz, 2.2 Hz, 1H), 5.54 (dd, $J$ = 4.1 Hz, 3.1 Hz, 1H), 6.46 (d, $J$ = 2.4 Hz, 1H), 7.05 (ddd, $J$ = 8.0 Hz, 7.0 Hz, 1.1 Hz, 1H), 7.17 (ddd, $J$ = 8.2 Hz, 7.0 Hz, 1.1 Hz, 1H), 7.35 (dm, $J$ = 8.2 Hz, 1H), 7.53−7.58 (m, 2H), 7.61 (dm, $J$ = 8.0 Hz, 1H), 7.82 (ddd, $J$ = 8.2 Hz, 7.2 Hz, 1.6 Hz, 1H), 8.31 (bs, 1H), 8.35 (ddd, $J$ = 8.2 Hz,1.6 Hz, 0.5 Hz, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75.5 MHz) $\delta$ 26.7 (t), 31.3 (t), 41.9 (t), 48.0 (t), 48.9 (d), 55.7 (d), 107.6 (s), 111.8 (d), 118.2 (d), 119.0 (d), 119.7 (s), 121.7 (d), 124.6 (d), 126.4 (d), 126.6 (d), 126.9 (d), 127.4 (s), 135.0 (d), 135.5 (s), 146.7 (s), 150.2 (s), 159.7 (s), 163.1 (s); mass-spectrum (EI), *m/z* (relative intensity) 432 ($M^+$, 2), 414 (8), 285 (13), 245 (7), 170 (6), 130 (100), 69 (3); exact mass calcd for $C_{23}H_{20}N_4O_3S$ *m/z* 432.1256, found *m/z* 432.1270; mass-spectrum (FAB), *m/z* 433 ($M + 1^+$).

**Sulfide 40.** A 500 mL flame-dried, three-necked, round-bottomed flask was fitted with a magnetic stirrer and three wire-bound septa, flushed with argon, and charged with 75 mL of freshly distilled THF and 0.80 mL (5.7 mmol) of freshly distilled *i*-$Pr_2NH$ via syringe. The resulting solution was cooled to −78 °C in a dry ice−acetone bath, and then 3.9 mL (6.3 mmol) of *n*-BuLi in hexanes was added via syringe over 10 min. The solution was stirred for 20 min, and then a solution of 0.82 g (2.9 mmol) of **14** in 75 mL of freshly distilled THF was cannulated into the cooled LDA solution over a period of 10 min under argon. The resulting deep orange solution was

permitted to stir for 40 min, and then 2.8 mL (2.8 mmol) of $Li_2CuCl_4$ (0.1 M solution in THF) was added via syringe over 5 min, followed by 0.50 mL (3.4 mmol) of *m*-methoxybenzyl bromide via syringe in one portion. The reaction was permitted to stir overnight at the cold bath temperature with gradual warming to room temperature. The dark mixture was then concentrated in vacuo to give a solid residue which was partitioned in 600 mL EtOAc−1 M HCl (2:1). The organic phase was washed with two 150-mL portions of water, and the combined washes were back-extracted with 200 mL of EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give a dark solid residue. The residue was chromatographed over 100 g of flash grade silica gel (EtOAc:hexanes, 3:2) to provide 546 mg (47%) of **40** as a white foam: IR (KBr) 2936, 1676, 1591, 1567, 1467, 1437 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.12 (s, 3H), 2.96−3.08 (m, 2H), 3.37 (dd, $J$ = 14.0, 3.4 Hz, 1H), 3.41−3.63 (m, 2H), 3.47 (s, 3H), 4.83 (ddd, $J$ = 12.5, 8.0. 4.4 Hz, 1H), 5.54 (dd, $J$ = 5.6, 4.4 Hz, 1H), 6.36 (s, 1H), 6.43 (d, $J$ = 12.8 Hz, 1H), 6.65 (d, $J$ = 8.0 Hz, 1H), 7.02 (t, $J$ = 8.0 Hz, 1H), 7.47 (t, $J$ = 7.2 Hz, 1H), 7.63 (d, $J$ = 8.0 Hz, 1H), 7.73 (t, $J$ = 6.4 Hz, 1H), 8.27 (d, $J$ = 8.0 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) $\delta$ 28.7 (t), 31.4 (q), 37.7 (t), 46.9 (t), 55.5 (q), 58.6 (d), 72.5 (s), 114.3 (d), 115.4 (d), 120.6 (s), 122.8 (d), 127.3 (d), 127.8 (d), 130.2 (d), 135.2 (d), 136.9 (s), 147.5 (s), 152.5 (s), 160.4 (s), 160.7 (s), 162.6 (s) one aromatic CH (possibly at $\delta$ 127.8) was not observed due to magnetic equivalence; mass-spectrum (EI), *m*/*z* (relative intensity) 407 ($M^+$, 100), 161 (56), 121 (53), 286 (33), 214 (29), 102 (24), 130 (23), 91 (20); exact mass calcd for $C_{22}H_{21}N_3O_3S$ *m*/*z* 407.1304, found *m*/*z* 407.1311.

**Sulfoxide 37.** A 250-mL, one-necked round-bottomed flask was fitted with a magnetic stirrer and charged with 400 mg (0.99 mmol) of **40** and 140 mL of $CH_2Cl_2$. The resultant solution was cooled to −78 °C in a dry ice−acetone bath, and then a solution of 300 mg (1.3 mmol) of MCPBA (80 wt %) in 10 mL of $CH_2Cl_2$ was added dropwise via syringe over 5 min. The reaction mixture was stirred for 45 min at the cold bath temperature and was then transferred to a separatory funnel and washed successively with 125 mL of saturated aqueous $Na_2SO_3$, 125 mL of saturated aqueous $NaHCO_3$, and 125 mL of water. The aqueous washes were back-extracted with $CH_2Cl_2$, and the organic extracts were combined, dried ($MgSO_4$), filtered, and evaporated to give a solid residue. This solid was chromatographed over flash grade silica gel (EtOAc:MeOH, 95:5) to give 375 mg (90%) of **37** as a white foam which could be used directly in the next step: mp 167−171 °C ($CH_2Cl_2$/hexanes); IR (KBr) 2948, 1682, 1660, 1589, 1560, 1489, 1470, 1453, 1404 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.75 (s, 3H), 2.98 (ddd, $J$ = 13.1, 9.2, 3.8 Hz, 1H), 3.08 (ddd, $J$ = 14.6, 9.8, 6.9 Hz, 1H), 3.43 (dd, $J$ = 14.1, 3.1 Hz, 1H), 3.50 (s, 3H), 3.59 (ddd, $J$ = 13.4, 9.5, 3.6 Hz, 1H), 3.65 (dd, $J$ = 14.1, 5.3 Hz, 1H), 5.10 (ddd, $J$ = 13.0, 9.2, 6.9 Hz, 1H), 5.67 (dd, $J$ = 5.2, 3.2 Hz, 1H), 6.36 (s, 1H), 6.46 (d, $J$ = 7.5 Hz, 1H), 6.74 (dd, $J$ = 8.1, 2.2 Hz, 1H), 7.09 (t, $J$ = 7.9 Hz, 1H), 7.56 (td, $J$ = 8.1, 1.0 Hz, 1H), 7.71 (d, $J$ = 8.1 Hz, 1H), 7.81 (td, $J$ = 8.4, 1.5 Hz, 1H), 8.36 (dd, $J$ = 8.0, 1.4 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) $\delta$ 20.9 (q), 37.6 (t), 44.0 (t), 47.1 (t), 55.5 (q), 58.0 (d), 87.5 (s), 114.4 (d), 115.4 (d), 120.7 (s), 122.8 (d), 127.4 (d), 127.8 (d), 128.2 (d), 130.3 (d), 135.4 (d), 136.6 (s), 147.3 (s), 147.9 (s), 160.4 (s), 160.6 (s), 165.1 (s); mass-spectrum (EI), *m*/*z* (relative intensity) 423 ($M^+$, 1), 245 (100), 405 (99), 161 (51), 121 (47), 91 (21), 284 (19), 212 (14); exact mass calcd for $C_{22}H_{21}N_3O_4S$ *m*/*z* 423.1253, found *m*/*z* 423.1267.

**Rearrangement Product 44.** A 100-mL round-bottomed flask was fitted with a reflux condenser and magnetic stirrer and charged with 100 mg (0.24 mmol) of **37**, 30 mL of $CHCl_3$, and 3 mL (39 mmol) of trifluoroacetic acid. The resulting burgundy-colored solution was heated at reflux for 48 h. The reaction mixture was then transferred to a separatory funnel and washed successively with two-50 mL portions of 1 M aqueous $Na_2CO_3$. The aqueous washes were back-extracted with $CHCl_3$, and the organic extracts were combined, dried ($MgSO_4$), filtered, and evaporated to give a white solid residue. The residue was chromatographed over 13 g of flash grade silica gel (EtOAc:hexanes, 3:2) to provide 68 mg (71%) of **44** as a white solid. The solid was recrystallized from $CH_2Cl_2$/hexanes: mp 146−149 °C; IR (KBr) 2923, 1670, 1602, 1548, 1472, 1405, 1331, 1263 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 2.88−2.97 (m, 3H), 3.27−3.28 (m, 2H), 3.55 (s, 3H), 5.17 (ddd, $J$ = 14, 8.0, 3.3 Hz, 1H), 5.79 (dd, $J$ = 3.2, 3.2 Hz, 1H), 6.32 (m, 2H), 6.77 (dd, $J$ = 7.7, 2.5 Hz, 1H), 6.86 (d, $J$ = 1.0 Hz, 1H), 7.05 (t, $J$ = 8.1 Hz, 1H), 7.48 (td, $J$ = 8.1, 1.1 Hz, 1H), 7.61 (d, $J$ = 8.1 Hz, 1H), 7.75 (td, $J$ = 8.4, 1.6 Hz, 1H), 8.30 (dd, $J$ = 8.0, 1.3 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) $\delta$ 25.2 (t), 38.2 (t), 38.3 (t), 55.5 (q), 56.4 (d), 113.1 (d), 113.4 (d), 116.2 (d), 120.0 (s), 122.7 (d), 123.5 (s), 126.9 (d), 127.3 (d), 127.6 (d), 130.1 (d), 135.3 (d), 135.8 (s), 144.8 (s), 147.9 (s), 159.9 (s), 160.7 (s), 163.6 (s); mass-spectrum (HREI), *m*/*z* (relative intensity) 405 ($M^+$, 60), 245 (100), 161 (22), 121 (19), 69 (24); exact mass calcd for $C_{22}H_{19}N_3O_3S$ *m*/*z* 405.1147, found *m*/*z* 405.1155.

**Furan 41.** A 1-L flame-dried, three-necked, round-bottomed flask was fitted with a magnetic stirrer and three wire-bound septa, flushed with argon, and charged with 175 mL of freshly distilled THF and 1.95 mL (14 mmol) of freshly distilled *i*-$Pr_2$-NH via syringe. The resulting solution was cooled to −78 °C in a dry ice-acetone bath and then 9.6 mL (15.4 mmol) of *n*-BuLi in hexanes was added via syringe over 2−3 min. The solution was stirred for 15 min and then a solution of 2.0 g (7.0 mmol) of **14** in 175 mL of freshly distilled THF was cannulated into the cooled LDA solution over a period of 10 min under argon. The resulting deep orange solution was permitted to stir for 40 min, and then 7.0 mL (0.7 mmol) of $Li_2CuCl_4$ (0.1 M solution in THF) was added via syringe over 2−3 min, followed by 1.4 g (8.4 mmol) of 3-(bromomethyl)furan via syringe in one portion. The reaction was permitted to stir for 90 min at the cold bath temperature. The dark mixture was then concentrated in vacuo to give a solid residue which was partitioned in 700 mL EtOAc−1 M HCl (3:4). The organic phase was washed with 200 mL of water, and the combined washes were back-extracted with 150 mL of EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give a dark solid residue. The residue was chromatographed over 110 g of flash grade silica gel (hexanes: EtOAc, 2:1) to provide 1.24 g (49%) of **41** as a white foam (trace impurities by $^1H$ NMR; used in next step): IR (KBr) 2944, 1682, 1592, 1567, 1468, 1442, 1400 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.53 (s, 3H), 3.08 (ddd, $J$ = 10.6, 7.8, 7.8 Hz, 1H), 3.16 (ddd, $J$ = 10.8, 7.9, 4.4 Hz, 1H), 3.27 (dd, $J$ = 14.9, 3.4 Hz, 1H), 3.45 (dd, $J$ = 14.9, 5.9 Hz, 1H), 3.56 (ddd, $J$ = 12.6, 7.7, 7.7 Hz, 1H), 4.89 (ddd, $J$ = 12.5, 8.1, 4.4 Hz, 1H), 5.50 (dd, $J$ = 5.9, 3.5 Hz, 1H), 6.02 (s, 1H), 7.09 (s, 1H), 7.26 (d, $J$ = 1.9 Hz, 1H), 7.52 (td, $J$ = 7.8, 1.0 Hz, 1H), 7.71 (d, $J$ = 7.9 Hz, 1H), 7.79 (td, $J$ = 8.3, 1.4 Hz, 1H), 8.30 (dd, $J$ = 8.0, 1.4 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) $\delta$ 27.5 (t), 28.8 (t), 31.9 (q), 47.1(t), 58.0 (d), 72.5 (s), 112.5 (d), 118.7 (s), 120.5 (s), 127.2 (d), 127.7 (d), 127.8 (d), 135.3 (d), 141.2 (d), 143.6 (d), 147.5 (s), 152.4 (s), 160.7 (s), 162.8 (s); mass-spectrum (EI), *m*/*z* (relative intensity) 367 ($M^+$, 33), 121 (24), 81 (22), 61 (23), 43 (100); exact mass calcd for $C_{19}H_{17}N_3O_3S$ *m*/*z* 367.0991, found *m*/*z* 367.0970.

**Sulfoxide 38.** A 100-mL, one-necked, round-bottomed flask was fitted with a magnetic stirrer and charged with 1.22 g (3.3 mmol) of **41** and 50 mL of $CH_2Cl_2$. The resultant solution was cooled to −78 °C in a dry ice−acetone bath, and then 990 mg (4 mmol) of MCPBA (70 wt %) in 10 mL of $CH_2Cl_2$ was added dropwise via syringe over 2−3 min. The reaction mixture was stirred for 90 min at the cold bath temperature and was then transferred to a separatory funnel and washed successively with 75 mL of saturated aqueous $Na_2SO_3$, 75 mL of saturated aqueous $NaHCO_3$, and 75 mL of water. The aqueous washes were back-extracted with $CH_2Cl_2$, and the organic extracts were combined, dried ($MgSO_4$), filtered, and evaporated to give 1.19 g (94%) of **38** as an amorphous solid residue which could be used directly in the next step without further purification. The solid was recrystallized from $CH_2Cl_2$/hexanes: mp 186−187 °C; IR (KBr) 2987, 1686, 1591, 1565, 1475, 1440, 1402 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.14 (s, 3H), 3.01 (ddd, $J$ = 13.2, 9.3, 3.8 Hz, 1H), 3.14 (ddd, $J$ = 14.5, 9.8, 6.8 Hz, 1H), 3.30 (dd, $J$ = 14.9, 3.0 Hz, 1H), 3.53 (dd, $J$ =

14.9, 5.0 Hz, 1H), 3.66 (ddd, $J$ = 13.3, 9.9, 3.7 Hz, 1H), 5.11 (ddd, $J$ = 12.9, 9.2, 6.8 Hz, 1H), 5.58 (dd, $J$ = 5.0, 3.2 Hz, 1H), 5.96 (s, 1H), 7.06 (s, 1H), 7.28 (s, 1H), 7.55 (t, $J$ = 7.8 Hz, 1H), 7.72 (d, $J$ = 8.1 Hz, 1H), 7.81 (td, $J$ = 8.3, 1.3 Hz, 1H), 8.32 (dd, $J$ = 8.0, 1.3 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 100.6 MHz) $\delta$ 21.2 (q), 27.4 (t), 44.1 (t), 47.2 (t), 57.6 (d), 87.6 (s), 112.7 (d), 118.4 (s), 120.7 (s), 127.3 (d), 128.0 (d), 128.2 (d), 135.4 (d), 141.3 (d), 143.6 (d), 147.3 (s), 147.8 (s), 160.5 (s), 165.3 (s); mass-spectrum (EI), $m/z$ (relative intensity) 383 ($M^+$, 1), 365 (89), 246 (29), 245 (100), 121 (43), 81 (35); exact mass calcd for $C_{19}H_{17}N_3O_4S$ $m/z$ 383.0940, found $m/z$ 383.0947.

**Rearrangement Products 45 and 46.** A 250 mL round-bottomed flask was fitted with a reflux condenser and magnetic stirrer and charged with 680 mg (1.8 mmol) of **38**, 90 mL of $CHCl_3$, and 10 mL (130 mmol) of trifluoroacetic acid. The resulting rose-colored solution was heated at reflux for 18 h. The reaction mixture was then transferred to a separatory funnel and washed successively with two 125 mL portions of 1 M $Na_2CO_3$ and 75 mL of water. The aqueous washes were back-extracted with $CHCl_3$, and the organic extracts were combined, dried ($MgSO_4$), filtered, and evaporated to give an amorphous solid residue. The residue was chromatographed using MPLC over silica gel (hexanes:EtOAc, 4:3). The title compounds were inseparable by these means, and chromatography fractions containing both compounds were pooled and concentrated in vacuo to give a white foam. High purity **45** (210 mg, 32%) was obtained via fractional recrystallization of the foam from EtOAc/hexanes, leaving the mother liquor highly enriched in **46**. The mother liquor was concentrated to give a solid residue which was recrystallized from EtOAc/hexanes to give 100 mg (15%) of **46**. Spectral data for **45**: mp 189−192 °C (EtOAc/hexanes); IR (KBr) 3140, 3059, 2933, 1664, 1606, 1572, 1552, 1503, 1471, 1400 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.94 (ddd, $J$ = 13.2, 10.8, 3.0 Hz, 1H), 3.01−3.05 (m, 1H), 3.07 (ddd, $J$ = 13.1, 11.1, 2.2 Hz, 1H), 3.20 (dd, $J$ = 14.3, 3.5 Hz, 1H), 3.25 (dd, $J$ = 14.8, 4.5 Hz, 1H), 5.18 (ddd, $J$ = 13.2, 3.2, 3.2 Hz, 1H), 5.72 (dd, $J$ = 4.3, 4.3 Hz, 1H), 5.99 (s, 1H), 6.90 (s, 1H), 7.12 (d, $J$ = 1.6 Hz, 1H), 7.29 (dd, $J$ = 1.6, 1.6 Hz, 1H), 7.47 (td, $J$ = 7.2, 0.8 Hz, 1H), 7.65 (d, $J$ = 8.1 Hz, 1H), 7.77 (td, $J$ = 8.0, 1.6 Hz, 1H), 8.28 (dd, $J$ = 7.9, 1.4 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 100.6 MHz) $\delta$ 25.4 (t), 28.2 (t), 38.5 (t), 55.9 (d), 112.0 (d), 113.1 (d), 117.6 (s), 120.1 (s), 123.8 (s), 127.0 (d), 127.3 (d), 127.8 (d), 135.3 (d), 141.5 (d), 144.0 (d), 144.5 (s), 148.0 (s), 160.7 (s), 163.7 (s); mass-spectrum (HREI), $m/z$ (relative intensity) 365 ($M^+$, 63), 246 (17), 245 (100), 121 (24), 81 (18); exact mass calcd for $C_{19}H_{15}N_3O_3S$ $m/z$ 365.0834, found $m/z$ 365.0853. Spectral data for **46**: mp 249−251 °C (EtOAc/hexanes); IR (KBr) 3129, 2924, 1682, 1615, 1564, 1462, 1436, 1414, 1381 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.82 (td, $J$ = 12.1, 5.6 Hz, 1H), 2.91 (dm, $J$ = 12.4 Hz, 1H), 3.08 (dd, $J$ = 17.6, 4.4 Hz, 1H), 3.24−3.32 (m, 1H), 3.28 (dd, $J$ = 17.6, 2.8 Hz, 1H), 3.90 (d, $J$ = 14.9 Hz, 1H), 3.97 (d, $J$ = 14.9 Hz, 1H), 4.50 (ddd, $J$ = 14.1, 5.5, 2.7 Hz, 1H), 5.99 (dd, $J$ = 4.3, 2.8 Hz, 1H), 6.22 (d, $J$ = 1.8 Hz, 1H), 7.34 (d, $J$ = 1.8 Hz, 1H), 7.49 (td, $J$ = 8.0, 0.9 Hz, 1H), 7.69 (d, $J$ = 8.2 Hz, 1H), 7.75 (td, $J$ = 8.4, 1.4 Hz, 1H), 8.28 (dd, $J$ = 8.4, 1.8 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 100.6 MHz) $\delta$ 25.5 (t), 26.0 (t), 28.0 (t), 38.2 (t), 54.1 (d), 59.8 (s), 112.6 (d), 117.5 (s), 121.3 (s), 127.3 (d), 127.9 (d), 128.4 (d), 135.1 (d), 143.1 (d), 146.9 (s), 147.4 (s), 152.1 (s), 160.5 (s), 169.4 (s); mass-spectrum (HREI), $m/z$ (relative intensity) 365 ($M^+$, 73), 332 (11), 263 (12), 237 (100); exact mass calcd for $C_{19}H_{15}N_3O_3S$ $m/z$ 365.0834, found $m/z$ 365.0848.

***N*-Boc Indole 42.** A 250 mL flame-dried, three-necked, round-bottomed flask was fitted with a magnetic stirrer and three wire-bound septa, flushed with argon, and charged with 70 mL of freshly distilled THF and 725 $\mu$L (5.2 mmol) of freshly distilled *i*-$Pr_2NH$ via syringe. The resulting solution was cooled to −78 °C in a dry ice−acetone bath, and then 3.6 mL (5.8 mmol) of 1.6 M *n*-BuLi in hexanes was added via syringe over 3−4 min. The solution was stirred for 15 min, followed by addition of 742 mg (2.6 mmol) of **14** in 75 mL of freshly distilled THF via cannula over a period of 10 min. The resulting deep orange solution was permitted to stir for 40 min, and then 2.6 mL (0.26 mmol) of $Li_2CuCl_4$ (0.1 M solution in THF) was added via syringe over 2−3 min, followed by 950 mg (3.1 mmol) of *N*-Boc-2-bromomethylindole in 8 mL of freshly distilled THF via syringe in one portion. The reaction was permitted to stir for 2 h at the cold bath temperature. The dark mixture was then concentrated in vacuo to give a solid residue which was partitioned in 450 mL EtOAc−1 M HCl (2:1). The organic phase was washed with two 100-mL portions of water, and the combined aqueous phases were back-extracted with 75 mL of EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give a dark solid residue. The residue was chromatographed over 50 g of flash grade silica gel (hexanes:EtOAc, 2:1) to provide 760 mg (57%) of **42** as a yellow solid which was used in the next step without further purification. The solid was recrystallized from $CH_2Cl_2$−hexanes: mp 194−195 °C; IR (KBr) 3068, 2978, 1732, 1593, 1567, 1475, 1451, 1405 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.57 (s, 9H), 1.95 (s, 3H), 3.10 (ddd, $J$ = 10.9, 7.8, 6.9 Hz, 1H), 3.21 (ddd, $J$ = 11.0 7.7, 5.3 Hz, 1H), 3.60−3.69 (m, 2H), 4.18 (dd, $J$ = 14.4, 6.7 Hz, 1H), 4.74 (ddd, $J$ = 12.7, 7.9, 5.3 Hz, 1H), 5.81 (dd, $J$ = 6.7, 6.7 Hz, 1H), 6.46 (s, 1H), 7.14 (t, $J$ = 7.2 Hz, 1H), 7.22 (td, $J$ = 7.3, 1.2 Hz, 1H), 7.35 (d, $J$ = 7.4 Hz, 1H), 7.43 (td, $J$ = 6.8, 1.4 Hz, 1H), 7.69 (d, $J$ = 7.0 Hz, 1H), 7.73 (td, $J$ = 6.8, 1.4 Hz, 1H), 7.96 (d, $J$ = 8.3 Hz, 1H), 8.10 (d, $J$ = 7.6 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 100.6 MHz) $\delta$ 28.5 (q, 3C), 28.7 (t), 32.1 (q), 32.9 (t), 47.8 (t), 57.6 (d), 73.0 (s), 84.7 (s), 111.7 (d), 116.4 (d), 120.6 (d), 120.8 (s), 123.1 (d), 124.4 (d), 127.2 (d), 127.5 (d), 127.5 (d), 129.2 (s), 134.9 (d), 135.6 (s), 136.8 (s), 147.3 (s), 151.0 (s), 152.9 (s), 160.5 (s), 162.8 (s); mass-spectrum (EI), $m/z$ (relative intensity) 516 ($M^+$, 0.2), 416 (19), 130 (100), 55 (26), 41 (52); exact mass calcd for $C_{28}H_{28}N_4O_4S$ $m/z$ 516.1831, found $m/z$ 516.1842.

**Indole 43.** A 50-mL, one-necked, round-bottomed flask was charged with 460 mg (0.89 mmol) of **42**. The flask was heated to 200 °C in an oil bath for 1−2 min, during which time gas evolution began and then ceased. The heating gave 371 mg (100%) of **43** as a dark solid residue which could be used directly in the next step without further purification. The solid was recrystallized from $CH_2Cl_2$/hexanes: mp 265−267 °C; IR (KBr) 3285, 3087, 2948, 1682, 1649, 1594, 1568, 1469, 1401 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.45 (s, 3H), 3.10 (ddd, $J$ = 10.9, 8.0, 6.5 Hz, 1H), 3.19 (ddd, $J$ = 10.9, 7.7, 5.1 Hz, 1H), 3.53 (dd, $J$ = 15.0, 2.5 Hz, 1H), 3.67−3.74 (m, 2H), 4.76 (ddd, $J$ = 12.8, 8.0, 5.6 Hz, 1H), 5.58 (dd, $J$ = 6.1, 3.2 Hz, 1H), 6.16 (s, 1H), 7.04 (t, $J$ = 7.1 Hz, 1H), 7.13 (t, $J$ = 7.1 Hz, 1H), 7.31 (d, $J$ = 8.1 Hz, 1H), 7.44 (d, $J$ = 7.7 Hz, 1H), 7.55 (t, $J$ = 7.1 Hz, 1H), 7.73 (d, $J$ = 8.2 Hz, 1H), 7.82 (t, $J$ = 7.3 Hz, 1H), 8.34 (d, $J$ = 8.0 Hz, 1H), 8.71 (bs, 1H); $^{13}$C NMR ($CDCl_3$, 100.6 MHz) $\delta$ 28.5 (t), 32.3 (q), 32.4 (t), 47.8 (t), 57.7 (d), 72.8 (d), 103.5 (d), 111.2 (d), 120.3 (d), 120.6 (s), 120.7 (d), 122.4 (d), 127.3 (d), 127.9 (d), 127.9 (d), 128.7 (s), 132.8 (s), 135.5 (d), 136.9 (s), 147.5 (s), 152.2 (s), 160.8 (s), 163.3 (s); mass-spectrum (HREI), $m/z$ (relative intensity) 416 ($M^+$, 23), 414 (19), 170 (15), 130 (100), 103 (5); exact mass calcd for $C_{23}H_{20}N_4O_2S$ $m/z$ 416.1307, found $m/z$ 416.1304.

**Sulfoxide 39.** A 100-mL, one-necked round-bottomed flask was fitted with a magnetic stirrer and charged with 605 mg (1.5 mmol) of **43** and 40 mL of $CH_2Cl_2$. The resultant solution was cooled to −78 °C in a dry ice−acetone bath, and then 430 mg (1.7 mmol) of MCPBA (70 wt %) in 10 mL of $CH_2Cl_2$ was added dropwise via syringe over 2−3 min. The reaction mixture was stirred for 90 min at the cold bath temperature and was then transferred to a separatory funnel and washed successively with 75 mL of saturated aqueous $Na_2SO_3$, two 75-mL portions of saturated aqueous $NaHCO_3$, and 50 mL of water. The aqueous washes were back-extracted with $CH_2Cl_2$, and the organic extracts were combined, dried ($MgSO_4$), filtered, and evaporated to give 615 mg (98%) of sulfoxide **39** as an amorphous solid residue which could be used directly in the next step without further purification. The solid was recrystallized from $CH_2Cl_2$/hexanes: mp 173−190 °C; IR (KBr) 3310, 3055, 2939, 1681, 1594, 1567, 1470, 1456, 1403 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.76 (s, 3H), 2.98−3.03 (m, 2H), 3.59−3.66 (m, 2H), 3.81 (dd, $J$ = 15.2, 4.6 Hz, 1H), 5.05 (ddd, $J$ = 12.8, 8.8, 7.2 Hz, 1H), 5.63 (t, $J$ = 4.0 Hz, 1H), 5.98 (s, 1H), 7.02 (t, $J$ = 7.0 Hz, 1H), 7.10 (td, $J$ = 7.1, 1.0 Hz, 1H), 7.23 (d, $J$ = 8.1 Hz, 1H), 7.40 (d, $J$ = 7.8 Hz, 1H), 7.57 (td, $J$

= 8.0, 1.0 Hz, 1H), 7.72 (d, $J$ = 8.0 Hz, 1H), 7.83 (td, $J$ = 8.3, 1.5 Hz, 1H), 8.30 (bs, 1H), 8.34 (dd, $J$ = 8.0, 1.0 Hz, 1H); $^{13}$C NMR (DMSO-$d_6$, 100.6 MHz) $\delta$ 20.9 (q), 31.5 (t), 44.5 (t), 46.5 (t), 57.2 (d), 87.9 (s), 102.5 (d), 112.0 (d), 119.9 (d), 120.4 (d), 120.8 (s), 121.8 (d), 127.4 (d), 128.0 (d), 128.7 (d), 128.9 (s), 132.8 (s), 136.2 (d), 137.1 (s), 147.4 (s), 149.1 (s), 160.3 (s), 164.6 (s); mass-spectrum (EI), *m*/*z* (relative intensity) 432 ($M^+$, 0.4), 414 (19), 245 (22), 170 (24), 130 (100), 103 (6); exact mass calcd for $C_{23}H_{20}N_4O_3S$ *m*/*z* 432.1256, found *m*/*z* 432.1275.

**Rearrangement Product 47.** A 100-mL round-bottomed flask was fitted with a reflux condenser and magnetic stirrer and charged with 331 mg (0.78 mmol) of **39**, 50 mL of $CHCl_3$, and 5 mL (65 mmol) of trifluoroacetic acid. The resulting burgundy-colored solution was heated at reflux for 6 h and then stirred overnight at room temperature. The reaction mixture was then transferred to a separatory funnel and washed successively with two 75-mL portions of saturated aqueous $NaHCO_3$ and 50 mL of water. The aqueous washes were back-extracted with $CHCl_3$, and the organic extracts were combined, dried ($MgSO_4$), filtered, and evaporated to give a dark solid residue. The residue was chromatographed over 13 g of flash grade silica gel (hexanes:EtOAc, 2:1) to provide 155 mg (49%) of **47** as a yellow solid which was pure by $^1$H NMR. The solid was recrystallized from benzene: mp 250−252 °C; IR (KBr) 3311, 3062, 2934, 1691, 1662, 1619, 1577, 1560, 1472, 1452, 1401 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.89 (dd, $J$ = 14.7, 5.0 Hz, 1H), 3.47 (dd, $J$ = 14.2, 4.5 Hz, 1H), 3.58 (dd, $J$ = 14.9, 5.3 Hz, 1H), 3.66 (td, $J$ = 14.5, 4.7 Hz, 1H), 4.04 (dd, $J$ = 14.8, 1.7 Hz, 1H), 4.36 (s, 1H), 5.22−5.30 (m, 2H), 5.72 (d, $J$ = 3.1 Hz, 1H), 7.10−7.20 (m, 3H), 7.36 (t, $J$ = 7.5 Hz, 1H), 7.59 (d, $J$ = 8.4 Hz, 1H), 7.67 (d, $J$ = 7.0 Hz, 1H), 7.71 (t, $J$ = 7.2 Hz, 1H), 8.10 (d, $J$ = 8.0 Hz, 1H), 8.39 (bs, 1H); $^{13}$C NMR (DMSO-$d_6$, 100.6 MHz) $\delta$ 30.3 (t), 31.5 (t), 43.8 (t), 52.9 (d), 97.7 (t), 105.2 (s), 112.1 (d), 117.9 (d), 120.1 (d), 120.6 (s), 122.1 (d), 126.8 (d), 127.1 (d), 127.8 (d), 129.7 (s), 135.0 (d), 135.3 (s), 135.7 (s), 135.9 (s), 144.3 (s), 147.3 (s), 159.8 (s), 165.6 (s); mass-spectrum (HREI), *m*/*z* (relative intensity) 414 ($M^+$, 100), 188 (59), 253 (45), 271 (21), 312 (21); exact mass calcd for $C_{23}H_{18}N_4O_2S$ *m*/*z* 414.1150, found *m*/*z* 414.1149.

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**Supporting Information Available:** Experimental procedures not provided in the Experimental Section, $^1$H and $^{13}$C NMR spectra for most compounds, crystallographic data for **5**, **19**, **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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