Characterization and Synthesis of a 6-Substituted Benzo[*b*]thiophene

Anthony R. Haight,*,† Gregory S. Wayne,† Gregory S. Lannoye,† Shyamal I. Parekh,† Weijiang Zhang,† Richard R. Copp,† and L. Steven Hollis‡

Chemical Process Research, D54P, and Structural Chemistry, D-418, Abbott Laboratories, North Chicago, Illinois 60064

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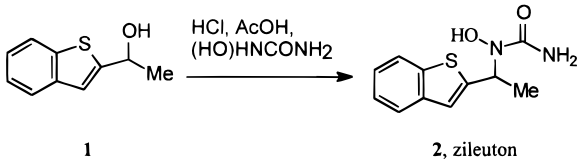
An impurity observed during the synthesis of zileuton (Zyflo) has been isolated and characterized as a benzo[*b*]thiophene derivative that has undergone electrophilic substitution in the 6 position (**4**). A nine-step synthesis confirms the structural assignment. Key steps in the synthesis include a regioselective Friedel−Crafts coupling between 2-hydroxythioanisole, **8**, and 1-(benzo[*b*]thien-2-yl)ethanol, **1**, and formation of a benzo[*b*]thiophene from an *o*-methylthiobenzaldehyde, **14**, and chloroacetone. The synthesis provides a potentially general route to substituted benzo[*b*]thiophenes.

Inhibition of leukotriene synthesis has been an area of intense pharmaceutical interest as a means of targeting inflammatory and vascular diseases.[1] The 5-lipoxygenase enzyme catalyzes the formation of leukotriene-A_4 ultimately from arachidonic acid.[2] Zileuton (Zyflo), **2**, a 5-lipoxygenase inhibitor discovered at Abbott Laboratories,[3] is the first selective 5-lipoxygenase inhibitor to receive approval by the FDA. The compound is marketed as the racemate, with several racemic syntheses having been reported to date.[2,4] A synthetic route currently being developed for the large scale manufacture of zileuton produces impurities from di- and/or O-alkylation of hydroxyurea in the final crystallized product (eq 1). The only other impurity present with any regularity,



(1)

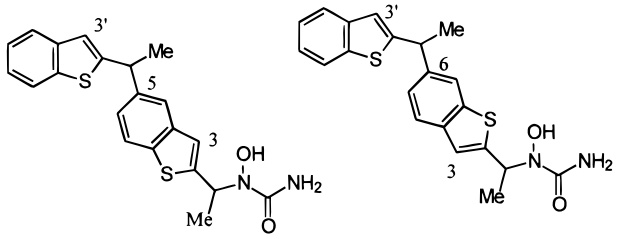
1 **2**, zileuton

in amounts greater than 0.1% by HPLC, was an unknown compound varying from 0.0 to 0.6%. In order to do more detailed toxological testing of this impurity, larger amounts were required. Thus, an effort was undertaken to characterize and synthesize the unknown impurity.

Isolation and Characterization

A 10 g sample of zileuton containing 0.6% of the impurity was separated by a combination of C-18 functionalized flash and prep-TLC plates. This yielded 18 mg of material that coeluted with the impurity by HPLC. The isolated material was obtained as a pale yellow solid and had a mass of 396, suggesting zileuton had condensed again with **1** under the reaction conditions. ^{1}H NMR analysis of the impurity in CD_3CN showed a quartet at 5.63 ppm consistent with the hydroxyurea having condensed on the benzylic carbon. However, another quartet appeared at 4.53 ppm and suggested that another benzylic center had coupled on a benzo[*b*]-thiophene ring system.

In the downfield region of the spectrum, singlets at 7.80, 7.21, and 7.17 ppm and doublets at 7.75, 7.71, and 7.69 ppm all integrated to one proton each. This is in agreement with the impurity having two benzo[*b*]-thiophenes with one substituted at the 2 position and the other at the 2 and either the 5 or 6 position (**3** or **4**).



3 **4**

^{13}C-NMR DEPT analysis of the impurity confirmed that there were nine unsubstituted aryl carbons present, and seven quaternary carbons, as would be expected in either **3** or **4**. Two of the methine carbon signals showed splitting which was presumed to be the result of spectral resolution of the diastereomers of the compound.

One-dimensional nuclear Overhauser effect (NOE) difference spectral analysis showed a NOE on the doublet at 7.69 ppm by irradiation at 7.21 ppm. Irradiation of the singlet at 7.17 ppm showed a NOE on the doublet at 7.71 ppm, not the singlet at 7.80 ppm. This is in agreement with structure **4** as the correct assignment.

Results and Discussion

With the regiochemistry assigned, a synthetic route capable of preparing gram quantities of **4** was required. A mimetic approach was not considered feasible since

† Chemical Process Research.
‡ Structural Chemistry.

(1) Brooks, C. D.; Summers, J. B. *J. Med. Chem.* **1996**, *39*, 2629.
(2) Brooks, D. W.; Carter, G. W. In *The Search for Antiinflammatory Drugs*; Merluzzi, V. J., Adams, J., Eds.; Burkhauser: Boston, 1995; Chapter 5.
(3) Summers, J. B.; Gunn, B. P.; Brooks, D. W. U.S. Patent 4,873,-259, Oct 10, 1989.
(4) (a) Kolasa, T.; Brooks, D. W. *Synth. Commun.* **1993**, *23*, 743. (b) Basha, A.; Ratajczyk, J. D.; Brooks, D. W. *Tetrahedron Lett.* **1991**, *32*, 3783.

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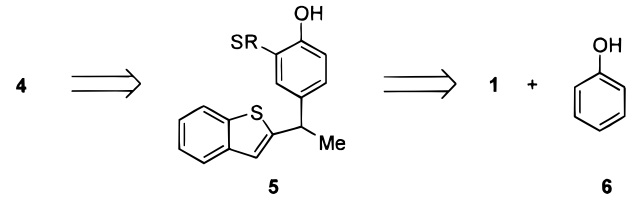
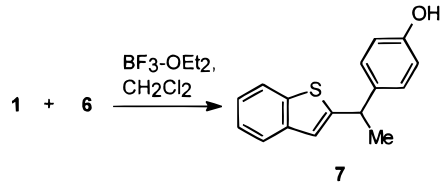
Scheme 1



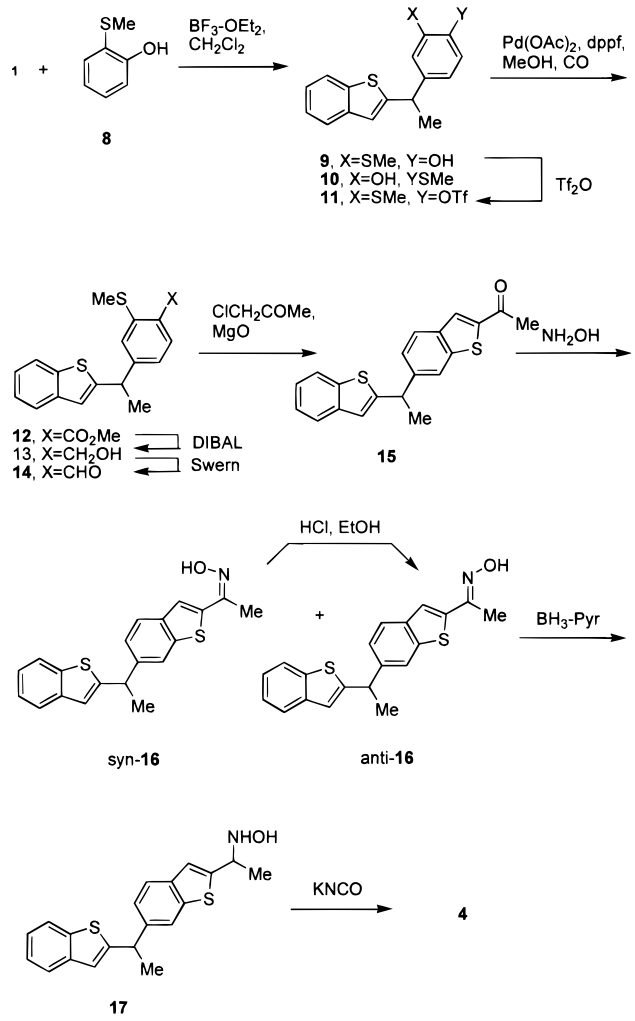
electrophilic substitution in the 6-position is not favored.[5] We envisioned a 6-substituted benzo[*b*]thiophene as arising from a 2-(alkylthio)benzaldehyde derivative, **5** (Scheme 1).[6] This in turn was seen as coming from a *para*-selective Friedel−Crafts coupling of the alcohol, **1**, with phenol **6**.[7] Treatment of **1** with 2 equiv of **6** in the presence of 1 equiv of BF_3Et_2O afforded a 89:11 ratio of HPLC products (eq 2).[8] Purification gave the *p*-phenol, **7**, in 56% overall yield. Unfortunately, attempts at



introducing a sulfur into **7** using $(MeS)_2/AlCl_3$,[9] $POCl_3$/DMSO,[10] or $(MeS)_2/SO_2Cl_2$[11] gave incomplete or complex reaction mixtures. A modification to this approach was to carry out the alkylation with the alkylthio group incorporated in the Friedel−Crafts substrate. Treatment of a mixture of the alcohol, **1**, with 2 equiv of 2-hydroxythioanisole, **8**, in the presence of BF_3Et_2O gave a 88:12 mixture favoring the desired alkylation product **9** over the methylthio-directed alkylation product **10** (Scheme 2).[8] None of the product where the condensation occurred *ortho* to the hydroxy was observed. Careful chromatographic separation of the two isomers gave **9** in 35% yield. A cursory examination of Lewis acids in the condensation demonstrated that the regioselectivity could be improved using Et_2AlCl (12:1, **9:10**) or $SnCl_4$ (42:1, **9:10**). However, the reaction profile using these acids was much more complex, and the yield of isolated product was significantly lower in the case of the $SnCl_4$.

Assignment of the regiochemistry in the alkylation products **9** and **10** was based on analysis of the ^{1}H NMR. The proton *ortho* to the hydroxy in **9** appears as a doublet at 6.93 ppm with a coupling constant of 8.4 Hz consistent with a ^3J coupling. In **10** the proton *ortho* to the hydroxy in **10** appears as a doublet at 6.94 ppm with coupling constant of 1.9 Hz, consistent with a ^4J coupling.[12]

Scheme 2



Phenol **9** was treated with triflic anhydride to afford **11** in 95% yield. Carbonylation of the triflate **11** was accomplished with 2 equiv triethylamine in methanol using $Pd(dppf)Cl_2-CH_2Cl_2$ as the catalyst.[13] Heating to 140 °C under 200 psi carbon monoxide gave the methyl ester **12** in 43% yield. The major impurity was the phenol **9**. Reduction of the ester with 1 equiv of DIBAL gave unselective reduction mixtures. Treatment of **12** with 2 equiv of DIBAL cleanly gave the primary alcohol **13**. Following Swern oxidation,[14] the aldehyde **14** was obtained in 80% overall yield from the ester.

Treatment of aldehyde **14** with neat chloroacetone at reflux for 36−80 h afforded the desired bis-benzo[*b*]-thiophene **15** in 76% yield.[6b] The reaction was found to be much cleaner in the presence of magnesium oxide as a base. Presumably this reaction involves initial formation of a sulfonium salt, although no intermediates were observed by HPLC during the reaction. Oximation with aqueous hydroxylamine gave **16** as a 1:4 mixture of the *syn:anti* isomers.[15]

Reduction of the oxime mixture with BH_3−pyridine in the presence of ethanolic HCl[16] required 15 equiv of BH_3−

(5) Electrophilic substitution typically occurs at the 3-position on 2-substituted benzo[*b*]thiophenes: Scrowton, R. M. *Adv. Heterocycl. Chem.* **1981**, *29*, 199.

(6) (a) Basha, A.; Brooks, D. W. *J. Org. Chem.* **1993**, *58*, 1293. (b) Kagano, H.; Goda, H.; Yoshida, K.; Nakano, M. U.S. Pat. 5,298,630, 1994.

(7) Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1984; Vol. 3, p 310.

(8) Ratios were determined by HPLC.

(9) Votterro, C., Labat, Y., Poisier, J. M., U.S. Pat. 5113019, 1992.

(10) Stokker, G. E., Deana, A. A., deSolms, S. J., Schultz, E. M., Smith, R. L., Cragoe, E. J., Baer, J. E., Ludden, C. T., Russo, H. F., Scriabine, A., Sweet, C. S., Watson, L. S. *J. Med. Chem.* **1980**, *23*, 1414.

(11) Farah, B. S., Gilbert, E. E. *J. Org. Chem.* **1963**, *28*, 2807.

(12) Assignment of the regiochemistry of **9** and **10** was additionally based on comparison of an authentic sample of **14** to an authentic sample of the 5′-regioisomer of 14 prepared independently (A. R. Haight, G. S. Wayne, G. S. Lannoye, W. Zhang, unpublished results).

(13) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 3931.

(14) Mancuso, A. J.; Brownfair, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.

(15) The isomers were assigned based on the ^{13}C shifts of the methyl groups (Hawkes, G. E.; Herwig, K.; Roberts, J. D. *J. Org. Chem.* **1974**, *39*, 1017).

pyridine and greater than 5 h to give the desired *N*-hydroxylamine **17**. Presumably a competition between oxime reduction and BH_3−pyridine decomposition under the reaction conditions accounts for the large excess of BH_3−pyridine required. Careful analysis of the reaction by HPLC revealed that *syn*-**16** was being consumed faster than *anti*-**16**, suggesting that the reduction rate is dependent upon the stereochemistry of the oxime.[17]

To take advantage of this rate difference, the oxime mixture was equilibrated with ethanolic HCl to a 5/1 (*syn*/*anti*) mixture of oximes **16**. Reduction of the *syn* rich oxime mixture with only 4 equiv of BH_3−pyridine gave 72% conversion in only 1.5 h.[18] Addition of 3 equiv more of BH_3−pyridine gave the hydroxylamine quantitatively in 2 h.

Treatment of the unstable hydroxylamine immediately with potassium cyanate gave the desired final material **4** in 91% yield from ketone **15**. Comparison of the ^{1}H and ^{13}C NMR confirmed that the product was identical to the isolated impurity **4**.

By exploiting the Friedel−Crafts alkylation of *o*-hydroxylthioanisole and the condensation of chloroacetone with *o*-methylthiobenzaldehydes, a new tactic to 6-substituted benzo[*b*]thiophenes has been developed. The regioselectivity of the Friedel−Crafts alkylation appears to be tunable by the choice of the Lewis acid; however, byproduct formation may be a limitation.

Experimental Section

General Methods. All commercial reagents were used as purchased without any further purification. 2-Hydroxythioanisole was obtained from Lancaster Synthesis. 2-Acetylbenzothiophene was obtained from Sumitomo Seika. Melting points were determined in open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained at 300 and 75.5 MHz, respectively. Analytical thin-layer chromatography (TLC) was performed on Merck silica $60F_{254}$ or C18-silica 60 plates. Flash chromatography was performed using Silica Gel 60 (230−400 mesh) or C-18 Silica Gel 60. HPLC analyses were run on a Zorbax SB-C8 reverse-phase column using CH_3CN: 0.1%H_3PO_4 (60:40) as the mobile phase (λ = 254 nm).

Isolation of 4. C-18 Functionalized silica (400 g) was slurried in methanol and packed on a flash chromatography column. The column was flushed with 1 L of methanol/water (v/v, 80/20) to equilibrate. A solution of impure **2** (10 g) in methanol (ca. 100 mL) was eluted with 14 L of methanol/water (v/v, 80/20) followed by methanol (600 mL). The fractions containing the impurity were collected and concentrated *in-vacuo* to 200 mg. The residue was eluted on C18-silica 60 TLC plates with methanol/water (v/v, 80/20), followed by extraction with methanol to give 30 mg of a solid. The solid was dissolved in ethyl acetate and filtered. The organics were concentrated *in-vacuo* to a light yellow solid (18 mg). ^{1}H NMR (CD_3CN) δ 7.80 (s, 1H), 7.75 (d, 1H, J = 8.0 Hz), 7.71 (d, 1H, J = 7.5 Hz), 7.69 (d, 1H, 8.0 Hz), 7.33−7.23 (m, 2H), 7.21 (s, 1H), 7.17 (s, 1H), 7.07 (br s, 1H), 5.63 (q, 1H, J = 7.0 Hz), 4.53 (q, 1H, 7.0 Hz), 1.78 (d, 3H, J = 7.0 Hz), 1.57 (d, 3H, 6.5 Hz); ^{13}C NMR (CD_3CN) δ 162.0, 153.0, 147.0, 143.0, 141.0, 140.9, 140.3, 139.4, 125.3(+), 125.3/125.2(+), 124.9(+), 124.5(+), 124.2(+), 123.2(+), 122.5(+), 121.6(+), 121.1(+), 54.0(+), 42.2(+), 23.0(+), 17.6(+); MS (CI) m/z (rel intensity 397 ([M + 1]$^+$, 100).

1-(Benzo[*b*]thien-2-yl)ethanol (1). To a solution of 2-acetylbenzo[*b*]thiophene (25.0 g, 0.14 mol) in methanol (100 mL) cooled to 0 °C was added $NaBH_4$ (6.4 g, 0.17 mol). After 20 min, the solution was quenched with water (200 mL) and extracted twice with ethyl acetate (200 mL). The organics were combined, washed with water (100 mL), and concentrated *in-vacuo* to a solid. The product was crystallized from heptane/ethyl acetate (200 mL/15 mL) to give 21.7 g (87%) **1**: Mp 60−62 °C (lit.[19] 62−63 °C); ^{1}H NMR ($CDCl_3$) δ 7.90−7.70 (m, 2H), 7.40−7.20 (m, 2H), 7.20 (s, 1H), 5.25 (qd, 1H, J = 6.3, 5.4 Hz), 2.15 (d, 1H, J = 5.4 Hz), 1.70 (d, 3H, J = 6.3 Hz).

4-[1-(Benzo[*b*]thien-2-yl)ethyl]phenol (7). To a solution of phenol, **6** (53 g, 0.56 mol), and **1** (50 g, 0.28 mol) in CH_2Cl_2 (3L), at −6 °C, was slowly added BF_3−OEt_2 (34.4 mL, 0.28 mol). The solution was stirred for 15 min at 0−5 °C before quenching with saturated sodium bicarbonate (1 L). The organics were separated and washed with water (500 mL). Concentration *in-vacuo* gave 91 g of oil as a 89:11 ratio of isomers.[20] Column chromatography (C-18 functionalized silica gel; MeOH/H_2O, 50/50 to 70/30) gave, after crystallization from methanol/water (v/v, 50/50), 40 g (56%) of phenol **7** as a white crystalline solid: Mp 112−113 °C; IR 3431 (br), 1599, 1509, 1449, 1230 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.62 (d, 1H, J = 8.4 Hz), 7.54 (d, 1H, J = 8.4 Hz), 7.20-7.10 (m, 2H), 7.10-7.02 (m, 2H), 6.90 (s, 1H), 6.70-6.65 (m, 2H), 4.62 (br s, 1H), 4.22 (q, 1H, J = 7.3 Hz), 1.62 (d, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) (DEPT) δ 154.2, 152.0, 139.9, 139.5, 137.6, 128.6(+), 124.0(+), 123.6(+), 123.0(+), 122.1(+), 119.9(+), 115.3(+), 40.6(+), 22.9(+). Anal. Calcd for $C_{16}H_{14}OS$: C, 75.56; H, 5.55; S, 12.61. Found: C, 75.50; H, 5.41; S, 12.58.

4-[1-(Benzo[*b*]thien-2-yl)ethyl]-2-(methylthio)phenol (9). To a solution of 2-hydroxythioanisole, **8** (15.8 g, 113 mmol), **1** (10.0 g, 56.0 mmol), and CH_2Cl_2 (200 mL) at ambient temperature was added BF_3−OEt_2 (6.8 mL, 56.0 mmol). The reaction was stirred 1 h and quenched with saturated sodium bicarbonate (70 mL), and the layers were separated. The aqueous layer was back-extracted with CH_2Cl_2 (100 mL), and the organics were combined and concentrated *in-vacuo*. The biphasic residue was diluted with CH_2Cl_2 (200 mL) and separated, and the organics were dried over $MgSO_4$. Concentration *in-vacuo* gave a syrup containing the two regioisomers in a ratio of 88:12 by HPLC. Flash chromatography (silica; ethyl acetate/heptanes, 1/99) yielded 5.9 g (34.5%) of the major isomer **9**. ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 1H, J = 7.8 Hz), 7.65 (d, 1H, J = 7.8 Hz), 7.41 (d, 1H, J = 2.3 Hz), 7.31−7.19 (m, 2H), 7.16 (dd, 1H, J = 8.4, 2.3 Hz), 7.00 (br s, 1H), 6.93 (d, 1H, J = 8.4 Hz), 6.56 (s, 1H), 4.30 (q, 1H, J = 7.1 Hz), 2.29 (s, 3H), 1.72 (d, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) (DEPT) δ 155.0, 151.5, 139.8, 139.4, 137.8, 133.4(+), 129.7(+), 124.1(+), 123.6(+), 123.0(+), 122.1(+), 120.8, 119.9(+), 114.8(+), 40.5(+), 22.8(+), 19.8(+); IR (microscope) 3410 (br), 1483 cm^{-1}; MS (CI) m/z (rel intensity 301 ([M + 1]$^+$, 100)). Anal. Calcd for $C_{17}H_{16}OS_2$ C, 67.96; H, 5.37; S, 21.35. Found: C, 67.85; H, 5.16; S, 20.97. Minor isomer (0.2 g, 1%) **10**. IR 3400 (br), 1567, 1489, 1433 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.72 (d, 1H, J = 8.2 Hz), 7.66 (d, 1H, J = 7.3 Hz), 7.42 (d, 1H, J = 7.9 Hz), 7.32−7.20 (m, 2H), 7.05 (br s, 1H), 6.94 (d, 1H, 1.9 Hz), 6.82 (dd, 1H, J = 8.0, 1.9 Hz), 6.62 (s, 1H), 4.33 (q, 1H, J = 7.1 Hz), 2.29 (s, 3H), 1.73 (d, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) (DEPT) δ 156.3, 150.5, 148.5, 139.8, 139.4, 134.9(+), 124.1(+), 123.7(+), 123.0(+), 122.1(+), 120.2(+), 120.1(+), 119.0, 113.7(+), 41.2(+), 22.5(+), 19.9(+).

[4-[1-(Benzo[*b*]thien-2-yl)ethyl]-2-(methylthio)phenyl] Trifluoromethanesulfonate (11). To a solution of **9** (7.0 g, 23 mmol) in methylene chloride (125 mL) was added triethylamine (7.0 g, 69 mmol). The solution was cooled to −40 °C and maintained under a nitrogen atmosphere. A solution of trifluoroacetic anhydride (9.7 g, 35 mmol) was added over a period of 15 min while maintaining the temperature between −35 and −40 °C. The mixture was warmed to ambient temperature for 1 h. The reaction was quenched with saturated aqueous sodium bicarbonate (160 mL). The organic

(16) Herscheid, J. D. M.; Ottenheijm, H. C. J. *Tetrahedron Lett.* **1978**, 5143.

(17) We are unaware of any examples where the rate of reduction of an oxime is dependent upon the stereochemistry of the oxime.

(18) At 72% conversion, the *syn*/*anti* ratio was 2/1 by HPLC.

(19) Hill, E. A.; Gross, M. L.; Stasiewicz, M.; Manion, M. *J. Am. Chem. Soc.* **1969**, *91*, 7381.

(20) The minor isomer in the HPLC has tentatively been assigned as the *ortho* condensation product based on analysis of the ^{1}H NMR spectrum of the crude reaction mixture. It was not possible to isolate the minor isomer in a pure form.

layer was separated, washed with saturated brine (160 mL), dried over $MgSO_4$, and passed through a plug of silica gel. The silica was washed with methylene chloride (200 mL), and the combined eluents were concentrated *in-vacuo* give 9.8 g of a red liquid (97% yield) in >90% HPLC purity. This material was used immediately without further purification. ^{1}H NMR ($CDCl_3$) δ 7.75-7.72 (m, 1H), 7.70-7.66 (m, 1H), 7.34-7.20 (m, 3H), 7.17 (s, 1H), 7.13 (dd, 1H, J = 2.1, 8.6 Hz), 7.04 (s, 1H), 4.40 (q, 1H, J = 7.2 Hz), 2.45 (s, 3H), 1.75 (d, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) (DEPT) δ 149.7, 146.0, 145.9, 139.6, 139.4, 132.9, 127.5(+), 125.6(+), 124.3(+), 124.0(+), 123.2(+), 122.2-(+), 121.6(+), 120.5(+), 118.6 (J_{CF} = 319.8 Hz), 41.0(+), 22.7-(+), 15.7(+); IR (microscope) 1144, 1206, 1211, 1422 cm^{-1}.

Methyl 4-[1-(Benzo[*b*]thien-2-yl)ethyl]-2-(methylthio)-benzoate (12). A solution of **11** (31.5 g, 72.9 mmol) in methanol (100 mL) and DMF (200 mL) was charged to a high pressure reactor. To this was added triethylamine (14.7 g, 145 mmol) and Pd(dppf)Cl_2 (3.0 g, 3.7 mmol). The reactor was heated to 140 °C and pressurized with carbon monoxide to 200 psi. After 16 h the mixture was filtered and the filtrate concentrated *in-vacuo* to give a dark oil. This was dissolved in toluene (500 mL) and washed twice with saturated aqueous sodium bicarbonate. After washing with brine and subsequent drying over $MgSO_4$, the solution was concentrated to a dark oil (32.1 g). This was purified by column chromatography (10% ethyl acetate in heptane) to provide a yellow oil (11.2 g, 45%). A small sample was purified again by column chromatography (chloroform) to provide a pale yellow oil for use as an analytical sample. ^{1}H NMR ($CDCl_3$) δ 7.95 (1H, d, J = 8.1 Hz), 7.75-7.39 (m, 2H), 7.34-7.22 (m, 2H), 7.20 (d, 1H, J = 1.5 Hz), 7.09 (dd, 1H, J = 1.8, 8.1 Hz), 7.04−7.02 (m, 1H), 4.43 (q, 1H, J = 7.1 Hz), 3.90 (s, 3H), 2.42 (s, 3H), 1.78 (d, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ (DEPT) 166.6, 149.9, 149.8, 143.7, 139.7, 139.4, 131.7(+), 125.2, 124.2(+), 123.9(+), 123.4(+), 123.1(+), 122.6-(+), 122.1(+), 120.5(+), 52.0(+), 41.6(+), 22.5(+), 15.6(+); IR ($CHCl_3$) 1710 cm^{-1}; MS (CI) m/z (rel intensity 343 ([M + 1]$^+$, 100). Anal. Calcd for $C_{19}H_{18}O_2S_2$: C, 69.19; H, 5.16; S, 20.52. Found: C, 69.05; H, 5.13; S, 20.36.

4-[1-(Benzo[*b*]thien-2-yl)ethyl]-2-(methylthio)benzen-emethanol (13). A solution of **12** (10.4 g, 30.4 mmol) in methylene chloride (150 mL) was cooled to −75 °C. To this was added, dropwise over 5 min, a solution of 1.0 M DIBAL (61 mL, 61 mmol). The temperature was maintained below −55 °C during the addition and then stirred at −75 °C for 30 min. The reaction was warmed to room temperature and quenched with saturated aqueous NH_4Cl (50 mL), followed by 5% aqueous HCl (100 mL). The organic layer was removed and the aqueous back-extracted with methylene chloride (100 mL). The combined organics were washed with water (150 mL), dried over $MgSO_4$, and concentrated *in-vacuo* to give a yellow oil (8.06 g, 84%). ^{1}H NMR ($CHCl_3$) δ 7.74-7.64 (m, 2H), 7.33−7.20 (m, 4H), 7.11 (dd, 1H, J = 1.8, 8.1 Hz), 7.03 (m, 1H), 4.72 (d, 2H, J = 6.3 Hz), 4.38 (q, 1H, J = 7.0 Hz), 2.45 (s, 3H), 1.75 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CHCl_3$) δ (DEPT) 150.9, 145.5, 139.7, 139.4, 137.4, 136.8, 128.3(+), 125.8(+), 124.5(+), 124.1(+), 123.7(+), 123.0(+), 122.1(+), 120.2(+), 63.2-(−), 41.2(+), 22.7(+), 16.2(+), IR ($CHCl_3$) 3380 (br) cm^{-1}; MS (DCI/NH_3) m/z (rel intensity 332 ([M + NH_4]$^+$, 100). Anal. Calcd for $C_{18}H_{18}OS_2$: C, 68.75; H, 5.77; S, 20.39. Found: C, 68.48; H, 5.73; S, 20.15.

4-[1-(Benzo[*b*]thien-2-yl)ethyl]-2-(methylthio)benzaldehyde (14). Oxalyl chloride (3.1 mL, 36 mmol) in methylene chloride (40 mL) was cooled to −78 °C. To this was added DMSO (5.1 mL, 72 mmol) dropwise, and the reaction was stirred at −78 °C for 15 min. A solution of **13** (7.5 g, 24 mmol) in methylene chloride (25 mL) was added dropwise to the reaction and stirred at −78 °C for 15 min. Triethylamine (7.2 g, 72 mmol) was added and the reaction allowed to warm to room temperature. The reaction mixture was diluted with methylene chloride (200 mL) and washed with water (200 mL). After drying over $MgSO_4$, the solution was concentrated *in-vacuo* to a dark brown oil (7.2 g). Purification by column chromatography (silica gel, $CHCl_3$) afforded a yellow oil (6.67 g, 90%), which solidified on standing. A small amount was recrystallized (isopropyl acetate/heptane) to provide an analytical sample: Mp 88.5−89.5 °C; ^{1}H NMR ($CHCl_3$) δ 10.21 (s, 1H), 7.75 (d, 1H, J = 8.1 Hz), 7.75−7.66 (m, 2H), 7.34−7.22 (m, 3H), 7.20 (dd, 1H, J = 1.5, 8.1 Hz), 7.06 (m, 1H), 4.45 (q, 1H, J = 7.0 Hz), 2.47 (s, 3H), 1.79 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CHCl_3$) δ (DEPT) 190.8(+), 151.6, 149.4, 143.7, 139.6, 139.4, 133.7(+), 131.6, 124.6(+), 124.3(+), 124.0(+), 123.6(+), 123.2(+), 122.2(+), 120.6(+), 41.7(+), 22.4(+), 15.4(+); IR (microscope) 1680 cm^{-1}; MS (CI) m/z (rel intensity 313 ([M + H]$^+$, 100). Anal. Calcd for $C_{18}H_{16}OS_2$: C, 69.19; H, 5.16; S, 20.52. Found: C, 69.05; H, 5.13; S, 20.36.

1-{6-[1-(Benzo[*b*]thien-2-yl)ethyl]benzo[*b*]thien-2-yl}-ethanone (15). A solution of **14** (2.0 g, 6.4 mmol) and MgO (13 mg, 0.32 mmol) in chloroacetone (5.1 mL, 64 mmol) was heated to reflux (115 °C). After 8 h the reaction was greater than 90% complete (HPLC). Excess chloroacetone was removed by vacuum distillation, leaving a dark brown oil. Purification by chromatography (silica gel, $CHCl_3$) gave a yellow oil (1.75 g, 81%) which precipitated from *tert*-butyl methyl ether (MTBE). Recrystallization from MTBE provided an analytical sample: Mp 136−137 °C; ^{1}H NMR ($CHCl_3$) δ 7.89 (d, 1H, J = 0.7 Hz), 7.81 (d, 1H, J = 8.5 Hz), 7.80−7.78 (m, 1H), 7.74−7.66 (m, 2H), 7.36−7.22 (m, 3H), 7.09 (m, 1H), 4.51 (q, 1H, J = 7.0 Hz), 2.63 (s, 3H), 1.82 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CHCl_3$) δ (DEPT) 192.1, 150.5, 145.2, 143.9, 143.1, 139.7, 139.5, 137.9, 129.4(+), 126.0(+), 125.2(+), 124.2(+), 123.8(+), 123.1(+), 122.2(+), 121.3(+), 120.4(+), 41.6(+), 26.7(+), 22.7-(+), IR (microscope) 1660 cm^{-1}; MS (CI) m/z (rel intensity 337 ([M + H]$^+$, 100). Anal. Calcd for $C_{20}H_{16}OS_2$: C, 71.39; H, 4.79; S, 19.06. Found: C, 71.01; H, 4.90; S, 18.73.

***syn/anti*-1-{6-[1-(Benzo[*b*]thien-2-yl)ethyl]benzo[*b*]thien-2-yl}ethanone, Oximes (16).** To a homogeneous solution of **15** (1.2 g, 3.6 mmol) in isopropyl alcohol (30 mL) and ethyl acetate (30 mL) were added 3 drops concd HCl and 50% hydroxylamine (0.44 mL, 7.1 mmol). The mixture was heated to reflux for 3 h followed by addition of more 50% hydroxylamine (0.11 mL). After 30 min, the reaction was cooled to room temperature and concentrated *in-vacuo* to give a solid. The solid was dissolved in ethyl acetate (100 mL), washed with water (50 mL), dried over $MgSO_4$, and concentrated *in-vacuo* to give a yellow solid (1.2 g, 94% yield). HPLC showed a 3.7:1 ratio of *anti:syn* isomers. This mixture was used without further purification. MS (CI) m/z (rel intensity 352 ([M + H]$^+$, 100). *anti*-**16**: ^{1}H NMR ($CDCl_3$) δ 7.79−7.62 (m, 4H), 7.42 (s, 1H), 7.35−7.20 (m, 3H), 7.06 (s, 1H), 4.49 (q, 1H, J = 7.2 Hz), 2.36 (s, 3H), 1.81 (d, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 152.3, 151.1, 143.1, 140.2, 140.1, 139.8, 139.5, 138.2, 124.5, 124.1, 124.0, 123.7, 123.3, 123.1, 122.2, 120.7, 120.2, 41.4, 22.8, 11.9. *syn*-**16**: ^{1}H NMR ($CDCl_3$) δ 7.79−7.62 (m, 4H), 7.41 (s, 1H), 7.35−7.20 (m, 3H), 7.06 (s, 1H), 4.50 (q, 1H, J = 7.2 Hz), 2.42 (s, 3H), 1.85 (d, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 151.3, 147.7, 143.3, 142.5, 141.9, 140.8, 139.7, 136.2, 126.7, 125.6, 124.6, 124.1, 123.6, 123.3, 123.1, 122.4, 120.3, 41.6, 22.9, 20.2.

N-(1-{6-[1-(Benzo[b]thien-2-yl)ethyl]benzo[b]thien-2-yl}ethyl)-N-hydroxyurea (4). To a solution of oximes **16** (1.1 g, 3.1 mmol) in methylene chloride (20 mL) was added a solution of ethanolic HCl (1.6 g in 15 mL). This was stirred at ambient temperature overnight. Analysis of the reaction mixture by HPLC showed 83% syn oxime. The mixture was concentrated in-vacuo to an oil and redissolved in ethanol (20 mL) and methylene chloride (20 mL). The solution was cooled to 15 °C, and BH_3−pyridine (1.16 g, 12.5 mmol) was slowly added. A solution of HCl(g) in ethanol (840 mg in 10 mL) was slowly added to the mixture over 10 min. The temperature was maintained below 19 °C during the addition. After 1.5 h, additional BH_3−pyridine (1.0 g, 10.8 mmol) was added. The reaction was shown by HPLC to be >90% complete after 3.5 h. The mixture was concentrated to a foam and dissolved into ethyl acetate (50 mL) and water (25 mL). While stirring rapidly and with the temperature below 10 °C, the pH was raised to >10 by the addition of 50% NaOH solution. The originate layer was separated and the aqueous extracted with ethyl acetate. The ethyl acetate layers were combined and carried on without isolation.

To the ethyl acetate solution was added 25 mL of aqueous potassium cyanate (254 mg, 3.1 mmol), and the mixture was

cooled to 10−15 °C. While stirring rapidly, concd HCl was added dropwise until the pH was <2. The reaction mixture was allowed to warm to room temperature and stirred for 10 min. HPLC showed that the reaction was complete. The ethyl acetate layer was separated and the aqueous extracted with ethyl acetate (25 mL). The combined ethyl acetate layers were dried over $MgSO_4$ and concentrated *in-vacuo* to a tan-colored solid (1.15 g, 95% overall). The crude product was recrystallized from toluene (20 mL) to provide a creme-colored powder (620 mg, 50%). Mp 125 °C (dec); ^{1}H NMR (CD_3CN) δ 7.80 (s, 1H), 7.75 (d, 1H, J = 8.0 Hz), 7.71 (d, 1H, J = 7.5 Hz), 7.69 (d, 1H, 8.0 Hz), 7.33−7.23 (m, 2H), 7.21 (s, 1H), 7.17 (s, 1H), 7.07 (br s, 1H), 5.63 (q, 1H, J = 7.0 Hz), 4.53 (q, 1H, 7.0 Hz), 1.78 (d, 3H, J = 7.0 Hz), 1.57 (d, 3H, 6.5 Hz); ^{13}C NMR (CD_3CN) δ 162.0, 153.0, 147.0, 143.0, 141.0, 140.9, 140.3, 139.4, 125.3(+), 125.3/125.2(+), 124.9(+), 124.5(+), 124.2(+), 123.2(+), 122.5(+), 121.6(+), 121.1(+), 54.0(+), 42.2(+), 23.0(+), 17.6(+); IR (KBr) 1620 cm^{-1}; MS (CI) m/z (rel intensity 337 ([M + H]$^+$ 100). Anal. Calcd for $C_{20}H_{16}N_2O_2S_2$: C, 63.61; H, 5.08; N, 7.06; S, 16.17. Found: C, 63.32; H, 5.15; N, 7.04; S, 15.88.

Supporting Information Available: Copies of NMR spectra (29 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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