JOC*Article*

Synthesis of Constrained Raloxifene Analogues by Complementary Use of Friedel−Crafts and Directed Remote Metalation Reactions

Alexey V. Kalinin,[†] Mark A. Reed,[†] Bryan H. Norman,[‡] and Victor Snieckus*,[†]

Queen's University, Department of Chemistry, Kingston, Ontario, Canada K7L 3N6, and Eli Lilly and Company, Discovery Chemistry Research, Lilly Corporate Center, Indianapolis, Indiana 46285

snieckus@chem.queensu.ca

Received March 11, 2003

New constrained heterocyclic analogues, **2a**,**b** and **3**, of Raloxifene (**1**) have been prepared by complementary Directed remote Metalation (DreM)/Friedel−Crafts cyclization approaches. Utilization of a benzylidene-thiolactone rearrangement was successfully implemented to construct benzothiophenes **13a**−**c** in good yields. Selective deprotection of **13a** and **13b** induced by complexation followed by triflation gave **18** and **23**, thereby allowing efficient Suzuki−Miyaura cross coupling with borolane **16** to give biaryls **19** and **24**. Treatment of **19** with BCl_3 induced an intramolecular *para* Fridel−Crafts cyclization and concomitant double deprotection to furnish analogue **2a**, a new 5,6,6,6-($C_4S-C_6-C_6-C_6$) sulfur-containing heterocycle. Exposure of **25** with excess LDA induced a DreM cyclization delivering the *ortho*-substituted 5,6,6,6-($C_4S-C_6-C_6-C_6$) heterocylic analogue **26** in 70% yield. Similar treatment of **13c** and **27** afforded **30**, representing the novel 5,5,6,6-($C_4S-C_5-C_6-C_6$) ring system, which was subjected to Suzuki−Miyaura cross coupling with **16** to give the biaryl **31** in 93% yield; deprotection furnished the final constrained analogue **3**.

Introduction

In 1984, Lilly scientists reported that [6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl]-[4-(2-(1-piperidinyl)-ethoxy]phenyl]methanone exhibited strong estrogen antagonist activity, an incisive discovery that eventually led to the new commercial drug Raloxifene (**1**, Figure 1),[1a−c] which was approved by the U.S. Food and Drug Administration for the prevention and treatment of osteoporosis in postmenopausal women. Extensive research and clinical trials are in progress to assess the potential of Raloxifene for the prevention of breast cancer,[1d] lower lipid production,[1e] control of uterine cancer,[1f,g] and treatment of Alzheimer's disease.[1h]

Molecular modeling studies at the Lilly Laboratories[2a−d] posited the new constrained Raloxifene analogues **2a**,**b** and **3** as potential candidates for biological evaluation. Herein we report the efficient syntheses of **2a**,**b** and **3**.

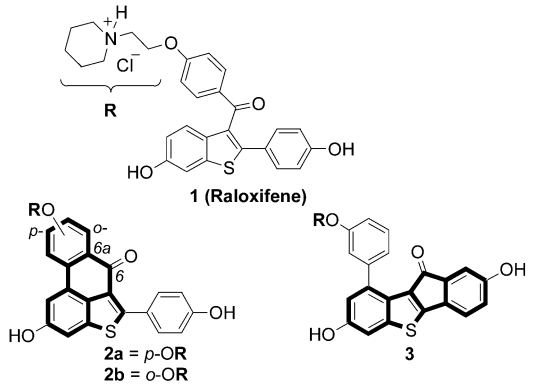


FIGURE 1. Raloxifene and constrained analogues synthesized.

Results and Discussion

The retrosynthetic plans for analogues **2** and **3** were envisaged through a rational combination of Friedel−

* To whom correspondence should be addressed. Phone: (613) 533-2239. Fax: (613) 533-2837.
[†] Queen's University.
[‡] Eli Lilly and Company.

(1) (a) Jones, C. D.; Jevnikar, M. G.; Pike, A. J.; Peters, M. K.; Black, L. J.; Thompson, A. R.; Falcone, J. F.; Clemens, J. A. *J. Med. Chem.* **1984**, *27*, 1057−1066. (b) Jordan, V. C. *J. Med. Chem.* **2003**, *46*, 883−908. (c) Jordan, V. C. *J. Med. Chem.* **2003**, *46*, 1081−1111. (d) Jordan, V. C. *J. Steroid Biochem. Mol. Biol.* **2002**, *74*, 269−277. (e) Rossouw, J. E. *Curr. Opin. Lipidol.* **1999**, *10*, 429−434. (f) Goldfrank, D.; Haytoglu, T.; Frishman, W. H.; Mohammad, Z. *J. Clin. Pharmacol.* **1999**, 39, 767−774. (g) Gustafsson, J.-A. *Nat. Med.* **1998**, *4*, 152. (h) McCormick, W. C.; Abrass, I. B. *Lancet* **1998**, *352* (Suppl 4), 6.

(2) (a) Grese, T. A.; Sluka, J. P.; Bryant, H. U.; Cole, H. W.; Kim, J. R.; Magee, D. E.; Rowley, E. R.; Sato, M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 903−908. (b) Grese, T. A.; Sluka, J. P.; Bryant, H. U.; Cullinan, G. J.; Glasebrook, A. L.; Jones, C. D.; Matsumoto, K.; Palkowitz, A. D.; Sato, M.; Termine, J. D.; Winter, M. A.; Yang, N. N.; Dodge, J. A. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 14105−14110. (c) Schmid, C. R.; Sluka, J. P.; Duke, K. M.; Glasebrook, A. W. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 523−528. (d) Grese, T. A.; Pennington, L. D.; Sluka, J. P.; Adrian, M. D.; Cole, H. W.; Fuson, T. R.; Magee, D. E.; Phillips, D. L.; Rowley, E. R.; Shetler, P. K.; Short, L. L.; Venugopalan, M.; Yang, N. N.; Sato, M.; Glasebrook, A. L.; Bryant, H. U. *J. Med. Chem.* **1998**, *41*, 1272−1283.

10.1021/jo034325k CCC: $25.00
Published on Web 06/28/2003

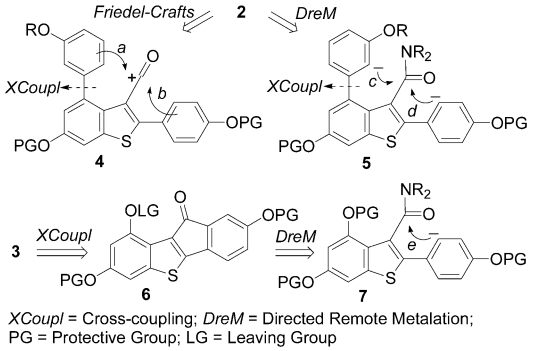
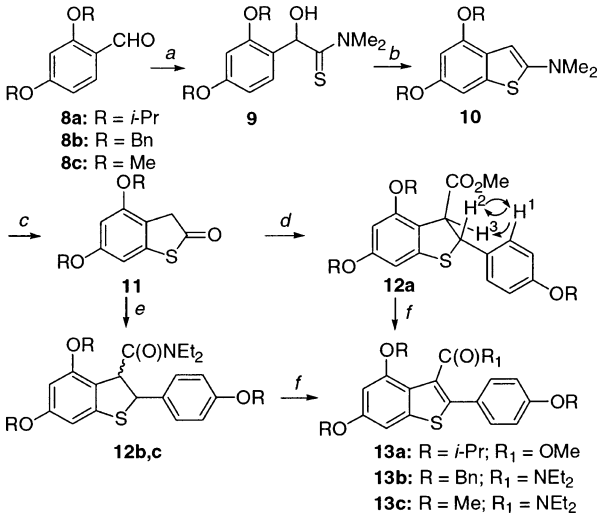


FIGURE 2. Retrosynthetic analysis for constrained analogues **2** and **3**.

Crafts,[3a] Directed remote Metalation (DreM)[3b] and Suzuki−Miyaura cross-coupling[4] reactions (Figure 2). Thus, for **2a**, dissection at the C_6-C_{6a} bond would predispose Friedel−Crafts ring closure (path *a*, **4**), favorably assisted by the *para* orientation of the OR substituent over path *b*, and the precursor 4-aryl benzothiophene derived by the Suzuki−Miyaura cross-coupling reaction. On the other hand, consideration of the DreM strategy implicates cyclization driven by the OR-directed metalation group (DMG), path *c*, **5**, the alternate path *d*, is not DMG-assisted and is therefore less likely.[3] The approach to **3** may be envisaged by initial dissection to the Suzuki−Miyaura precursor **6**, which perforce avoids the above dichotomy and allows consideration of regioselective, DreM-induced five-memered ring cyclization of the benzothiophene derivative **7** (path *e*).

The synthesis of **2** was initiated with the preparation of the key intermediate benzothiophenes **13** (Scheme 1). Use of the conditions developed by Ablenas[5] converted the readily available aldehydes **8** into the corresponding hydroxythioacetamides **9** by reaction with lithio anion of *N*,*N*-dimethylthioformamide. Dehydrative carbocationic cyclization of **9**, promoted by $MeSO_3H$, resulted in formation of intermediate aminobenzothiophenes **10**,[5] which were subjected to acid-catalyzed hydrolysis to deliver the benzothiophenones **11**. In contrast to the synthetic approach to a series of Raloxifene analogues with variable 2-aryl substituents via either aryl Grignard additions to 2-(dimethylamino)-3-aroylbenzothiophenes or Stille couplings of crude 2-stannyl-3-aroylbenzothiophenes with aryl bromides,[2d,6] we pursued a modification of the

SCHEME 1. Synthesis of Intermediate 13 via a Benzylidene−Thiolactone Rearrangement[a]



[a] Reagents and conditions: (a) LDA, $HC(S)NMe_2$, THF, −78 °C to rt, 69% (**a**), 41% (**b**), 50% (**c**); (b) $MeSO_3H$, DCM 0 °C to rt; (c) EtOH or MeOH, 3 N HCl, reflux/68% (**a**), 59% (**b**), 62% (**c**); (d) 10 mol % $C_5H_{11}N$, 4-(*i*-PrO)C_6H_4CHO, HOAc, reflux and then cat 50% aq KOH, MeOH, rt, 77%; (e) 10 mol % $HNET_2$, 4-(BnO)C_6H_4CHO (**b**) or 4-(MeO)C_6H_4CHO (**c**), HOAc, reflux and then $HNET_2$, MeCN or THF, reflux, 69% (**b**), 81% (**c**); (f) DDQ, PhH or PhMe, reflux, 92% (**a**), 63% (**b**), 93% (**c**).

method developed by Heindel for the synthesis of dihydro- and benzothiophenes involving a base-catalyzed benzylidene−thiolactone rearrangement.[7] We found that performing condensations of **11** with aromatic aldehydes in refluxing HOAc catalyzed by bases such as piperidine (for **11a**) or diethylamine (for **11b**,**c**) was more efficient than carrying out the reactions in anhydrous EtOH as reported.[5] Basification (catalytic amount of 50% aqueous KOH solution) of a MeOH solution of the crude product from the condensation of **11a** and *p*-(*i*-PrO)benzaldehyde produced methyl ester **12a** as a single *trans* isomer in 77% yield. The relative trans stereochemistry of **12a** was assigned by NOE observations. Thus, irradiation at the resonance frequency of H^1 protons (δ 7.32) showed NOEs for H^2 (δ 5.21) and H^3 (δ 4.35), while irradiation of H^2 resulted in response from the H^1 proton only.[8] Similarly, condensation of **11b** and **11c** with *p*-(BnO)- and *p*-(MeO)-benzaldehyde, respectively, followed by treatment of the intermediate benzylidenes[7] with an excess of diethylamine in refluxing MeCN or THF led directly to diethylamides **12b** and **12c**, formed as mixtures of isomers in 81% and 69% yields, respectively. Oxidation of **12a**−**c** with DDQ completed the synthesis of the requisite benzothiophenes **13a**−**c**.[7a]

The borolane **16**, required for the proposed Suzuki−Miyaura reaction, was prepared by sequential alkylation of 3-bromophenol **14** with 1-(2-chloroethyl)piperidine hydrochloride in aqueous NaOH solution[9] to give ether **15** followed by sequential lithium−bromine exchange, $B(OMe)_3$ quench, and *in situ* re-esterification with pinacol

(3) (a) Olah, G. A. *Friedel−Crafts Chemistry*; New York: Wiley, 1973; Roberts, R. M.; Khalaf, A. A. *Friedel−Crafts Alkylation Chemistry: A Century of Discovery*; Marcel Dekker: New York, 1984. (b) Anctil, E. J.-G.; Snieckus, V. *J. Organomet. Chem*. **2002**, *653*, 150−160. Snieckus, V. *Chem. Rev*. **1990**, *90*, 879−933. For an illustrative example of DreM application in total synthesis, see: Chauder, B. A.; Kalinin, A. V.; Taylor, N. T.; Snieckus, V. *Angew. Chem., Int. Ed*. **1999**, *38*, 1435−1438 and refs cited therein. For an application to bioactive molecules, see: Ciske, F. L.; Jones, W. D., Jr. *Synthesis* **1998**, 1195−1198.

(4) Suzuki, A. In *Metal-catalysed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998, p 49. Suzuki, A. *J. Organomet. Chem*. **2002**, *653*, 83−90.

(5) Ablenas, F. J.; George, B. E.; Maleki, M.; Jain, R.; Hopkinson, Lee-Ruff, E. *Can. J. Chem*. **1987**, *65*, 1800−1803.

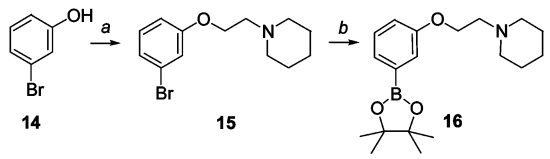
(6) Grese, T. A.; Cho, S.; Finley, D. R.; Godfrey, A. G.; Jones, C. D.; Lugar, C. W., III; Martin, M. J.; Matsumoto, K.; Pennington, L. D.; Winter, M. A.; Adrian, M. D.; Cole, H. W.; Magee, D. E.; Phillips, D. L.; Rowley, E. R.; Short, L. L.; Glasebrook, A. L.; Bryant, H. U. *J. Med. Chem*. **1997**, *40*, 146−167. Bradley, D. A.; Godfrey, A. G.; Schmid, C. R. *Tetrahedron Lett*. **1999**, *40*, 5155−5159.

(7) (a) Conley, R. A.; Heindel, N. D. *J. Org. Chem*. **1976**, *41*, 3743−3746. (b) Conley, R. A.; Heindel, N. D. *J. Org. Chem*. **1975**, *40*, 3169−3173.

(8) See ref 7a for the corresponding assignments of H^2 and H^3.

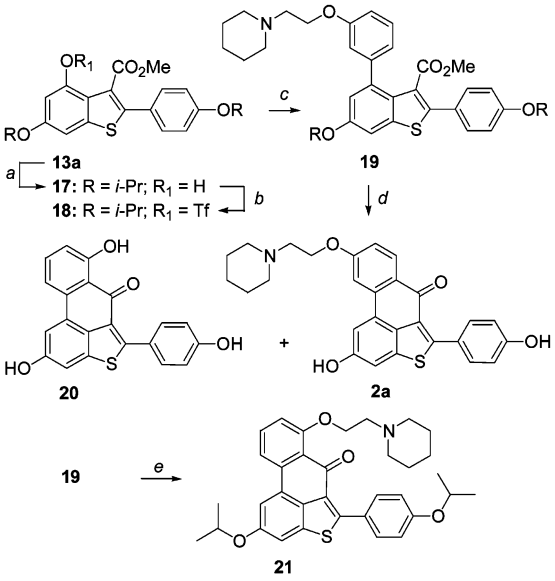
(9) Mason, J. P.; Malkiel, S. *J. Am. Chem. Soc*. **1940**, *62*, 1448−1450.

SCHEME 2. Synthesis of Borolane Cross-Coupling Partner 16[a]



[a] Reagents and conditions: (a) $ClCH_2CH_2NC_5H_{10}$ HCl, NaOH, H_20, reflux, 69%; (b) *n*-BuLi, THF, −78 °C and then $B(OMe)_3$, pinacol, rt, 74%.

SCHEME 3. Synthesis of Analogue 2a by Friedel−Crafts and Analogue 21 by Directed Remote Metalation Key Reactions[a]

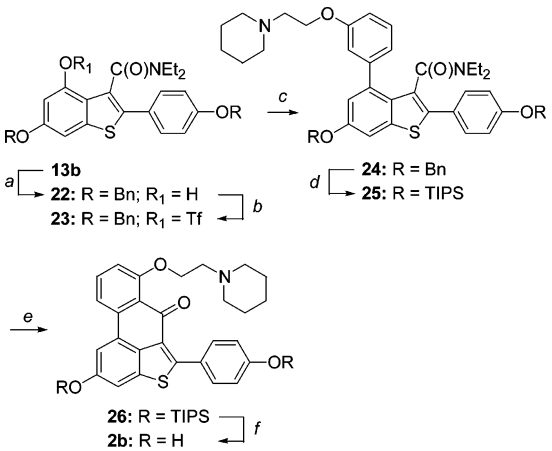


[a] Reagents and conditions: (a) BCl_3, DCM, −78 to 0 °C, 96%, (b) Tf_2O, TEA, DCM, 0 °C, 83%; (c) **16**, DME−2 M Na_2CO_3, 2 mol % $Pd(PPh_3)_4$, reflux, 95%; (d) BCl_3, DCM, 0 °C, 56% (**2a**) and 15% (**20**); (e) LDA, THF, −78 °C to rt, 33%.

(Scheme 2). Purification of borolane **16** by vacuum distillation ensured its chemical purity and proved to be more convenient than handling the corresponding boronic acid.

Peri proximity of CO_2Me to the 4-(*i*-PrO)-substituent in **13a** allowed the regioselective deisopropylation with BCl_3 at low temperature[10] to give the phenol **17** (quantitative yield), which was converted into triflate **18** and then subjected to Suzuki−Miyaura cross coupling with 1.2 equiv of **16**, a reaction effectively catalyzed by 2 mol % $Pd(PPh_3)_4$ and completed within 30 min to furnish the biaryl **19** in 95% yield (Scheme 3). Completion of the synthesis was achieved through a mild BCl_3-mediated one-pot electrophilic cyclization−double-deprotection sequence of **19** leading selectively to six-membered ketones **2a** (56%) and **20** (15%) and reflecting a typical *para*:*ortho* ratio observed for Friedel−Crafts reactions.[3a] Clearly, side chain loss in the formation of **20** was induced by BCl_3 coordination to the *ortho*-carbonyl group.[10] Optimization of the reaction conditions showed that 5 equiv of BCl_3 were required to accomplish the reaction, and conducting

SCHEME 4. Synthesis of Analogue 2b by a Combined Suzuki−Miyaura/Regioselective Directed Remote Metalation Strategy[a]



[a] Reagents and conditions: (a) 9-Br-9-BBN, DCM, −78 °C to rt, 82%; (b) Tf_20, TEA, DCM, 0 °C, 85%; (c) **16**, DME−2 M Na_2CO_3, 5 mol % $Pd(PPh_3)_4$, reflux, 80%; (d) 1,4-cyclohexadiene, Pd−C, EtOAc−HOAc, rt, and then TIPSCl, $NEt(i\text{-}Pr)_2$, DMAP, DCM, rt, 82%; (e) LDA, THF, -40 to 0 °C, 70%; (f) TBAF, THF, rt, 86%.

the reaction at low concentration (c 0.025 M) appeared to be crucial due to the limited solubilities of reaction intermediates.[11] The synthesis of analogue **2a** was thus achieved by a nine-step sequence in 14.1% overall yield based on **8a**.

As suggested in Figure 2, two modes of DreM-induced cyclization may be envisaged for intermediate **4**. In the event, **19** upon treatment with excess LDA delivered **21**, the expected product of anionic cyclization *ortho* with respect to the amino ether side chain, in 33% yield. Due to the low yield and the problem of subsequent side chain cleavage upon deprotection of the isopropyl groups, our attention was turned to an alternative synthesis of analogue **2b** (Scheme 4). Commencing with **13b**, treatment (−78 °C/DCM) with 9-Br−BBN[12] effected regioselective C-4 debenzylation to furnish the phenol **22**, which was subsequently subjected to Tf_2O/pyridine treatment to afford the triflate **23**. Suzuki−Miyaura coupling of **23** with borolane **16** under our standard conditions furnished the biaryl **24**. Treatment of **24** with LDA provided none of the desired cyclized product. To overcome this observed incompatibility of the benzyl protecting groups, a silicon for benzyl protecting group interchange was envisaged. Thus, exposure of **24** to catalytic transfer hydrogenation conditions (1,4-cyclohexadiene and 10% Pd−C)[13] gave the intermediate diphenol which, upon treatment with triisopropylsilyl chloride (3 equiv) in the presence of *N*,*N*-diisopropylethylamine and catalytic DMAP furnished **25** in 82% yield over two steps. Subjection of **25** to 3 equiv of LDA (THF/0 °C to room temperature/4 h) smoothly delivered the DreM product **26** in 70% yield. Deprotection with TBAF afforded the target analogue **2b** in 13 steps and 6.6% overall yield based on **8b**.

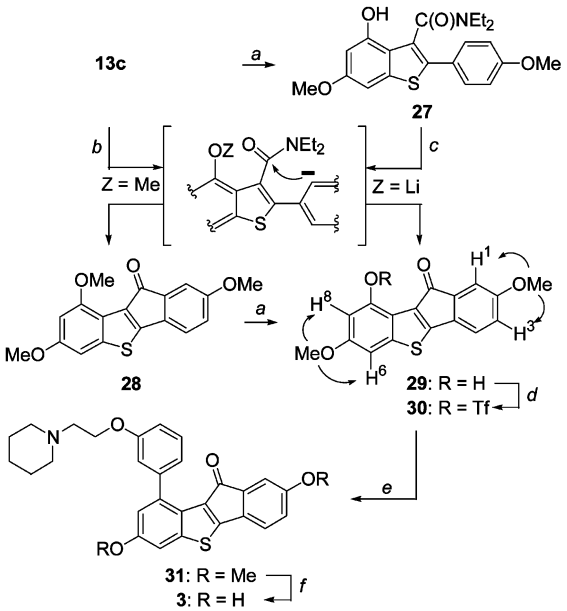
(10) Nagaoka, H.; Schmid, G.; Iio, H.; Kishi, Y. *Tetrahedron Lett.* **1981**, *22*, 899−902.

(11) Upon addition of more than 1 equiv of BCl_3 to a solution of **20**, the reaction mixture immediately changes from colorless to a dark green-blue, an observation that could be used for in situ confirmation of BCl_3 concentration.

(12) Bhatt, M. V. *J. Organomet. Chem.* **1978**, *156*, 221−226.

(13) Felix, A. M.; Heimer, E. P.; Lambros, T. J.; Tzougraki, X. C.; Meienhofer, J. *J. Org. Chem.* **1978**, *43*, 4194−4196.

SCHEME 5. Synthesis of Analogue 3 by a Combined Suzuki−Miyaura/Regioselective Directed Remote Metalation Strategy[a]



[a] Reagents and conditions: (a) BCl_3, DCM, 0 °C to rt, 75% (**27**), 95% (**29**); (b) LDA, THF, 0 °C to rt, 65%; (c) LDA, THF, 0 °C to reflux, 79%; (d) Tf_2O, Py, 0 °C to rt, 61%; (e) **16**, DME−2 M Na_2CO_3, 5 mol % $Pd(PPh_3)_4$, reflux, 93%; (f) NaSEt, DMF, 100 °C, 59%.

The synthesis of analogue **3** commenced with **13c** and implemented two variations of the LDA-induced anionic cyclization,[3b] both of which delivered the key intermediate **29** (Scheme 5). In the first variant, exposure of **13c** to 3 equiv of LDA (THF/0 °C to room temperature/3 h) cleanly furnished the 10*H*-benzo[*b*]indeno[2,1-d]thiophen-10-one **28** in 65% yield after recrystallization (Scheme 5, Z = Me). Proximity of the C-10-(C=O) and the 9-(OMe) groups resulted in a high-yielding BCl_3-induced regioselective demethylation[10] to give compound **29**. The second variant of the DreM reaction[3b] was conducted on the corresponding phenol **27**, obtained similarly to **29** by selective C-4 demethylation of **13c** with BCl_3.[10] In the case of **27**, the use of 4 equiv of LDA at higher reaction temperatures (THF/reflux/5 h) was found to be obligatory to achieve good conversion, presumably due to internal complexation of neighboring OZ (Z = Li) and $CONEt_2$ groups. However, these admittedly harsh conditions gave **29** in 79% yield. With the synthesis of **29** achieved by two different routes, qualitative NOE studies were performed to confirm the positions of two methoxy and phenolic functionalities. Irradiation of both methoxy groups with the center at δ 3.78 ppm showed a clear NOE effect with protons H^1 (δ 6.97), H^3 (δ 6.89), H^6 (δ 7.12), and H^8 (δ 6.43), thus unequivocally establishing the substitution pattern of **29**.

Triflation of **29** under typical conditions (Tf_2O/pyridine) afforded the dark-red benzoindenothiophenone **30**, which was subjected to standard Suzuki−Miyaura conditions using 1.5 equiv of coupling partner **16** to afford **31** in 93% yield. Demethylation of **31** with NaSEt[14] in DMF (100 °C/5 h) provided **3** in 59% yield, thus concluding the synthetic objective in an 11-step protocol and ∼4.7% overall yield based on **8c**.

In summary, the synthesis of three novel heterocylic analogues **2a**,**b** and **3**[15] of the drug Raloxifene (**1**) has been accomplished by routes involving key directed remote metalation (DreM) and electrophilic cyclization strategies combined with Suzuki−Miyaura cross-coupling processes. The cyclization precursors **25** and **13c** (or **27**) underwent LDA-mediated regioselective ring closure to give **2b** and **3**, respectively (paths *c* and *e*, Figure 2), while treatment of **19** with BCl_3 induced a Friedel−Crafts cyclization (path *a*) followed by concomitant global deprotection to give **2a**. In view of the efficient and contra-Friedel−Crafts nature of the anionic reactions, the broader use of DreM as a pivotal strategy for the construction of complex aromatics and heteroaromatics may be anticipated.

Experimental Section

All reactions requiring anhydrous conditions were carried out using syringe−septum cap techniques in flame-dried glassware under a positive argon/nitrogen atmosphere. Solvents and anhydrous liquid reagents were purified and dried according to established procedures.

Methyl 4-Hydroxy-6-*iso*-propoxy-2-(4-*iso*-propoxyphenyl)benzo[*b*]thiophene-3-carboxylate (17). To a cooled (−78 °C) solution of **13a** (4.74 g, 10.71 mmol) in CH_2Cl_2 (200 mL) was added slowly BCl_3 (11.2 mL, 1 M solution in heptane). The reaction mixture was stirred for 1 h at −78 °C, warmed to 0 °C over 30 min, and stirred for an additional 30 min, and the reaction was quenched with saturated Rochell's salt solution (100 mL). After 1 h stirring at room temperature, EtOAc (200 mL) was added and the organic layer was separated, dried (Na_2SO_4) and concentrated in vacuum. The resulting residue was passed through a short column (silica gel, EtOAc−hexanes 1:4) affording **17** (4.10 g, 10.24 mmol, 96% yield) as a pale yellowish solid: mp 129−130 °C (hexanes); IR (KBr) υ_{max} 1654, 1614, 1557, 1459, 1363, 1284, 1216, 1117, 1013, 951 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 11.11 (s, 1H), 7.32−7.26 (m, 2H), 6.94−6.87 (m, 2H), 6.79 (d, J = 2.1 Hz, 1H), 6.56 (d, J = 2.1 Hz, 1H), 4.66−4.53 (m, 2H), 3.65 (s, 3H), 1.39−1.34 (comp, 12H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 168.3, 158.4, 157.7, 154.1, 152.0, 141.1, 130.5, 126.7, 120.3, 120.2, 115.2, 102.9, 98.9, 70.4, 70.0, 52.4, 22.1 (2), 22.0 (2); EI MS (*m*/*z*, relative intensity) 402 (M^+ + 2, 5), 401 (M^+ + 1, 14), 400 (M^+, 59), 326 (16), 285 (18), 284 (100), 283 (10), 255 (13); EI HRMS (calcd for $C_{22}H_{24}O_5S$) 400.1344, found 400.1342. Anal. Calcd for $C_{22}H_{24}O_5S$: C, 65.98; H, 6.04; S, 8.01. Found: C, 66.20; H, 6.13; S, 8.07.

Methyl 6-*iso*-Propoxy-2-(4-*iso*-propoxyphenyl)-4-{[(trifluoromethyl)sulfonyl]oxy}benzo[*b*]-thiophene-3-carboxylate (18). To a cooled (ice bath) solution of **17** (4.00 g, 10.00 mmol) and NEt_3 (2.80 mL, 20.00 mmol) in CH_2Cl_2 (150 mL) was slowly added Tf_2O (2.0 mL, 12.00 mmol). The reaction mixture was stirred for 30 min at the ice bath temperature and then for an additional 30 min at room temperature, washed with H_2O (200 mL), dried (Na_2SO_4), and concentrated in a vacuum. The resulting residue was purified by column chromatography (silica gel, EtOAc−hexanes 1:9) to give **18** (4.42 g, 8.30 mmol, 83% yield) as colorless needles: mp 119−120 °C (hexanes); IR (KBr) υ_{max} 2985, 1724, 1613, 1536, 1500,

(14) Feutrill, G. I.; Mirrington, R. N. *Aust. J. Chem.* **1972**, *25*, 1719−1729, 1731−1735.

(15) Compounds **2a**, **2b**, and **3** were tested in an estrogen receptor (ER) binding assay to determine their ability to displace ^3H-estradiol at the ERα and ERβ receptors. For a complete description of the assay details, see: Wallace, O. B. PCT Int. App. WO 0294788, 2002. While **2a** and **2b** showed no binding affinity at either receptor (up to 10 uM), **3** demonstrated some binding affinity at both receptors: K_i ERα = 82.6 ± 4.6 nM.; K_i ERβ = 274 ± 17 nM.

1466, 1427, 1278, 1231, 1139, 1107, 1007 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.44 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 2.0 Hz, 1H), 7.00 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 4.65−4.54 (m, 2H), 3.83 (s, 3H), 1.38 (d, J = 6.0 Hz, 6H), 1.37 (d, J = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 158.8, 155.7, 144.7, 143.7, 142.2, 130.1, 124.4, 121.6, 118.6 (q, $^1J_{C-F}$ = 321 Hz), 115.8, 108.7, 106.8, 70.0, 52.7, 22.0 (2), 21.8 (2); EI MS (*m*/*z*, relative intensity) 534 (M^+ + 2, 10), 533 (M^+ + 1, 20), 532 (M^+, 76), 501 (8), 447 (8), 400 (31), 399 (100), 357 (71), 315 (89), 286 (22), 284 (30), 255 (17), 171 (11); EI HRMS (calcd for $C_{23}H_{23}O_7F_3S_2$) 532.0837, found 532.0811.

Methyl 6-*iso*-Propoxy-2-(4-*iso*-propoxyphenyl)-4-[3-(2-piperidinoethoxy)phenyl]benzo[*b*]-thiophene-3-carboxylate (19). To a degassed solution of **18** (1.065 g, 2.00 mmol), **16** (0.795 g, 2.40 mmol), and $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) in DME (25 mL) was added 2 M Na_2CO_3 solution (20 mL), and the reaction mixture was refluxed under argon for 30 min, cooled to room temperature, and concentrated in vacuum to remove most of the DME. The formed residue was partitioned between Et_2O (100 mL) and H_2O (50 mL), and the whole was stirred for 30 min. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined extract was dried (Na_2SO_4) and concentrated in vacuum, and the resulting residue was purified by column chromatography (silica gel, EtOAc−hexanes−TEA 1:1:0.05) to give **19** (1.119 g, 1.90 mmol, 95% yield) as a colorless glass: IR (film) υ_{max} 2975, 2933, 1726, 1591, 1494, 1446, 1246, 1206, 1160, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J = 8.5 Hz, 2H), 7.28 (t, J = 7.9 Hz, 1H), 7.25 (d, J = 2.3 Hz, 1H), 6.96 (d, J = 7.5 Hz, 1H), 6.94−6.88 (m, 3H), 6.86 (d, J = 8.5 Hz, 2H), 4.65−4.58 (m, 1H), 4.58−4.51 (m, 1H), 4.20−4.10 (m, 2H), 3.07 (s, 3H), 2.79−2.70 (m, 2H), 2.55−2.45 (m, 4H), 1.63−1.55 (m, 4H), 1.45−1.36 (m, 2H), 1.36 (d, J = 6.0 Hz, 6H), 1.33 (d, J = 6.1 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.4, 158.6, 158.4, 155.2, 142.9, 142.3, 141.1, 138.9, 130.3, 129.7, 129.1, 125.2, 124.9, 121.0, 118.2, 115.5, 114.4, 114.1, 106.3, 70.6, 69.8, 65.8, 57.8, 54.9, 51.4, 25.7, 24.0, 21.9 (4); EI MS (*m*/*z*, relative intensity) 588 (M^+ + 1, 5), 587 (M^+, 14), 586 (M^+ − 1, 1), 476 (9), 392 (11), 345 (6), 112 (5), 99 (16), 98 (100); EI HRMS (calcd for $C_{35}H_{41}NO_5S$) 587.2705, found 587.2731.

2-Hydroxy-5-(4-hydroxyphenyl)-9-(2-piperidinoethoxy)-6*H*-phenanthro[1,10-*bc*]thiophen-6-one Hydrochloride (2a) and 2,7-Dihydroxy-5-(4-hydroxyphenyl)-6*H*-phenanthro[1,10-*bc*]thiophen-6-one (20). To a cooled (ice bath) solution of **19** (657 mg, 1.12 mmol) in CH_2Cl_2 (45 mL) was added slowly BCl_3 (5.80 mL, 1 M solution in heptane). The reaction mixture was stirred for 1 h at 0 °C; the reaction was slowly quenched with saturated $NaHCO_3$ solution (30 mL), and the whole was extracted with 1:1 EtOAc−THF mixture (5 × 75 mL). The combined organic extract was concentrated in vacuum, and the resulting solid residue was dissolved in 1:1 MeOH−acetone mixture (∼100 mL) and treated with 5 g of Florisil. The resulting suspension was evaporated in vacuum, and the Florisil absorbent was placed in a column and eluted sequentially with acetone (∼200 mL) and MeOH (∼200 mL). The acetone fraction was evaporated in vacuum and redissolved in acetone, and the resulting precipitate was collected and combined with the MeOH fraction. The filtrate was concentrated in a vacuum. The resulting residue was purified by column chromatography (silica gel, hexanes−EtOAc 1:1 to EtOAc) to give **20** as a brown-red solid (62 mg, 0.172 mmol, 15% yield): mp > 300 °C; IR (KBr) υ_{max} 3353 (br), 1606, 1593, 1503, 1448, 1356, 1256, 1175, 822 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 13.87 (s, 1H, exchange with D_2O), 10.12 (br s, 2H, exchange with D_2O), 7.85−7.76 (m, 4H), 7.69 (t, J = 8.0 Hz, 1H), 7.54 (d, J = 1.6 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 6.90 (d, J = 8.6 Hz, 2H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 184.2, 164.3, 159.6, 157.6, 156.5, 137.0, 136.1, 135.9, 131.4, 128.5, 126.5, 122.9, 121.5, 116.7 (CH and C), 115.1, 113.8, 110.1, 108.9; EI MS (*m*/*z*, relative intensity) 361 (M^+ + 1, 24), 360 (M^+, 100), 359 (M^+ − 1, 65), 331 (10), 180 (8), 157 (11), 245 (5); EI HRMS (calcd for $C_{21}H_{12}O_4S$) 360.0456; found 360.0452. Anal. Calcd for $C_{21}H_{12}O_4S$ + 0.5H_2O: C, 68.28; H, 3.55; S, 8.68. Found: C, 68.79; H, 3.67; S, 8.82.

The MeOH fraction was acidified with concentrated HCl and evaporated to dryness, and the resulting solid residue was redissolved in MeOH. Et_2O was added, and the resulting precipitate was collected and washed (acetone, Et_2O) to give hydrochloride monohydrate **2a** (328 mg, 0.624 mmol, 56% yield) as a yellow-orange solid: mp > 300 °C (dec); IR (KBr) υ_{max} 3680−2400 (br), 1630, 1607, 1487, 1436, 1346, 1279, 1225, 1208, 1174, 1120 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 10.90 (br s, 1H, concentration-dependent δ; exchange with D_2O), 10.23 (s, 1H, exchange with D_2O), 10.16 (s, 1H, exchange with D_2O), 8.23 (d, J = 8.8 Hz, 1H), 7.92 (d, J = 1.4 Hz, 1H), 7.84 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 1.4 Hz, 1H), 7.18 (dd, J = 8.8, 2.0 Hz, 1H), 6.89 (d, J = 8.6 Hz, 2H), 4.68 (br s, 2H), 3.53 (br s, 4H), 3.03 (br s, 2H), 2.39 (s, 1H, exchange with D_2O), 1.82 (br s, 6 H), 1.68 (br s, 1H), 1.39 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 177.4, 161.5, 159.4, 156.4, 154.8, 137.1 (2), 131.3, 130.3, 129.5, 127.2, 126.7, 123.1, 122.3, 116.0, 115.0, 110.3, 108.6, 107.5, 62.7, 54.5, 52.5, 22.3, 21.2; EI MS (*m*/*z*, relative intensity) (M^+ not registered), 447 (53), 446 (100), 260 (5), 223 (12), 184 (7), 168 (15), 141 (15), 115 (14); ES HRMS (calcd for $C_{28}H_{26}NO_4S$ − Cl) 472.1583, found 472.1574.

2-*iso*-Propoxy-5-(4-*iso*-propoxyphenyl)-7-(2-piperidinoethoxy)-6*H*-phenanthro[1,10-*bc*]thiophen-6-one (21). To a cooled (−78 °C) solution of **19** (346 mg, 0.589 mmol) in THF (6 mL) was cannulated a solution of LDA [2.94 mmol; prepared from HN(*i*-Pr)$_2$ (0.41 mL) and *n*-BuLi (2.10 mL, 1.38 M in hexane)] in THF (4 mL). The mixture was stirred for 30 min at −78 °C followed by 1 h at 0 °C and 2 h at room temperature before the reaction was quenched with saturated NH_4Cl solution (20 mL). The mixture was extracted with Et_2O (4 × 20 mL); the combined organic extract was evaporated in vacuum, and the resulting residue was redissolved in Et_2O, loaded on silica gel, and purified by column chromatography (silica gel, EtOAc−hexanes−NEt_3 70:25:5) followed by recrystallization to afford **21** (108 mg, 0.194 mmol, 33% yield) as yellow crystals: mp 159−161 °C (hexanes); IR (KBr) υ_{max} 2930, 1648, 1591, 1478, 1438, 1252, 1182, 1107, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.9 Hz, 2H), 7.80 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 1.9 Hz, 1H), 7.57 (t, J = 8.1 Hz, 1H), 7.34 (d, J = 1.9 Hz, 1H), 7.06 (d, J = 8.1 Hz, 1H), 6.94 (d, J = 8.9 Hz, 2H), 4.75−4.60 (m, 2H), 4.27 (t, J = 6.5 Hz, 2H), 2.92 (t, J = 6.5 Hz, 2H), 2.60−2.50 (m, 4H), 1.65−1.55 (m, 4H), 1.55−1.45 (m, 2H), 1.42 (d, J = 6.0 Hz, 6H), 1.39 (d, J = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7, 161.7, 159.2, 156.5, 154.4, 137.9, 137.5, 133.3, 131.4, 131.3, 127.9, 125.2, 124.8, 123.5, 115.5, 115.1, 114.0, 111.5, 107.9, 71.2, 69.9, 67.8, 57.6, 55.2, 26.0, 24.2, 22.1 (2); EI MS (*m*/*z*, relative intensity) 556 (M^+, 2), 555 ($M - 1^+$, 5), 446 (10), 445 (28), 444 (77), 402 (12), 361 (16), 360 (54), 359 (35). Anal. Calcd for ($C_{34}H_{37}NO_4S$) C, 73.48; H, 6.71; N, 2.52. Found: C, 73.29; H, 6.80; N, 2.46.

***N*,*N*-Diethyl 6-(Benzyloxy)-2-[4-(benzyloxy)phenyl]-4-hydroxybenzo[*b*]thiophene-3-carboxamide (22).** To a cooled (−78 °C) solution of **13b** (1.70 g, 2.71 mmol) in CH_2Cl_2 (30 mL) was slowly added 9-Br-BBN (2.84 mL, 1 M CH_2Cl_2 solution). The solution was slowly allowed to warm to room temperature (∼6 h) and the reaction sequentially slowly quenched with saturated $NaHCO_3$ solution (30 mL) and ethanolamine (0.33 g, 5.42 mmol). This mixture was stirred for an additional 2 h and extracted with CH_2Cl_2 (3 × 75 mL). The combined organic extract was concentrated in vacuum, and the resulting solid residue was recrystallized from MeOH to furnish **22** (1.19 g, 2.22 mmol, 82% yield) as a colorless microfine crystalline solid: mp 218 °C (MeOH); IR (KBr) υ_{max} 3168 br, 1611, 1570, 1500, 1422, 1378, 1289, 1243, 1180, 1133, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (br s, 1H), 7.50−7.30 (m, 12H), 7.01 (d, J = 8.7 Hz, 2H), 6.94 (d, J = 1.2 Hz, 1H), 6.55 (s, 1H), 5.10 (s, 4H), 3.85−3.75 (m, 1H), 3.35−3.15 (m, 2H), 2.85−2.75 (m, 1H), 1.10 (t, J = 7.0 Hz, 3H), 0.63 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 159.4, 158.3, 153.3, 141.2,

138.2, 136.9, 136.5, 129.9, 128.7, 128.6, 128.2, 128.0, 127.5 (2), 126.3, 123.3, 122.4, 115.4, 102.2, 98.7, 70.4, 70.1, 43.7, 39.9, 13.2, 12.0; FAB MS (*m*/*z*, relative intensity) 540 ($MH^+ + 2$, 1), 539 ($MH^+ + 1$, 4), 538 (MH^+, 11), 537 ($MH^+ - 1$, 2), 392 (3), 391 (9), 277 (8), 185 (100), 167 (8), 149 (30), 132 (14), 113 (7); ES HRMS (calcd for $C_{33}H_{32}NO_4S$, M + 1) 538.2052, found 538.2055. Anal. Calcd for $C_{33}H_{31}NO_4S$: C, 73.72; H, 5.81; N, 2.61. Found: C, 73.47; H, 5.86; N, 2.65.

6-(Benzyloxy)-2-[4-(benzyloxy)phenyl]-3-[(diethylamino)carbonyl]benzo[*b*]thiophen-4-yl Trifluoromethanesulfonate (23). To a cooled (ice bath) solution of **22** (0.52 g, 0.97 mmol) and NEt_3 (0.27 mL, 1.94 mmol) in CH_2Cl_2 was slowly added triflic anhydride (0.19 mL, 1.16 mmol). The reaction mixture was stirred for 1.5 h at 0 °C, warmed to room temperature, washed with cold H_2O, dried (Na_2SO_4), and concentrated in vacuum. The resulting residue was purified by column chromatography (silica gel, EtOAc−hexanes 1:4) followed by recrystallization to give **23** (0.55 g, 0.82 mmol, 85% yield) as colorless light needles: mp 150 °C (EtOAc−hexanes); IR (KBr) υ_{max} 2982, 1627, 1536, 1499, 1458, 1426, 1274, 1216, 1139, 1104, 1023, 814 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 8.8 Hz, 2H), 7.49−7.30 (m, 11H), 7.07 (d, J = 1.9 Hz, 1H), 6.95 (d, J = 8.8 Hz, 2H), 5.12 (s, 2H), 5.10 (s, 2H), 4.05−3.95 (m, 1H), 3.12−2.91 (m, 3H), 1.11 (t, J = 7.2 Hz, 3H); 0.65 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 159.4, 156.5, 144.2, 142.7, 139.3, 136.5, 135.8, 130.0, 128.8, 128.6, 128.4, 128.1, 127.6, 127.5, 125.4, 125.0, 124.7, 119.3 (q, $^1J_{C-F}$ = 319 Hz), 115.2, 107.5, 105.7, 71.1, 70.1, 43.7, 39.7, 13.4, 12.4; FAB MS (*m*/*z*, relative intensity) 671 ($MH^+ + 1$, 4), 670 (MH^+, 9), 669 ($M^+ - 1$, 2), 391 (8), 285 (16), 284 (73), 185 (76), 148 (45), 132 (100), 114 (18); ES HRMS (calcd for $C_{34}H_{31}F_3NO_6S_2$, M + 1) 670.1545, found 670.1547. Anal. Calcd for $C_{34}H_{30}NO_6S_2$: C, 60.97; H, 4.51; N, 2.09. Found: C, 60.92; H, 4.40; N, 2.12.

***N,N*-Diethyl 6-(Benzyloxy)-2-[4-(benzyloxy)phenyl]-4-[3-(2-piperidinoethoxy)phenyl]benzo[*b*]-thiophene-3-carboxamide (24).** To a solution of **23** (0.635 g, 0.95 mmol), **16** (0.315 g, 1.11 mmol), and $Pd(PPh_3)_4$ (55 mg, 0.05 mmol) in DME (15 mL) was added 2 M Na_2CO_3 solution (8 mL). The mixture was refluxed for 3 h, cooled to room temperature, and concentrated in vacuum to remove most of the DME; the resulting slurry was partitioned between Et_2O (40 mL) and H_2O (20 mL), and the whole was stirred for 30 min. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined extract was dried (Na_2SO_4) and concentrated in vacuum, and the resulting residue was purified by column chromatography (silica gel, EtOAc−hexanes−NEt_3 3:7:0.06) to give **24** (0.55 g, 0.76 mmol, 80% yield) as a colorless glass; IR (film) υ_{max} 2936, 1633, 1496, 1452, 1239,1026 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.60 (d, 1H, J = 2.4 Hz), 7.60−7.56 (m, 2H), 7.51 (d, 2H, J = 7.3 Hz), 7.46 (d, 2H, J = 7.2 Hz), 7.41−7.28 (comp, 6H), 7.23 (t, 1H, J = 7.9 Hz), 7.04 (d, 2H, J = 8.8 Hz), 6.91 (d, 1H, J = 2.4 Hz), 6.92−6.85 (br m, 3H), 5.24 (s, 2H), 5.14 (s, 2H), 4.35−4.15 (br m, 1H), 4.12−4.05 (m, 1H), 3.05−2.90 (m, 2H), 2.85−2.40 (m, 8H), 1.55−1.50 (m, 4H), 1.42−1.35 (m, 2H), 0.75 (t, 3H, J = 7.2 Hz), 0.55 (t, 3H, J = 7.2 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 165.6, 159.1, 158.1, 156.1, 141.1, 140.8, 139.6, 137.3, 137.2, 129.9, 129.0, 128.44, 128.40, 127.84, 127.79, 127.63, 127.59, 126.4, 117.4 (2), 115.5, 114.9, 105.2, 70.0, 69.6, 65.9, 58.0, 54.8, 43.9, 39.6, 26.0, 24.2, 13.3, 12.5; FAB MS (*m*/*z*, relative intensity) 726 ($MH^+ + 1$, 4), 725 (MH^+, 7), 635 (2), 369 (5), 277 (22), 185 (100), 167 (6), 133 (11), 112 (52); ES HRMS (calcd for $C_{46}H_{49}N_2O_4S$, M + 1) 725.3413, found 725.3399.

***N,N*-Diethyl 4-[3-(2-Piperidinoethoxy)phenyl]-6-[(1,1,1-tri-*iso*-propylsilyl)oxy]-2-4-[(1,1,1-tri-*iso*-propylsilyl)oxy]-phenylbenzo[*b*]thiophene-3-carboxamide (25).** To a solution of **24** (0.22 g, 0.30 mmol) and 10% w/w Pd−C (0.66 g, ∼30% substrate by weight) in a mixture of 3:2 EtOH−HOAc (5 mL) was added 1,4-cyclohexadiene (0.14 mL, 1.50 mmol). The reaction mixture was allowed to stir at ambient temperature for 3 days and then passed through a small pad of silica, which was then washed with EtOH (∼15 mL). The filtrate was concentrated in vacuum, ensuring complete removal of solvents, and the residue was redissolved in CH_2Cl_2 (5 mL). To this stirred solution was added *i*-Pr_2EtN (0.39 mL, 2.22 mmol) followed by triisopropylsilyl chloride (0.31 mL, 1.48 mmol) and then DMAP (70 mg, 0.057 mmol). The reaction mixture was stirred for 4 h and diluted with saturated NH_4Cl (5 mL), and the whole was extracted with CH_2Cl_2 (2 × 20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuum. The residue was purified by column chromatography (silica gel, EtOAc−hexanes−NEt_3 9:88:3) followed by recrystallization to give **25** as a colorless solid (0.21 g, 0.245 mmol, 82% yield): mp 116−118 °C (acetone); IR (film) υ_{max} 2941, 2867, 1631, 1603, 1584, 1495, 1443, 1388, 1265 cm^{-1}; ^1H NMR (500 MHz, 80 °C, DMF-d_7) δ 7.57 (d, J = 8.3 Hz, 2H), 7.53 (s, 1H), 7.28 (t, J = 7.7 Hz, 1H), 7.00−6.90 (comp, 5H), 6.85 (s, 1H), 4.28−4.20 (m, 1H), 4.20−4.33 (m, 1H), 3.10−2.95 (m, 3H), 2.78−2.70 (m, 3H), 2.70−2.60 (m, 1H), 2.55−2.49 (m, 4H), 1.58−1.51 (m, 4H), 1.45−1.27 (m, 8H), 1.17 (d, J = 7.3 Hz, 18H), 1.13 (d, J = 7.3 Hz, 18H), 0.80 (t, J = 7.0 Hz, 3H), 0.61 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, 80 °C, DMF-d_7) δ 166.2, 158.8, 157.0, 153.4, 141.6, 141.4, 140.1, 138.0, 130.9, 130.5, 129.8, 128.9, 127.4, 122.2, 121.6, 120.5, 116.7, 114.7, 111.6, 67.0, 58.4, 55.3, 44.2, 39.8, 26.5, 24.7, 18.00, 17.9, 13.6, 13.12, 13.07, 12.8; FAB MS (*m*/*z*, relative intensity) 859 ($MH^+ + 1$, 3), 858 (MH^+, 6), 857 ($MH^+ - 1$, 8), 146 (5), 133 (24), 112 (100); ES HRMS (calcd for $C_{50}H_{77}N_2O_4SSi_2$, M + 1) 857.5142, found 857.5147. Anal. Calcd for $C_{50}H_{76}N_2O_4SSi_2$: C, 70.04; H, 8.93; N, 3.27. Found: C, 70.09; H, 8.89; N, 3.25.

7-(2-Piperidinoethoxy)-2-[(1,1,1-tri-*iso*-propylsilyl)oxy]-5-4-[(1,1,1-tri-*iso*-propylsilyl)oxy]phenyl-6*H*-phenanthro-[1,10-*bc*]thiophen-6-one (26). To a cooled solution (−40 °C) of **25** (300 mg, 0.35 mmol) in THF (5 mL) was slowly added a solution of LDA (1.50 mL, 1.05 mmol, 0.70 M in THF). The solution was allowed rise to 0 °C over 5 h; the reaction was quenched with saturated $NHCl_4$ (15 mL), and the whole was extracted with EtOAc (3 × 20 mL). The combined organic extract was dried (Na_2SO_4) and subjected to filtration, and the filtrate was concentrated in vacuum. The resulting residue was purified by column chromatography (silica gel, EtOAc−hexanes−NEt_3 40:60:2.5) to give **26** as a bright yellow glass (192 mg, 0.245 mmol, 70% yield); IR (film) υ_{max} 2942, 2866, 1654, 1591, 1464, 1267 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 7.95 (d, J = 8.0 Hz, 1H), 7.88−7.83 (m, 3H), 7.66 (t, J = 8.2 Hz, 1H), 7.60 (d, J = 1.8 Hz, 1H), 7.21 (d, J = 8.2 Hz, 1H), 7.01 (d, J = 8.7 Hz, 2H), 4.20 (t, J = 5.8 Hz, 2H), 2.77 (t, J = 5.8 Hz, 2H), 2.63−2.50 (m, 4H); 1.60−1.45 (m, 4H), 1.45−1.30 (m, 8H), 1.18 (d, J = 7.3, 18H), 1.16 (d, J = 7.3 Hz, 18H); ^{13}C NMR (75 MHz, acetone-d_6) δ 179.5, 162.6, 158.3, 155.6, 154.2, 138.3, 138.2, 134.5, 132.25, 132.22, 128.8, 127.0, 125.8, 124.1, 1201, 116.3, 115.2, 114.6, 113.4, 69.4, 58.5, 55.9, 27.0, 25.1, 18.4, 18.3, 13.4; FAB MS (*m*/*z*, relative intensity) 785 ($MH^+ + 1$, 3), 784 (M^+, 5), 112 (100); ES HRMS (calcd for $C_{46}H_{66}NO_4SSi_2$, M + 1) 784.4251, found 784.4251.

2-Hydroxy-5-(4-hydroxyphenyl)-7-(2-piperidinoethoxy)-6*H*-phenanthro[1,10-*bc*]thiophen-6-one (2b). To a stirred solution of **26** (200 mg, 0.267 mmol) in THF (3 mL) was added TBAF (0.58 mmol, 1 M solution in THF), which was accompanied by an immediate color change to a dark violet. The mixture was stirred at room temperature for 2 h and concentrated in vacuum without heating, and the resulting residue was treated with MeOH (10 mL) and H_2O (10 mL). The formed red precipitate was collected by filtration and washed successively with H_2O (2 × 10 mL), 1% aq NH_4OH (5 mL), H_2O (2 × 10 mL), and acetone (2 × 5 mL). Drying in a vacuum gave a monohydrate of **2b** (108 mg, 0.229 mmol, 86% yield) as a red-brown solid: mp > 180 °C sublm; IR (KBr) υ_{max} 3435 br, 2933 br, 1708, 1591, 1453 br, 1350, 1259, 1169 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.30−9.50 (br s, 2H), 7.89 (d, J = 7.9 Hz, 1H), 7.74−7.62 (comp, 4H), 7.42 (d, J = 1.2 Hz, 1H), 7.20 (d, J = 8.2 Hz, 1H), 6.86 (d, J = 8.6 Hz, 2H), 4.17 (t, J = 5.8 Hz,

2H), 3.40−3.05 (br s, 4H), 2.73 (t, J = 5.8 Hz, 2H), 1.54−1.45 (m, 4H), 1.42−1.33 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.5, 161.9, 159.8, 157.1, 153.3, 137.9, 137.7, 134.6, 131.8, 130.1, 128.0, 124.9, 124.3, 123.5, 116.3, 115.9, 115.2, 110.7, 109.1, 68.7, 58.0, 55.3, 26.5, 24.7; FAB MS (m/z, relative intensity) 474 (MH^+ + 2, 4), 473 (MH^+ + 1, 10) 472 (MH^+, 24), 391 (4), 242 (7), 185 (31), 149 (16), 133 (35), 112 (100); ES HRMS (calcd for $C_{28}H_{26}NO_4S$, M + 1) 472.1582, found 472.1573. Anal. Calcd for $C_{28}H_{25}NO_4S\cdot H_2O$: C, 68.69; H, 5.56; N, 2.86. Found: C, 68.52; H, 5.33; N, 2.97.

***N*,*N*-Diethyl 4-Hydroxy-6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene-3-carboxamide (27).** To a cooled (ice bath) solution of **13c** (1.199 g, 3.00 mmol) in CH_2Cl_2 (30 mL) was added a solution of BCl_3 (6.10 mL, 1 M solution in heptane). The reaction mixture was stirred at 0 °C (0.5 h), at room temperature (3 h), and cooled in the ice bath and the reaction quenched by slow addition of saturated Rochell's salt solution (30 mL). EtOAc (40 mL) was added, and the heterogeneous mixture was stirred for 2 h. The organic layer was separated, and the aqueous layer was extracted with a mixture of 4:1 EtOAc−CH_2Cl_2 (4 × 25 mL). The combined organic extract was dried (Na_2SO_4), subjected to filtration, and evaporated in vacuum. The resulting solid residue was recrystallized to afford **27** (872 mg, 2.26 mmol, 75% yield) as pale yellow crystals: mp 171−172 °C (EtOAc−hexanes); IR (KBr) υ_{max} 3191 br, 1606, 1577, 1533, 1506, 1460, 1425, 1294, 1250, 1142, 1032 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.43 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 2.1 Hz, 1H), 6.55 (d, J = 2.1 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.86−3.75 (m, 1H), 3.35−3.15 (m, 2H), 2.85−2.70 (m, 1H), 1.16 (t, J = 7.1 Hz, 3H), 0.65 (t, J = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.0, 160.2, 159.2, 153.2, 141.2, 137.9, 129.9, 126.0, 123.3, 122.2, 114.4, 101.4, 97.4, 55.6, 55.4, 43.7, 39.9, 13.2, 12.0; EI MS (m/z, relative intensity) 387 (M^+ + 2, 3), 386 (M^+ + 1, 9), 385 (M^+, 41), 314 (8), 313 (26), 312 (100), 297 (19), 282 (5), 269 (10), 242 (7), 241 (7), 129 (5); EI HRMS (calcd for $C_{21}H_{23}NO_4S$) 385.1348, found 385.1342. Anal. Calcd for $C_{21}H_{23}NO_4S$: C, 65.43; H, 6.01; N, 3.63; S, 8.32; Found: C, 65.36; H, 6.07; N, 3.60; S, 8.26.

2,7,9-trimethoxy-10*H*-benzo[*b*]indeno[2,1-*d*]thiophen-10-one (28). To a cooled (ice bath) solution of LDA [10.00 mmol; prepared from HN(i-Pr)$_2$ (1.41 mL) and n-BuLi (7.00 mL, 1.43M in hexane)] in THF (25 mL) was added a solution of **13c** (1.336 g, 3.34 mmol) in THF (15 mL). The reaction mixture was stirred at 0 °C (0.5 h) and then at room temperature (2.5 h) and cooled in the ice bath, and the reaction was quenched with saturated NH_4Cl solution (50 mL). CH_2Cl_2 (20 mL) was added, and the reaction mixture was stirred for 1 h, the organic phase was separated, and the aqueous phase was extracted with a mixture of 4:1 EtOAc−DCM (4 × 25 mL). The combined organic extract was concentrated in vacuum, and the resulting residue was dissolved in CH_2Cl_2. This solution was subjected to filtration; the filtrate was passed through a silica gel column (CH_2Cl_2 eluent), and the red band fraction was collected. Evaporation of the collected fraction followed by recrystallization provided **28** (711 mg, 2.18 mmol, 65% yield) as deep red crystals; mp 185−186 °C (benzene−MeOH); IR (KBr) υ_{max} 1703, 1586, 1459, 1441, 1328, 1275, 1208, 1145, 1077, 1029 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.04 (d, J = 2.4 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 1.9 Hz, 1H), 6.72 (dd, J = 8.0, 2.4 Hz), 6.44 (d, J = 1.9 Hz, 1H), 3.98 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 184.8, 160.9, 159.7, 159.0, 155.7, 145.3, 138.5, 133.8, 130.5, 119.7, 118.3, 115.7, 111.0, 98.0, 97.5, 55.8, 55.6 (2); EI MS (m/z, relative intensity) 328 (M^+ + 2, 13), 327 (M^+ + 1, 21), 326 (M^+, 100), 312 (17), 311 (62), 283 (11), 268 (19), 253 (11), 240 (6), 225 (9), 163 (9); EI HRMS (calcd for $C_{18}H_{14}O_4S$) 326.0613, found 326.0615. Anal. Calcd for $C_{18}H_{14}O_4S$: C, 66.24; H, 4.32; S, 9.83; Found: C, 66.22; H, 4.36; S, 9.56.

9-Hydroxy-2,7-dimethoxy-10*H*-benzo[*b*]indeno[2,1-*d*]thiophen-10-one (29): From 27. To a cooled (ice bath) solution of LDA [2.52 mmol; prepared from HN(i-Pr)$_2$ (0.35 mL) and n-BuLi (1.42 mL, 1.77 M in hexane)] in THF (5 mL) was added a solution of **27** (243 mg, 0.63 mmol) in THF (15 mL). The reaction mixture was stirred at room temperature (1 h), refluxed (5 h), and cooled in an ice bath, and the reaction was quenched with saturated NH_4Cl solution (20 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 15 mL). The combined organic extract was concentrated in vacuum; the resulting residue was dissolved in CH_2Cl_2, and this solution was passed through a short silica gel column (CH_2Cl_2 eluent) to give **29** (156 mg, 0.50 mmol, 79% yield) as a black solid; mp 218−220 °C (EtOAc); IR (KBr) υ_{max} 3274 br, 2935, 2835, 1672, 1617, 1602, 1571, 1469, 1433, 1283, 1202, 1128, 1080, 1028 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 9.08 (s, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 1.9 Hz, 1H), 6.97 (d, J = 2.3 Hz, 1H), 6.89 (dd, J = 8.0, 2.3 Hz, 1H), 6.43 (d, J = 1.9 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 186.5, 160.7, 159.4, 159.3, 152.3, 145.4, 137.5, 133.1, 130.4, 121.6, 116.4, 116.2, 111.7, 100.7, 98.7, 55.8, 55.6; EI MS (m/z, relative intensity) 314 (M^+ + 2, 17), 313 (M^+ + 1, 28), 312 (M^+, 100), 298 (19), 297 (60), 269 (20), 254 (12), 226 (19), 198 (12), 156 (20), 117 (18); EI HRMS (calcd for $C_{17}H_{12}O_4S$) 312.0456, found 312.0466. **From 28.** To a cooled (ice bath) solution of **28** (825 mg, 2.53 mmol) in CH_2Cl_2 (50 mL) was added BCl_3 (5.30 mL, 1 M solution in heptane). The reaction mixture was stirred at 0 °C (15 min) and then at room temperature (24 h), and the reaction was quenched with 5% $NaHCO_3$ solution (50 mL). The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (4 × 75 mL), and the combined organic extract was dried (Na_2SO_4) and concentrated in vacuum. The resulting residue was recrystallized from EtOAc to give **29** (749 mg, 2.399 mmol, 95% yield), which was shown by physical and spectroscopic comparison to be identical to the material obtained from **27**.

2,7-Dimethoxy-10-oxo-10*H*-benzo[*b*]indeno[2,1-*d*]thiophen-9-yl Trifluoromethanesulfonate (30). To a cooled (ice bath) solution of **29** (229 mg, 0.73 mmol) in pyridine (15 mL) was added Tf_2O (0.19 mL, 1.10 mmol). The resulting solution was stirred at 0 °C (0.5 h) and then at room temperature (1 h) and cooled in the ice bath, and the reaction was quenched with 50% citric acid solution (50 mL). CH_2Cl_2 (50 mL) was added, and the organic phase was separated, dried (Na_2SO_4), and concentrated in a vacuum. The residue was purified by column chromatography (CH_2Cl_2 eluent) to give **30** (199 mg, 0.45 mmol, 61% yield) as a red solid; mp 213−214 °C (EtOAc); IR (KBr) υ_{max} 1708, 1618, 1599, 1558, 1476, 1428, 1341, 1269, 1242, 1138, 1068, 1025, 961 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.24 (d, J = 2.0 Hz, 1H), 7.12 (d, J = 2.4 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 2.0 Hz, 1H), 6.77 (dd, J = 8.0, 2.4 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.6, 167.4, 162.2, 155.7, 147.0, 144.2, 138.6, 129.4, 129.1, 123.5, 121.8, 118.8 (q, $^1J_{C-F}$ = 322 Hz), 116.9, 111.6, 104.7, 57.5, 55.8; EI MS (m/z, relative intensity) 446 (M^+ + 2, 7), 445 (M^+ + 1, 12), 444 (M^+, 51), 313 (19), 312 (48), 311 (100), 297 (41), 283 (18), 269 (11), 268 (40), 253 (15), 240 (15), 225 (17), 169 (8); EI HRMS (calcd for $C_{18}H_{11}F_3O_6S_2$) 443.9949, found 443.9957. Anal. Calcd for $C_{18}H_{11}F_3O_6S_2$: C, 48.65; H, 2.50. Found: C, 48.91; H, 2.67.

2,7-Dimethoxy-9-[3-(2-piperidinoethoxy)phenyl]-10*H*-benzo[*b*]indeno[2,1-*d*]thiophen-10-one (31). To a stirred suspension of **30** (603 mg, 1.36 mmol) and **16** (676 mg, 2.04 mmol) in a degassed DME−2 M Na_2CO_3 mixture (20:15 mL) was added $Pd(PPh_3)_4$ (81 mg, 0.07 mmol), and the mixture was refluxed for 2 h under argon and cooled to room temperature. The organic phase was separated; the aqueous phase was extracted with EtOAc (3 × 15 mL), and the combined organic extract was evaporated in vacuum to give a residue that was dissolved in EtOAc, dried (Na_2SO_4), subjected to filtration, and then concentrated in vacuum. Purification of the residue by column chromatography (EtOAc−hexanes−NEt_3 1:1:0.05) gave **31** (631 mg, 1.26 mmol, 93% yield) as a red solid: mp 149−150 °C (hexanes, *note:* very low solubility); IR (KBr) υ_{max} 2930,

1708, 1591, 1560, 1473, 1433, 1284, 1223, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (t, J = 7.8 Hz, 1H), 7.23 (d, J = 2.4 Hz, 1H), 7.05−6.89 (comp, 6H), 6.71 (dd, J = 8.0, 2.4 Hz, 1H), 4.14 (t, J = 6.2 Hz, 2H), 3.87 (s, 3H), 3.76 (s, 3H), 2.78 (t, J = 6.2 Hz, 2H), 2.60−2.45 (m, 4H), 1.65−1.50 (m, 4H), 1.50−1.40 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 184.3, 162.1, 161.1, 158.3, 157.0, 145.1, 142.7, 139.0, 138.6, 133.8, 130.2, 128.6, 126.0, 121.8, 120.1, 116.8, 116.1, 115.6, 113.9, 110.7, 105.7, 65.8, 58.0, 55.7, 55.6, 55.0, 26.0, 24.2; EI MS (*m*/*z*, relative intensity) 501 (M^+ + 2, 2), 500 (M^+ + 1, 6), 499 (M^+, 19), 388 (11), 373 (5), 99 (10), 98 (100); EI HRMS (calcd for $C_{30}H_{29}NO_4S$) 499.1817, found 499.1796. Anal. Calcd for $C_{30}H_{29}NO_4S$: C, 72.12; H, 5.85; N, 2.80. Found: C, 72.31; H, 5.86; N, 2.79.

2,7-Dihydroxy-9-[3-(2-piperidinoethoxy)phenyl]-10*H*-benzo[*b*]indeno[2,1-*d*]thiophen-10-one Hydrochloride (3). To a cooled (ice bath) suspension of **31** (293 mg, 0.586 mmol) and NaH (141 mg, 3.53 mmol, 60% w/w suspension in mineral oil) in DMF (8 mL) was carefully added EtSH (0.26 mL, 3.53 mmol), which was accompanied by an intensive gas evolution. The reaction mixture was stirred at 100−110 °C under an argon atmosphere for 5 h, cooled to room temperature, and diluted with EtOAc (20 mL), and the reaction was quenched with saturated NH_4Cl (10 mL). The organic layer was separated; the aqueous layer was extracted with a mixture of 1:1 EtOAc−THF (4 × 20 mL), and the combined organic extract was evaporated in vacuum. The resulting residue was redissolved in MeOH, and the solution was loaded on silica gel. Column chromatography (silica gel, DCM−MeOH−NEt_3 90:5:5) afforded a solid that was redissolved in MeOH, and the resulting solution was acidified with concentrated HCl. Solvent evaporation in vacuum gave **3** hydrochloride monohydrate as a blue powder (181 mg, 0.344 mmol, 59% yield): mp 180−185 °C (dec); IR (KBr) ν_{max} 3680−2400 br, 1694, 1615, 1576 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 10.12 (s, 1H, exchange with D_2O), 9.98 (s, 1H, exchange with D_2O), 9.97 (br s, 1H, exchange with D_2O), 7.37 (d, 1H, J = 2.1 Hz), 7.33 (t, 1H, J = 8.2 Hz), 7.17 (d, 1H, J = 7.8 Hz), 7.05−6.90 (comp, 3H), 6.77 (d, 1H, J = 2.1 Hz), 6.72−6.63 (comp, 2H), 4.37 (br s, 2H), 3.60−3.40 (br s, 4H), 3.32 (s, 1H, H_2O), 3.15−2.85 (m, 2H), 1.90−1.60 (m, 5H), 1.50−1.25 (1H, m); ^{13}C NMR (50 MHz, DMSO-d_6) δ 184.0, 161.9, 159.3, 156.8, 154.9, 145.0, 142.6, 137.9, 137.6, 132.4, 128.8, 127.8, 123.7, 122.0, 121.1, 117.7, 117.6, 115.6, 113.9, 111.5, 108.4, 62.1, 54.6, 52.5, 22.3, 21.1; EI MS (*m*/*z*, relative intensity) (as free amine: $C_{28}H_{25}NO_4S$): (M^+ not registered), 447 (20), 446 (65), 326 (7), 312 (50), 297 (34), 269 (10), 111 (28), 98 (10). Anal. Calcd for $C_{28}H_{26}ClNO_4S+H_2O$: C, 63.93; H, 5.37; N, 2.66; S, 6.10. Found: C, 63.44; H, 5.33; N, 2.65; S, 6.13.

Acknowledgment. We are grateful to Eli Lilly and Company, and particularly Dr. Homer Pierce, for the incentive to undertake this synthetic work and for financial support. We thank Dr. Marijan Stefinovic for preliminary observations.

Supporting Information Available: Experimental procedures for synthesis of compounds **8**−**13**, **15**, and **16**, copies of NMR spectra of compounds **16**, **19**, **2a**, **20**, **21**, **24**−**26**, **2b**, **31**, and **3**, and NOE experiment of compound **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034325K