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One-Pot Eschenmoser Episulfide Contractions in DMSO: Applications to the Synthesis of Fuligocandins A and B and a Number of Vinylogous Amides

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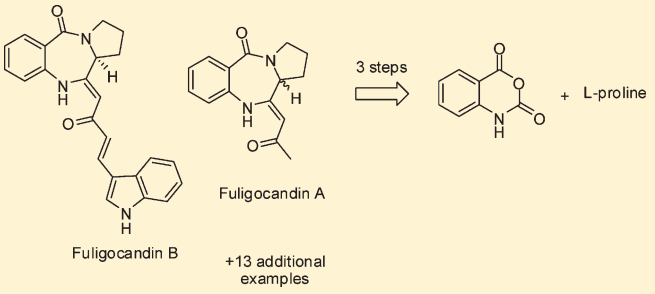
Supporting Information

ABSTRACT: Practical total syntheses of the natural products fuligocandin A (**2a**) and fuligocandin B (**3**) have been achieved through a convergent strategy depending on the Eschenmoser episulfide contraction as a key step. Conducting the reaction in DMSO proved to be an efficient and general method for the synthesis of a variety of vinylogous amides, such as azepan-2-ylidenepropan-2-one.



INTRODUCTION

In 2004, Nakatani et al. investigated an extract of the fruit bodies of the myxomycete *Fuligo candida* and isolated cycloanthraniloproline **1** and its derivatives **2a**, **3**, and **4** (Figure 1), whose structures where established largely by extensive NMR and MS studies.[1] Fuligocandin A (**2a**), obtained as colorless plates, was found to be the major constituent of the EtOAc-soluble fraction, while fuligocandin B (**3**) was isolated as a yellow pigment. A recent study has shown that fuligocandin B (**3**) sensitizes leukemia cells to apoptosis caused by a tumor necrosis factor-related apoptosis-inducing ligand (TRAIL).[2] Prompted by this interesting biological activity and our ongoing interest in cycloanthranilylproline-derived natural products we aimed at developing practical syntheses of both fuligocandin A and B.[3]

In addition to having the tricyclic cycloanthraniloproline core structure, both fuligocandin A and B contain a vinylogous amide function (Figure 1). Vinylogous amides are versatile reactants; i.e., they can act as ambient electrophiles but also as nucleophiles and are, furthermore, able to participate in pericyclic and radical processes, properties which endow them as valuable intermediates for synthesis of, e.g., natural products.[4] One particularly versatile and efficient method for preparation of vinylogous amides depends on alkylation of thioamides with an appropriate electrophilic reactant followed by extrusion of sulfur, resulting in a new carbon−carbon bond. Although the episulfide contraction was first studied by Knott,[5] it has emerged as an important carbon−carbon bond-forming process ever since the Eschenmoser−Woodward collaboration on vitamin B12, where it constituted one of the key coupling reactions.[6] This method, presently known as the Eschenmoser episulfide contraction,[7] has remained relatively unexplored although it has been applied to the synthesis of a number of natural products[8] and has been the subject of an excellent review by Shiosaki.[9]

There are two versions of the Eschenmoser episulfide contraction,[10] the first one depends on oxidative[6,11] and the second one on alkylative precoupling.[7] The latter variant (Scheme 1) begins by alkylation of thioamides (**I**) with enolizable α-halocarbonyl compounds (**II**), followed by 4 π-electrocyclic closure of the thiocarbonyl ylide (**III**) to the episulfide (**IV**), which upon thiophile-promoted extrusion of sulfur gives rise to vinylogous amides (**V**). This transformation is strongly dependent on the structural features of both the electrophilic and the nucleophilic partner. Substrates that undergo the episulfide contraction most readily are thioiminium salts obtainable from tertiary thioamides. On the other hand, secondary thiomidates often require harsher conditions, that is, stronger bases such as *tert*-butoxide, higher temperatures and longer reaction times.[12] The carbon−carbon bond formation occurs under mild conditions when a β-dicarbonyl halide is used (e.g., diethyl α-bromomalonate).[12] A problem that frequently encountered is reversibility of the thioamide alkylation, which occurs when the electrophile bears a nucleophilic leaving group, resulting in lower yields (<80%).[13] However, retro-alkylation can be avoided by employing an electrophile bearing a non-nucleophilic leaving group, such as triflate.[9]

RESULTS AND DISCUSSION

As the pyrrolo-1,4-benzodiazepine derivative **1** is readily prepared from proline and isatoic anhydride,[14] we considered it suitable as a common intermediate for synthesis of both fuligocandin A and B via Eschenmoser episulfide contraction. Success of this strategy

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will depend upon selective monothionation of cycloanthralinoproline **1** and for fuligocandin B also on a practical synthesis of the intermediate α-haloketone **9**.

As outlined in Scheme 2, en route to **3** via **9**, 1,3-dichloroacetone **5** was selectively combined with triphenylphosphine, and the resulting intermediate phosphonium salt was treated with a base to give the desired monoylide **6**.[15] Attempts to couple the aldehyde **7** with **6** failed even if the Wittig reaction was run in refluxing methanol for 5 days. This failure can be explained by delocalization of the nitrogen lone pair toward the carbonyl group, rendering it nonelectrophilic toward the ylide **6**. Hence, an electron-withdrawing protecting group was attached to the nitrogen atom in order to prevent the electron flow toward the formyl group. Accordingly, the aldehyde **7** was protected with benzenesulfonyl chloride to give **8a** and alternatively with *p*-nitrobenzenesulfonyl chloride (NsCl) to give **8b**. Both aldehydes (**8a** and **8b**) underwent a smooth Wittig reaction with the phosphorus ylide **6**, however, only when the reaction was conducted in refluxing methanol. Other solvents such as benzene, DMSO, H_2O, and DMF gave no reaction or poor yields of the required indole derivatives **9**. Attempts to obtain compound **11** by brominating the readily available molecule 3-(3-oxo-1-buteneyl)-indole (**10**)[16] with 2-pyrrolidone hydrotribromide failed since the bromination had a strong preference for the pyrrole moiety

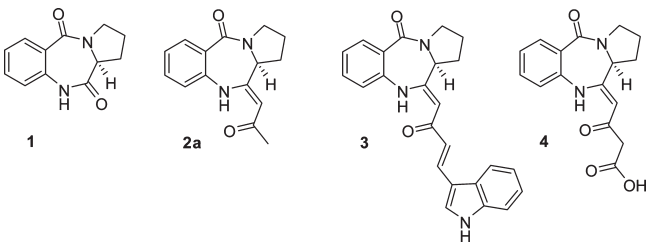
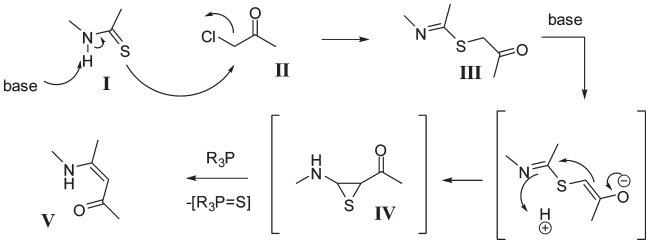


Figure 1. Alkaloids **1**−**4** isolated from *Fuligo candida*. Structures **2a** and **3** represent fuligocandin A and B, respectively.

Scheme 1. General Mechanism for the Episulfide Contraction Reaction via Alkylative Precoupling (R = Alkyl, Phenyl)

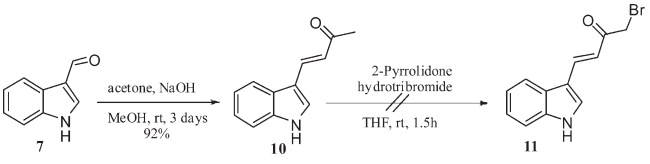


(Scheme 3). Interestingly, attempted Wittig coupling between **6** and *N*-*t*-BOC derivative of indole-3-carbaldehye **7** failed completely; instead, a rapid cleavage of the *N*-*t*-BOC group was observed.

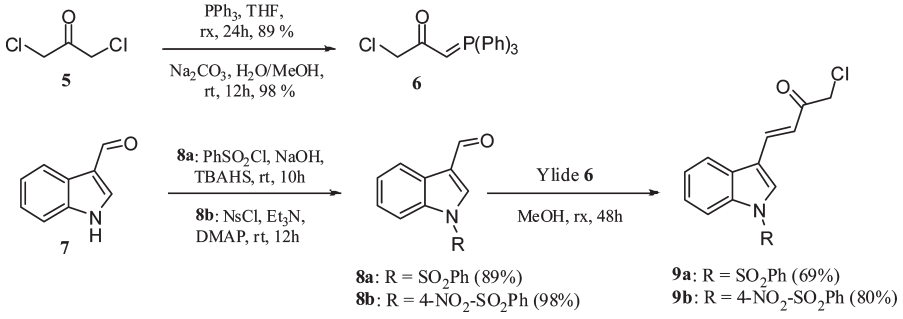
Next, the pyrrolo-1,4-benzodiazepine derivative **1** was readily prepared by heating isatoic anhydride and L-proline in DMSO.[14] Initial thionation attempts of **1** using literature methods proceeded in low yields due to poor selectivity. For example, when thionation was conducted using Lawesson's reagent in THF, xylene, or benzene, we encountered problems with either recovery of some unreacted diamide **1** or formation of the dithionated byproduct in all cases. This selectivity problem was finally solved by employing the P_2S_5−Py_2 complex (prepared by heating P_4S_{10} in pyridine)[21] to obtain the known monothione **12**[17] in 85% yield (Scheme 4).

With the monothione (**12**) in hand, we attempted to couple it with chloroacetone in order to obtain fuligocandin A (**2a**) via episulfide contraction. Initial attempts were based on previously described standard reagents and conditions such as *tert*-butoxide or triethylamine and triphenylphosphine in benzene or xylene at high temperatures. However, NMR analysis of the crude product mixtures indicated that the desired vinylogous amide was not formed since the spectra obtained lacked the characteristic ^1H signal at 5.29 ppm and the ^{13}C signal at 91.0 ppm. The failures to obtain fuligocandin A under these conditions led us to try the reaction in dimethyl sulfoxide as a solvent. We envisioned that dimethyl sulfoxide would facilitate not only the initial S_N2 alkylation but also the carbon−carbon bond formation by exposing the carbanion toward the electrophilic sp^2 carbon. Indeed, preliminary experiments on the alkylated intermediate **13** using DBU as a base gave the desired alkaloid **2a** in acceptable yield (40%). However, fuligocandin A was obtained in an excellent yield (98%) when DABCO was used as a base and trimethyl phosphite as sulfur scavenger. The unstable intermediate thioimidate **13** could be isolated, but the best results were obtained when it was used immediately in situ. The use of the relatively volatile trimethyl phosphite instead of more commonly used triethyl phosphite simplified the workup as it could be readily removed, along with its sulfur analogue (trimethyl thiophosphonate) by coevaporation with

Scheme 3. Attempted Synthesis of Compound 11



Scheme 2. Synthesis of the Indole Fragment of Fuligocandin B



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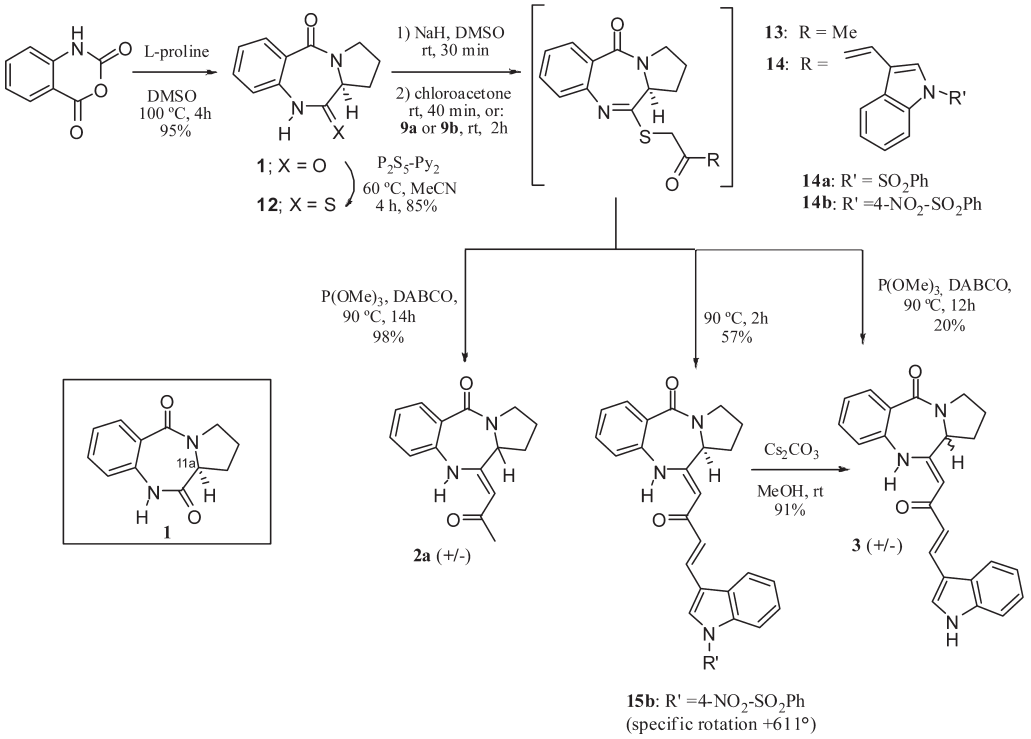
Scheme 4. Synthesis of Fuligocandins A and B



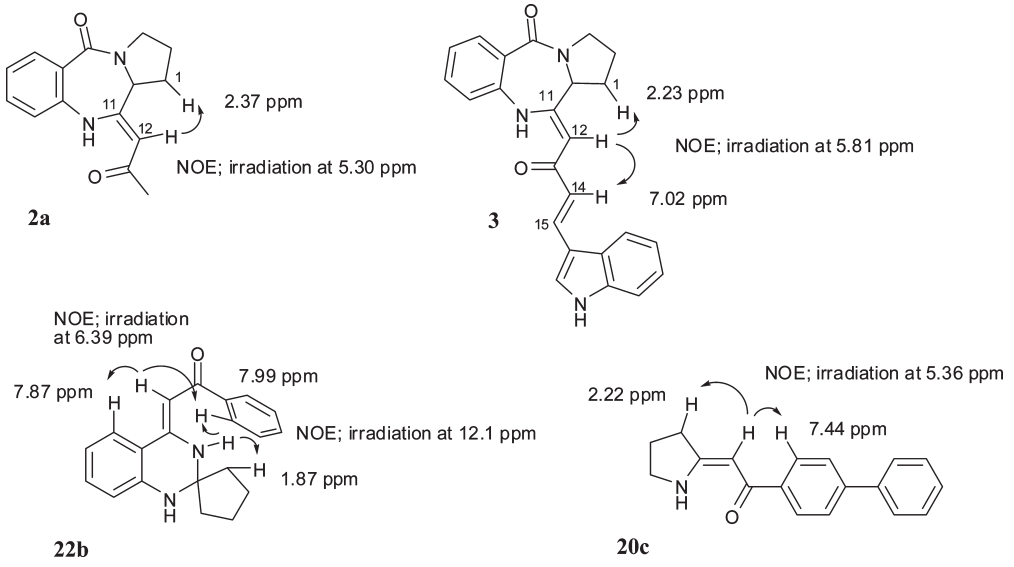


Figure 2. Nuclear Overhauser effect (NOE) correlations of **2a**, **3**, **20c**, **22b**.

ethanol. The resultant dark, semisolid residue was trituated with ethanol to induce precipitation of fuligocandin A as an off-white solid. Hence, a one-pot alkylation of the monothione **3** and subsequent sulfur extrusion gave fuligocandin A (**2a**) as the required *Z* isomer (Figure 2). This compound has recently been synthesized in six steps starting from azide derivatives by Satish et al.[18a] and by Ishibashi et al.[18b] using the Meyer−Schuster rearrangement; the Ishibashi group also obtained fuligocandin B.

Employing the convergent route, outlined in Scheme 4, we also obtained fuligocandin B (**3**) (as the required *Z*,*E*-isomer, Figure 2). Under the conditions employed (DABCO, $P(OMe)_3$, 90 °C) that successfully gave fuligocandin A, the indole *N*-protecting group was also removed; however, the racemic fuligocandin B was never isolated in more than 20% yield. Remarkably, TLC analysis during the alkylation step indicated that the episulfide contraction of the alkylated intermediate **14b** proceeded very rapidly in hot DMSO in the absence of both base and thiophile to give the *N*-protected fuligocandin B **15b** in 57% isolated yield. Likewise, contraction also proceeded thermally when **14a** was heated in DMSO, but the yield of **15a** was, however, slightly lower, i.e., 49%. To our knowledge, this is the

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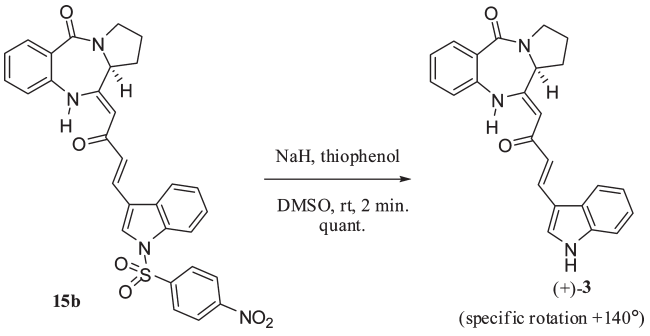
Scheme 5. N-Deprotection Employing Sodium Thiophenolate

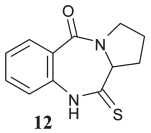
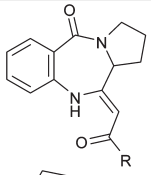
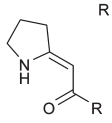
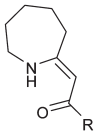
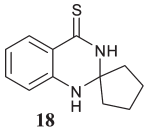
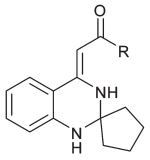
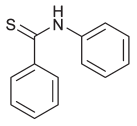
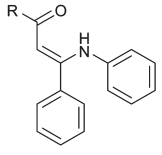


first example of a successful Eschenmoser episulfide contraction leading to vinylogous amides in the absence of both base and thiophile. After conversion of **14b** to the *N*-protected fuligocandin B, cautious *N*-deprotection was accomplished by adding Cs_2CO_3 and methanol to the reaction mixture. The choice of the protecting group somewhat influenced the overall yield. Ultimately, the use of a protecting phenylsulfonyl group gave fuligocandin B (**3**) in an isolated yield of 40%, while the use of a *p*-nitrophenylsulfonyl group resulted in a slightly better yield (53%). The relatively low overall yield resulting from this episulfide contraction is due to reversibility of the thioamide alkylation reaction which could be observed by TLC analysis.

The specific rotations of compounds **1**−**3** were determined and showed, somewhat surprisingly, that the chirality at C-11a (Scheme 3) of both fuligocandines A and B was lost in the last step. These racemizations probably occurred due to tautomerization brought on by the basic reaction conditions. It is known that similar pyrrolobenzodiazepines will racemize in the presence of base,[19] and this is also supported by the fact that compound **15b**, when prepared under neutral, thermal contraction conditions, was optically active, giving specific rotation of +611; subsequent deprotection under basic conditions ($MeOH/Cs_2CO_3$) led to loss of optical activity in the product fuligocandin B. An exceptionally mild deprotection strategy for 2- and 4-nitrobenzenesulfonamides was developed by Fukuyama.[30] This method typically involves the use of thiolates in DMF, at room temperature, to give amines in high yields. When deprotection was attempted employing sodium thiophenolate in DMSO we obtained fuligocandin B in optically active form (Scheme 5), with a specific rotation of +140 which is in agreement with Nakatani et al.,[1] who reported a value of +149. Racemic fuligocandin B was obtained when the N-deprotection was initially carried out using equimolar amounts of sodium hydride and thiophenol. Fortunately, the undesired racemization could be prevented by employing 1 equiv of sodium hydride and 2 equiv of thiophenol. Supposedly, the excess thiophenol acts as a Brønsted acid and neutralizes the basic species, which is formed as a result of protecting group removal.

After accomplishing the synthesis of racemic fuligocandin A and optically active fuligocandin B, we investigated the general applicability of this one-pot alkylation−sulfur extrusion protocol to obtain various vinylogous amides starting from thioamides **12** and **16**−**19**, and the results are summarized in Table 1. Secondary amides reacted well with primary halides to give vinylogous amides, whereas experiments involving secondary halides, α-halo esters and α-halo malonates gave poor yields or no reaction. It is

Table 1. Vinylogous Amides Obtained Using the Eschenmoser Protocol As Outlined in Scheme [4]

Entry	Thione	Vinylogous amide		Yield[a] (%)
1	 **12**		**2a**	98
			2b	93
			2c	89
2	 **16**		**20a**	83
			20b	87
			20c	85
3	 **17**		**21a**	77
			21b	89
			21c	-
4	 **18**		**22a**	82
			22b	80
			22c	81
5	 **19**		**23a**	84
			23b	85
			23c	87

[a] Yields of isolated, pure vinylogous amides. **a** = R = $-CH_3$; **b** = R = $-C_6H_5$; **c** = R = −*p*-biphenyl.

notable that attempts to obtain vinylogous amide **17c** (entry 3) gave complex reaction mixtures and compound **17c** was never isolated.

The desired C_{11}/C_{12} *Z*-configurations within both fuligocandin A and B were confirmed by NOE studies which revealed the expected through-space interactions between H_1/H_{12} (Figure 2). In case of fuligocandin B, C_{14}/C_{15} *E*-configuration was established by large (15.1 Hz) vicinal coupling constants in agreement with NMR data reported by Nakatani et al.[1] The *Z*-configuration of the double bond was also confirmed in compounds **20c** and **22b**.

CONCLUSIONS

The alkaloids fuligocandin A and B have been synthesized in a simple fashion, and a considerably improved procedure for the Eschenmoser coupling has been invented.

EXPERIMENTAL SECTION

(*S*)-11-Thioxo-2,3,11,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo-[1,2-*a*][1,4]diazepine-5-(10*H*)-one (12). To a MeCN solution (200 mL) of **1** (4.0 g, 20 mmol) was added a reagent (2.3 g, 6 mmol) produced by refluxing P_4S_{10} in pyridine,[21] and the mixture was heated to 60 °C for 3 h during which time a yellow precipitate was formed. The reaction mixture was allowed to stand at room temperature overnight in order to precipitate fully. The product was vacuum-filtered and washed with a small amount of cold MeCN to give **12** (3.9 g, 85%) as a pale-yellow solid: mp 268−270 °C (lit.[17a] mp 253−254 °C); $[\alpha]^{23}_D$ +971 (*c* 0.16, MeOH) [lit.[17a] $[\alpha]^{23}_D$ +873 (*c* 1.026, DMSO)]; IR ν_{max} 3170, 2979, 1616, 1602, 1477, 1374, 1271, 1141, 831, 813, 752,

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699 cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6) δ 1.89−1.94 (m, 1H), 1.99−2.16 (m, 2H), 2.84−2.94 (m, 1H), 3.40−3.50 (m, 1H), 3.53−3.60 (m, 1H), 4.27 (d, J = 6.11 Hz, 1H), 7.22−7.27 (m, 1H), 7.30−7.37 (m, 1H), 7.55−7.60 (m, 1H), 7.80−7.85 (m, 1H), 12.46 (br s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 22.7(t), 29.0 (t), 46.8 (t), 59.8 (d), 121.8 (d), 125.7 (d), 127.8 (s), 130.2 (d), 132.2 (d),136.5 (s),164.2 (s), 201.9 (s).

Spiro[cyclopentane-1,2′(1′*H*)-quinazolin]-4′(3′*H*)-thione (18). A reagent (0.96 g, 25 mmol) prepared from P_4S_{10} and pyridine[21] was added to a suspension of spiro[cyclopentane-1,2′(1′*H*)-quinazolin]-4′(3′*H*)-one[24] (1.0 g, 5 mmol) in acetonitrile (50 mL), and the reaction mixture was heated at reflux for 7 h. After being cooled to room temperature, the dark-red solution was poured into water and allowed to stand in refrigerator overnight. The precipitate was collected and washed with a small amount of cold MeCN to give **18** (0.97 g, 89%) as orange flakes: mp 226 °C; IR ν_{max} 3389, 3254, 3128, 2966, 1612, 1531, 1468, 1235, 1148, 994, 748 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.65−1.69 (m, 4H), 1.76−1.80 (m, 2H), 1.88−1.95 (m, 2H), 6.65−6.71 (2H, m), 7.08 (s, 1H), 7.24 (t, J = 7.6 Hz, 1H), 8.04 (d, J = 7.9 Hz, 1H), 10.29 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ ppm 22.2 (t), 38.5 (t), 77.1 (s), 114.8 (d), 116.9 (d), 119.4 (s), 131.4 (d), 133.7 (d), 143.6 (s), 188.5 (s). Anal. Calcd for $C_{12}H_{14}N_2S$: C, 66.02; H, 6.46; N, 12.83. Found: C, 65.92; H, 6.11; N, 12.53.

General Procedure for One-Pot Alkylation and Episulfide Contraction. To a solution of thioamide (2 mmol, 1.00 equiv) in DMSO (10 mL) was added NaH (95%) (22 mmol, 1.10 equiv), and the mixture was stirred at room temperature for 30 min under argon. The reaction mixture was treated with alkyl halide (1.05 mmol, 1.05 equiv), and after 30 min of stirring at rt, trimethyl phosphite (66 mmol, 3 equiv) and DABCO (66 mmol, 3 equiv) were added and the solution was allowed to stir at 90 °C (internal temperature) until all alkylated species were consumed according to TLC (2−14 h). (In cases when chloroacetone was used as electrophile, 2 equiv of NaH and 2.5 equiv of chloroacetone gave the best results. Aryl halides were usually added in 1.1 equiv amounts, but in some cases 1.00 or 1.10 equiv was used. The actual amounts are specified below for each experiment.) After this time, the reaction mixture was poured into distilled water (50 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic fractions were washed with water (5 × 80 mL), dried over Na_2SO_4, and evaporated under reduced pressure. Excess trimethyl phosphite and thioadducts were removed by coevaporation with ethanol. Crude products were usually solid, but in some cases the oily or semisolid crude material could be precipitated by addition of ethanol. Crude products were recrystallized from ethanol and oily products where purified by flash chromatography (EtOAc/Hep 1:4).

Isolation of the Thioimidate (13). To a solution of thioamide **12** (0.46 g, 2 mmol, 1.00 equiv) in DMSO (10 mL) was added NaH (95%) (4 mmol, 2 equiv) and the solution was stirred at room temperature for 30 min under argon. Chloroacetone (5 mmol, 2.5 equiv) was added (neat), and after 40 min, when TLC analysis showed that all starting material had been consumed, water was added and the phases were separated. The water phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic phases were washed with water (5 × 100 mL) and dried (Na_2SO_4). Evaporation of the crude mixture gave **13** as a yellow glistening solid (0.58 g, 100%). Compound **13** is unstable and had to be used immediately in the next step.

Fuligocandin A (2a). Prepared according to the general procedure using the monothione **12** (0.46 g, 2 mmol, 1 equiv) and chloroacetone (0.4 mL, 5 mmol, 2.5 equiv). Racemic fuligocandin A (**2a**) was obtained as an off-white solid (0.5 g, 98%): mp 156−157 °C from ethanol (lit.[1] mp 140−144 °C); IR IR ν_{max} 2984, 2877, 1631, 1592, 1557, 1405, 1263, 1252, 755, 733, 696 cm^{-1}; ^1H NMR (300 MHz acetone-d_6) δ ppm 2.00−2.10 (m, 2H), 2.11−2.29 (m, 4H), 2.34−2.46 (m, 1H), 3.64−3.70 (m, 1H), 3.80−3.85 (m, 1H), 4.30 (dd, J = 7.9, 1.6 Hz, 1H), 5.30 (s, 1H), 7.02−7.05 (m,1H), 7.19−7.24 (m, 1H), 7.43−7.48 (m, 1H), 7.96−7.98 (m, 1H), 12.6 (br s, 1H); ^{13}C NMR (75.5 MHz, acetone-d_6) δ ppm 23.6 (t), 27.2 (t), 30.0 (q), 47.2 (t), 55.6 (d), 91.4 (d), 122.4 (d), 124.8 (d), 127.3 (s), 131.4 (d), 132.8 (d), 137.2 (s), 159.3 (s), 165.9 (s), 198.4 (s).

These NMR data are in agreement with those previously reported by Nakatani et al.[1]

1-(4-Nitrophenylsulfonyl)-3-carbaldehyde (8b). A CH_2Cl_2 suspension (120 mL) of indole-3-carbaldehyde (9.0 g, 0.062 mol, 1.0 equiv), DMAP (0.005 mol, 0.61 g, 0.08 equiv), and triethylamine (13 mL, 0.093 mol, 1.5 equiv) was stirred for 10 min at rt, and then 4-nitrophenylsulfonyl chloride (15 g, 0.068 mol, 1.1 equiv) in 120 mL of CH_2Cl_2 was added dropwise over 10 min. The reaction mixture was allowed to stir at room temperature overnight and thereafter quenched with 300 mL of HCl aq (5.0%). The phases were separated, and the water phase was extracted several times with CH_2Cl_2. The red combined CH_2Cl_2 phases were dried with Na_2SO_4 and flushed through a short silica plug. Evaporation of the yellow filtrate in vacuo gave (20 g, 98%) **8b** as a beige solid: mp 160 °C (lit.[26] mp 115 °C, this value seems to be in error); IR ν_{max} 3111, 1684, 1529, 1380, 1347, 1179, 1126, 973, 737 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ ppm 7.43 (t, J = 5.8 Hz, 1H), 7.49 (t, J = 5.6 Hz, 1H), 8.00 (d, J = 6.2 Hz, 1H), 8.13 (d, J = 5.9 Hz, 1H), 8.41 (s, 4H), 8.96 (s, 1H), 10.11 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ ppm 113.1 (d), 121.9 (d), 122.2 (s), 125.3 (d), 125.5 (d), 125.8 (s), 126.6 (d), 128.9 (d), 134.4 (s), 138.4 (d), 141.0 (s), 151.1 (s), 186.8 (d); HRMS (FAB) m/z calcd for $C_{15}H_{10}N_2O_5S$ $[M + H]^+$ 330.0310, found 330.0302.

(*E*)-1-Chloro-4-(1-(phenylsulfonyl)-1*H*-indol-3-yl)but-3-en-2-one (9a). A suspension of the protected indole-3-carbaldehyde **8a** (5.7 g, 0.02 mol, 1 equiv) in MeOH (100 mL) was heated for 30 min, and then phosphorus ylide **6** (10.6 g, 0.03 mol, 1.5 equiv) was added (neat). After 3 days of gentle reflux, the yellow suspension turned brown, and the solvent was removed in vacuo to afford a brown semisolid crude material which was purified by column chromatography (EtOAc/heptane; 1:4) to give 5.40 g (69%) of **9a** as a pale yellow solid: mp 154−155 °C; IR ν_{max} 3137, 1708, 1613, 1446, 1360, 1174, 1131, 979, 744, 728 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ ppm 4.77 (s, 2H), 7.13 (d, J = 16 Hz, *1H*), 7.37−7.48 (m, 2H), 7.60−7.65 (m, 2H), 7.70−7.75 (m, 1H), 7.86 (d, J = 16 Hz, 1H), 7.99−8.01 (m, 1H), 8.04−8.13 (m, 3H), 8.56 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ ppm 48.3 (t), 113.4 (d), 117.9 (s), 121.1 (d), 123.0 (d), 124.4 (d), 125.8 (d), 126.9 (d), 127.5 (s), 130.0 (d), 131.0 (d), 134.8 (d), 134.8 (s), 135.0 (d), 136.5 (s), 191. One (s).

These NMR data are in agreement with those reported by Caballero et al.[27]

(*E*)-1-Chloro-4-(1-(4-nitrophenylsulfonyl)-1*H*-indol-3-yl)but-3-en-2-one (9b). Compound **9b** was obtained by the same procedure as described for **9a** using the protected indole-3-carbaldehyde **8b** (0.02 mol, 6.3 g, 1 equiv) and the phosphorus ylide **6** (0.023 mol, 8.1 g, 1.2 equiv) in MeOH (100 mL). After the reaction, a solid orange material appeared, and this precipitate was allowed to fully form during a few hours at rt. The crude product was collected by filtration then stirred in MeOH for a few minutes. Filtration of the orange solid gave (6.48 g, 80%) of **9b**: mp 174−175 °C; IR ν_{max} 3105, 1698, 1606, 1525, 1177, 1123, 1080, 984, 738 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ ppm 4.76 (s, 2H), 7.15 (d, J = 16 Hz, 1H), 7.40−7.51 (m, 2H), 7.85 (d, J = 16 Hz, 1H), 8.00−8.07 (m, 2H), 8.21−8.40 (m, 4H), 8.58 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ ppm 48.3 (t), 113.4 (d), 118.8 (s), 121.2 (d), 123.5 (d), 124.8 (d), 125.3 (d), 126.1 (d), 127.7 (s), 128.6 (d), 130.6 (d), 134.4 (d), 134.7 (s), 141.2 (s), 151.0 (s), 191.1 (s); HRMS (FAB) m/z calcd for $C_{18}H_{13}ClN_2O_5S$ $[M + H]^+$ 404.0234, found 404.0242.

Fuligocandin B (3) from 9b and 12. To a solution of the monothioamide **12** (1.0 mmol, 0.23 g, 1 equiv) in DMSO (5 mL) was added NaH (95%) (1.0 mmol, 0.027 g, 1 equiv). The mixture was stirred

at room temperature, and after 1 h, the indole derivative **9b** (1.0 mmol, 0.41 g, 1.0 equiv) was added. After 2 h at room temperature, TLC analysis still showed traces of starting materials; despite this fact, the reaction mixture was heated (90 °C internal temperature) for 2 h. After the mixture was cooled to room temperature (at this point, in place of proceeding with workup, in situ deprotection could be carried out using two different methods, namely (a) MeOH/Cs_2CO_3 and (b) sodium thiophenolate; see below), distilled water (50 mL) was added to the dark brown mixture and then extracted with CH_2Cl_2 several times. The combined organic fractions were washed with water (5 × 50 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The brownish crude material was purified using column chromatography EtOAc/heptane (2:1) to yield **15b** as a yellow solid (0.323 g, 57%): mp 175 °C dec; $[\alpha]^{23}_D$ +611 (*c* 0.19, MeOH); IR ν_{max} 3642, 3463, 3100, 1636, 1596, 1531, 1348, 1176, 1122, 984, 854, 739, 562 cm^{-1}, ^{1}HNMR (300 MHz, DMSO-d_6) δ ppm 2.02−2.04 (m, 2H), 2.11−2.18 (m, 1H), 2.43−2.49 (m, 1H), 3.40−3.55 (m, 1H), 3.62−3.66 (m, 1H), 4.45 (dd, *J* = 7.2, 1.5 Hz, 1H), 5.90 (s, 1H), 7.18−7.26 (m, 3H), 7.42−7.48 (m, 2H), 7.51−7.58 (m, 1H), 7.69 (d, *J* = 16.1 Hz, 1H), 7.82−7.84 (m, 1H), 8.01−8.03 (m, 1H), 8.12−8.15 (m, 1H), 8.30−8.40 (m, 4H), 8.46 (s, 1H), 13.17 (s, 1H); ^{13}CNMR (75.5 MHz, DMSO-d_6) δ ppm 23.2 (t), 26.5 (t), 46.8 (t), 55.1 (d), 92.9 (d), 113.4 (d), 119.7 (s), 121.6 (d), 122.1 (d), 124.3 (d), 124.7 (d), 125.3 (d), 125.9 (d), 126.0 (d), 127.1 (s), 127.9 (s), 128.6 (d), 129.4 (d), 129.9 (d), 130.8 (d), 132.6 (d), 134.9 (s), 136.7 (s), 141.4 (s), 151.0 (s), 160.6 (s), 164.5 (s), 188.0 (s); HRMS (FAB) *m/z* calcd for $C_{30}H_{24}N_4O_6S$ $[M + H]^+$ 568.1417, found 568.1438.

(a) Deprotection of ***15b*** *Using* Cs_2CO_3 *and MeOH.* MeOH (4 mL) and Cs_2CO_3 (3 mmol, 0.98 g, 3 equiv) were added to the reaction mixture and the stirring continued at rt. The deprotection was complete after 1 h, and the product could be observed as an intensively yellow band on a TLC plate at 365 nm. Distilled water (50 mL) was added to the dark-red mixture and the mixture extracted with CH_2Cl_2 several times. The combined organic fractions were washed with water (5 × 50 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The brownish crude material was purified using column chromatography EtOAc/heptane (1:1) to yield racemic fuligocandin B (0.20 g, 53%) as a yellow pigment: mp 160 °C dec; IR and NMR data are provided below.

(b) Deprotection of ***15b*** *Using Thiophenolate.* To a solution of thiophenol (0.22 g, 2 mmol) in DMSO (1 mL) was added NaH (0.027 g, 1 mmol), and after being stirred for 3 min the solution was added to the reaction mixture at rt. TLC analysis showed that the deprotection was complete after 2 min, and the product could be observed as an intensively yellow band at 365 nm. Distilled water (50 mL) was added to the dark-red mixture and the mixture extracted with CH_2Cl_2 several times. The combined organic fractions were washed with water (5 × 50 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The brownish crude material was purified using column chromatography EtOAc/heptane (1:1) to yield optically active fuligocandin B (0.25 g, 65%) as a yellow pigment: mp 160 °C dec; $[\alpha]^{23}_D$ + 140 (c 0.5, MeOH) ($[\alpha]^{23}_D$ +149 (c 0.6, MeOH)); IR ν_{max} 3222, 2950, 1590, 1565, 1456, 1269, 1131, 1102, 1084, 740, 590 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ ppm 2.06−2.17 (m, 2H), 2.27−2.30 (m, 1H), 2.57−2.62 (m, 1H), 3.55−3.65 (m, 2H), 4.46 (dd, 1H, *J* = 8.0, 1.6 Hz), 5.82 (s, 1H), 7.02 (d, 1H, *J* = 15.1 Hz), 7.13−7.16 (m, 1H), 7.19−7.23 (m, 3H), 7.50−7.62 (m, 2H), 7.82−7.85 (m, 1H), 7.87−7.91 (m, 1H), 7.93 (d, 1H, *J* = 15.1 Hz), 8.02−8.05 (m, 1H), 10.9 (br s, 1H), 13.4 (br s, 1H); ^{13}C NMR (75.5 MHz, acetone-$_{d6}$) δ ppm 24.1 (t), 29.0 (t), 47.6 (t), 56.2 (d), 93.6 (d), 113.0 (d), 114.1(s), 121.4 (d), 121.7 (d), 122.7 (d), 123.6 (d), 124.0 (d), 124.5 (d), 126.5 (s), 128.3 (s), 131.5 (d), 131.6 (d), 133.2 (d), 135.0 (d), 138.6 (s), 138.7 (s), 160.6 (s), 165.9 (s), 190.4 (s).

These NMR data are in agreement with those previously reported by Nakatani et al.[1]

Fuligocandin B was also isolated by this method using thione **12** and **9a** to give 0.17 g (44%) of the title compound.

Isolation of *N*-Phenylsulfonyl-Protected Fuligocandin B (15a). Compound **15a** was prepared according to the above method; however, the deprotection step was omitted, and after 2 h of heating at 90 °C water was added and the reaction mixture worked up as described above. The crude product was purified using column chromatography EtOAc/heptane (2:1) to yield **15a** as a brown solid (0.26 g, 49%): mp 170 °C dec; ^{1}HNMR (300 MHz, DMSO-d_6) δ ppm 2.02−2.03 (m, 2H), 2.13−2.17 (m, 1H), 2.43−2.48 (m, 1H), 3.45−3.54 (m, 1H), 3.62−3.66 (m, 1H), 4.45 (dd, *J* = 7.5, 1.3 Hz, 1H), 5.90 (s, 1H), 7.19−7.29 (m, 3H), 7.39−7.45 (m, 2H), 7.51−7.58 (m, 1H), 7.67−7.73 (m, 2H), 7.82−7.84 (m, 2H), 8.01−8.03 (m, 1H), 8.12−8.15 (m, 3H), 8.30−8.40 (m, 1H), 8.43 (s, 1H), 13.17 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ ppm 23.2 (t), 26.5 (t), 46.8 (t), 55.0 (d), 93.0 (d), 113.4 (d), 118.8 (s), 121.5 (d), 122.1 (d), 124.2 (d), 124.3 (d), 125.7 (d), 126.9 (d), 127.1 (s), 127.7 (s), 128.4 (d), 129.3 (d), 130.1 (d), 130.3 (d), 130.8 (d), 132.6 (d), 134.9 (s), 135.0 (d), 136.6 (s), 136.7 (s), 160.5 (s), 164.6 (s), 188.2 (s); MS analysis for **15a** was unsuccessful as attempts to obtain molecular ion for this compound failed due to decomposition with both EI, CI-CH_4, and with CI-NH_3.

(*Z*)-11-(2-Oxo-2-phenylethylidene)-2,3,11,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-5(10*H*)-one (2b). Prepared according to the general procedure using the monothione **12** (0.23 g 1 mmol, 1 equiv), 2-bromo-1-phenylethanone (0.23 g, 1.1 mmol, 1.1 equiv), and appropriate amounts of solvents and reagents to give **2b** as a pale yellow solid (0.30 g, 93%): mp 179 °C; IR ν_{max} 2971, 2874, 1634, 1592, 1549, 1482, 1266, 1253, 1166, 756, 733 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.02−2.06 (m, 2H), 2.06−2.19 (m, 1H), 2.62−2.67 (m, 1H), 3.49−3.52 (m, 1H), 3.62−3.67 (m, 1H), 4.49 (dd, *J* = 7.1, 1.4 Hz, 1H), 6.19 (s, 1H), 7.24−7.30 (m, 2H), 7.49−7.60 (m, 4H), 7.82−7.85 (m, 1H), 8.01−8.04 (m, 2H), 13.17 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ ppm 23.3 (t), 26.5 (t), 46.7 (t), 55.3 (d), 87.5 (d), 122.3 (d), 124.4 (d), 127.2 (s), 127.3 (d), 128.5 (d), 130.7 (d),131.8 (d), 132.5 (d), 136.6 (s), 138.8 (s), 161.3 (s), 164.5 (s), 189.6 (s). Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.11; H, 5.71; N, 8.62.

(*Z*)-11-(2-(Biphenyl-4-yl)-2-oxoethylidene)-2,3,11,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-5(10*H*)-one (2c). Prepared according to the general procedure using the thione **12** (0.23 g 1 mmol, 1 equiv), 1-(biphenyl-4-yl)-2-bromoethanone (0.29 g, 1.05 mmol, 1.05 equiv), and appropriate amounts of solvents and reagents to give **2c** as a yellow crystalline solid (0.35 g, 89%): mp 129−131 °C; IR ν_{max} 3059, 2874, 1614, 1588, 1561, 1476, 1268, 1195, 1098, 752, 696 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.04−2.06 (m, 2H), 2.13- 2.26 (m, 1H), 2.66−2.70 (m, 1H), 3.43−3.56 (m, 1H), 3.63−3.69 (m, 1H), 4.50 (dd, *J* = 7.1, 1.3 Hz, 1H), 6.24 (s, 1H), 7.25−7.28 (m, 2H), 7.42−7.44 (m, 1H), 7.48−7.54 (m, 3H), 7.73−7.86 (m, 5H), 8.11−8.13 (m, 2H), 13.15 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ ppm 23.3 (t), 26.5 (t), 46.7 (t), 55.3 (d), 87.6 (d), 122.3 (d), 124.4 (d), 126.8 (d), 126.9 (s), 127.2 (d), 128.0 (d), 128.1 (d), 129.0 (d), 130.7 (d), 132.5 (d), 136.6 (s), 137.7 (s), 139.1 (s), 143.3 (s), 161.3 (s), 164.5 (s), 189.0 (s). Anal. Calcd for $C_{26}H_{22}N_2O_2$: C, 79.17; H, 5.62; N, 7.10. Found: C, 79.22; H, 5.51; N, 6.98.

(*Z*)-1-(Biphenyl-4-yl)-2-(pyrrolidin-2-ylidene)ethanone (20c). Prepared according to the general procedure using thione **16** (0.10 g 1 mmol, 1 equiv), 1-(biphenyl-4-yl)-2-bromoethanone (0.30 g, 1.1 mmol, 1.1 equiv), and appropriate amounts of solvents and reagents to give **20c** as a beige solid (0.27 g, 85%): mp 186−187 °C; IR ν_{max} 3297, 2879, 1600, 1564, 1524, 1296, 1258, 1041, 854, 746, 692 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.39−148 (m, 2H), 2.22 (t, *J* = 8.09 Hz, 2H), 3.07 (t, *J* = 6.94 Hz, 2H), 5.36 (s, 1H), 6.86−6.90 (m, 1H), 6.96−7.01 (m, 2H), 7.20−7.23 (m, 4H), 7.41−7.44 (m, 2H), 9.67 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ ppm 20.9 (t), 32.8 (t), 47.7 (t), 85.4 (d), 126.5 (d), 126.8 (d), 127.3 (d), 127.8 (d), 129.0 (d), 138.9 (s), 139.5 (s), 141.9 (s), 168.7 (s), 184,8 (s). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.92; H, 6.32; 5.06.

(*Z*)-1-(1′*H*-Spiro[cyclopentane-1,2′-quinazoline]-4′(3′*H*)-ylidene)propan-2-one (22a). Prepared according to the general procedure using the thione **18** (0.44 g 2 mmol, 1 equiv), chloroacetone (0.4 mL, 5 mmol, 2.5 equiv), and appropriate amounts of solvents and reagents to give **22a** as a dark-red semisolid (0.40 g, 82%): IR ν_{max} 3255, 2957, 1614, 1599, 1522, 1485, 1358, 1328, 1293, 1252 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.39−1.48 (m, 4H), 1.69−1.77 (m, 4H), 1.99 (s, 3H), 5.64 (s, 1H), 6.63−6.68 (m, 1H), 6.72−6.74 (m, 1H), 6.91 (s, 1H), 7.20−7.24 (m, 1H), 7.54−7.56 (m, 1H), 11.43 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ ppm 21.8 (t), 29.1 (q), 38.9 (t), 74.2 (s), 87.5 (d), 113.6 (s), 115.5 (d), 117.3 (d), 125.0 (d), 132.6 (d), 145.9 (s), 153.8 (s), 193.6 (s). This compound starts to decompose in a matter of hours at room temperature; thus, no elemental analysis was performed.

(*Z*)-1-Phenyl-2-(1′*H*-spiro[cyclopentane-1,2′-quinazoline]-4′(3′*H*)-ylidene)ethanone (22b). Prepared according to the general procedure using the thione **18** (0.44 g 2 mmol, 1 equiv), 2-bromo-1-phenylethanone (0.44 g, 2.2 mmol, 1.1 equiv), and appropriate amounts of solvents and reagents to give **22b** as a dark yellow solid (0.49 g, 80%): mp 171 °C; IR ν_{max} 3298, 2948, 1613, 1592, 1513, 1350, 1149, 1024, 850, 749, 723, 684 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.73−1.80 (m, 4H), 1.85−1.89 (m, 4H), 6.39 (s, 1H), 6.69−6.79 (m, 2H), 7.03 (s, 1H), 7.24−7.27 (m, 1H), 7.44−7.47 (m, 3H), 7.85−7.87 (m, 1H), 7.97−8.00 (m, 2H), 12.12 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ ppm 21.9 (t), 39.1 (t), 74.4 (s), 84.1 (d), 114.0 (s), 115.5 (d), 117.4 (d), 125.7 (d), 126.8 (d), 128.2 (d), 129.3 (d), 133.0 (d), 140.3 (s), 146.0 (s), 155.9 (s), 186.2 (s). Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.52; H, 6.45; N, 9.16.

(*Z*)-1-(Biphenyl-4-yl)-2-(1′*H*-spiro[cyclopentane-1,2′-quinazoline]-4′(3′*H*)-ylidene)ethanone (22c). Prepared according to general procedure using the thione **18** (0.22 g 1 mmol, 1 equiv), 1-(biphenyl-4-yl)-2-bromoethanone (0.30 g, 1.1 mmol, 1.1 equiv), and appropriate amounts of solvents and reagents to give **22c** as a dark yellow solid (0.31 g, 81%): mp 170 °C dec; IR ν_{max} 3284, 2966, 1615, 1593, 1554, 1349, 1244, 1146, 1005, 856, 750, 698 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.57−1.81 (m, 4H), 1.88−1.90 (m, 4H), 6.45 (s, 1H), 6.71−6.80 (m, 2H), 7.05 (s, 1H), 7.26−7.28 (m, 1H), 7.39−7.42 (m, 1H), 7.46−7.51 (m, 3H), 7.72−7.75 (m, 4H), 7.88−7.91 (m, 1H), 8.07−8.10 (m, 2H), 12.16 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ ppm 21.8 (t), 39.1 (t), 74.5 (s), 84.0 (d), 114.1 (s), 115.5 (d), 117.4 (d), 125.8 (d), 126.5 (d), 126.8 (d), 127.5 (d), 128.2 (d), 128.7 (d), 133.0 (d), 139.2 (s), 139.5 (s), 142.0 (s), 146.0 (s), 155.9 (s), 185.6 (s); HRMS (FAB) *m*/*z* calcd for $C_{26}H_{24}N_2O$ $[M + H]^+$ 380.1889, found 380.1896.

(*Z*)-1-(Biphenyl-4-yl)-3-phenyl-3-(phenylamino)prop-2-en-1-one (23c). Prepared according to the general procedure using the thione **19** (0.21 g 1 mmol, 1 equiv), 1-(biphenyl-4-yl)-2-bromoethanone (0.33 g, 1.05 mmol, 1.05 equiv), and appropriate amounts of solvents and reagents to give **23c** yellow glistening needles (0.32 g, 87%): mp 184−185 °C; IR ν_{max} 3029, 1608, 1568, 1476, 1319, 1296, 1205, 1055, 761, 734, 688 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ ppm 6.26 (s, 1H), 6.84−6.86 (m, 2H), 7.00−7.05 (m, 1H), 7.16−7.21 (m, 2H), 7.41−7.52 (m, 8H), 7.53−7.80 (m, 4H), 8.05−8.12 (m, 2H), 12.85 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ ppm 96.7 (d), 123.0 (d), 124.2 (d), 127.2 (d), 127.2 (d), 128.0 (d), 128.3 (d), 128.5 (d), 128.6 (d), 1289 (d), 129.9 (d), 131.6 (d), 135.1 (s), 139.1 (s), 139.2 (s), 161.0 (s, 2C), 188.6 (s). Anal. Calcd for $C_{27}H_{21}NO$: C, 86.37; H, 5.64; N, 3.73. Found: C, 86.22; H, 5.63; N, 3.52.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details for compounds **1**, **6**, **8a**, **10**, and **12**. Compound characterization data for **1**, **6**, **8a**, **10**, **12**, **16**, **17**, **20a,b**, **21a,b**, and **23a,b**. Copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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