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# Development of a Scalable Synthesis to VEGFR Inhibitor AG-28262

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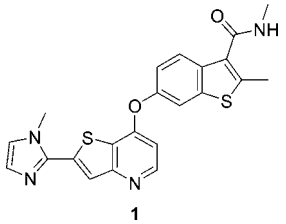
**Abstract:**

**The synthesis of *N*,2-dimethyl-6-(2-(1-methyl-1*H*-imidazol-2-yl)-thieno[3,2-*b*]pyridin-7-yloxy)benzo[*b*]thiophene-3-carboxamide (1, AG-28262) on kilogram scale is described. Initial syntheses of key components 2 and 3 worked well on laboratory scale but had significant drawbacks for larger-scale manufacture. Therefore, new routes to these two key fragments were developed and demonstrated to synthesize kilogram quantities. Key steps involve a two-step thiophenol alkylation/cyclization protocol to synthesize 2 in a convergent manner. A difficult Pd-mediated coupling to produce 3 was replaced with a more scalable stepwise imidazole synthesis. Key rationale for the new routes are discussed.**

## Introduction

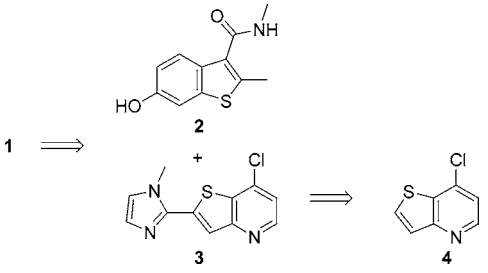
Small molecules that act via antagonism of the VEGFR signaling pathway are of interest as clinical anti-angiogenesis agents.[1] The emergence of AG-28262 (**1**) as a promising VEGFR kinase inhibitor within our Discovery program led us to seek a practical route to synthesize kilogram quantities required for regulatory toxicology studies and clinical evaluation.



**1**

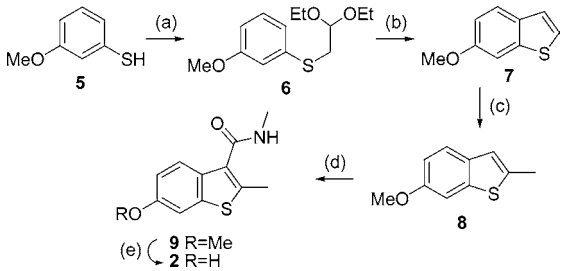
Scheme 1 outlines the basic retrosynthesis, identifying benzothiophene **2** and thienopyridine **3** as key intermediates. To provide ample opportunities to synthesize a variety of related compounds from a common substructure, our medicinal chemistry colleagues utilized a stepwise approach to synthesize the multisubstituted benzothiophene ring system **2**. The requirement of kilogram quantities for regulatory toxicology studies and clinical evaluation led us to develop a more efficient synthesis of **2**. The imidazole/thienopyridine portion of the molecule (**3**) was initially produced using challenging chemistry for multikilogram scale, but the major issue was residual Pd that was difficult to remove. An alternate Pd-free synthesis of this portion was developed and is described.

***Scheme 1***



**2** **3** **4**

***Scheme 2***[a]



[a] Reagents and conditions: (a) $BrCH_2CH(OEt)_2$, $K_2CO_3$; (b) $BF_3{\cdot}Et_2O$ (39%, 2 steps); (c) BuLi, MeI (91%); (d) i. $(COCl)_2$, $AlCl_3$ ii. $CH_3NH_2$ (72%); (e) $BBr_3$ (97%).

## Results and Discussion

The original synthesis of the substituted benzothiophene fragment **2** was developed with versatility as a primary goal: each appendage of the thiophene ring was added sequentially (Scheme 2).[2] The benzothiophene **7** was synthesized via cyclization of acetal **6**.[3] Due to the formation of polymeric material, this cyclization was run under high-dilution conditions to achieve the reported yield. The 2-position of **7** was then lithiated and alkylated, followed by acylation at the 3-position of the thiophene. Intermediates **5**−**8** were all fragrant oils, making them difficult to handle and purify on larger scale. Significant drawbacks to the outlined approach to **7** included the high dilution required for conversion of **6** to **7**, which was not desirable for a plant operation, and the laborious workup of the $AlCl_3$-catalyzed acylation which led to significantly lower yield on larger

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(1) Munchhof, M. J.; Beebe, J. S.; Casavant, J. M.; Cooper, B. A.; Doty, J. L.; Higdon, C.; Hillerman, S. M.; Soderstrom, C. I.; Knauth, E. A.; Marx, M. A.; Rossi, A. M. K.; Sobolov, S. B.; Sun, J. *Biorg. Med. Chem. Lett.* **2004**, *14*, 21−24 and references within.

(2) Romines, W. H.; Kania, R. S.; Lou, J.; Collins, M. R.; Cripps, S. J.; He, M.; Zhou, R.; Palmer, C. L.; Deal, J. G. PCT Int. Appl. WO 03/106462, 2003.

(3) Graham, S. L.; Shepard, K. L.; Anderson, P. S.; Baldwin, J. J.; Best, D. B.; Christy, M. E.; Freedman, M. B.; Gautheron, P.; Habecker, C. N.; Hoffman, J. M.; Lyle, P. A.; Michelson, S. R.; Ponticello, G. S.; Robb, C. M.; Schwam, H.; Smith, A. M.; Smith, R. L.; Sondey, J. M.; Strohmaier, K. M.; Sugrue, M. F.; Varga, S. L. *J. Med. Chem.* **1989**, *32*, 2548−2554.


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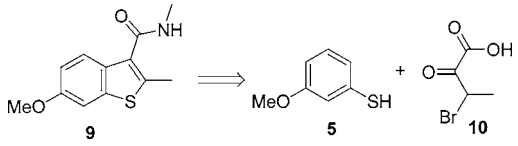
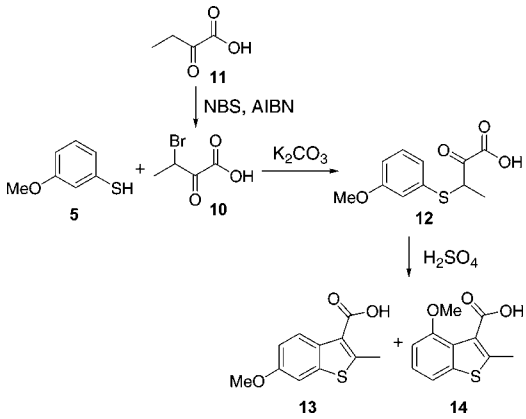
**Scheme 3**




**Scheme 4**




scale. Additionally, although the methylation of **7** was high yielding, minimization of the use of alkylating reagents was sought for scale-up.

We hoped to synthesize the benzothiophene in a convergent manner by addition of a functionalized 4-carbon unit to a thiophenol fragment followed by dehydrative cyclization (Scheme 3). This alkylation/cyclization approach to the synthesis of a 6-substituted benzothiophene using thiophenol **5** and ethyl bromopyruvate has been reported by Titus to synthesize a similar analog.[4]

We hoped to expand upon the published method by adding additional carbon substitution at the alkylation center. In addition, we hoped to utilize the free carboxylic acid directly in the alkylation to avoid the need to saponify the ester as a separate step. As the desired 4-carbon subunit **10** was not commercially available, it was synthesized by bromination of 2-ketobutyric acid (**11**) under radical conditions (NBS, AIBN) using 1,2-dichloroethane (DCE) as solvent (Scheme 4).[5] Since the product **10** is both hygroscopic and a reactive alkylating agent, it was undesirable to isolate this material. Instead, a telescoped procedure was developed where the solution of **10** in DCE was utilized directly in the subsequent alkylation step. It was found that the use of only DCE in the alkylation led to a poor reaction, but addition of acetone as a cosolvent provided clean conversion to the desired intermediate **12**.

Acid **12** was also an oil; thus, a workup procedure was developed utilizing pH adjustment for purification that allowed isolation of this material as a solution. After reaction of **5** with **10** and excess $K_2CO_3$, the basic reaction solution was extracted with heptane and water. The carboxylate salt of **12** remained in the basic water solution, and the organic layer was discarded, thus removing the majority of the organic byproducts. In the presense of 1:1 heptane/$CH_2Cl_2$, the pH of the aqueous layer was then adjusted with HCl to pH $<3$, and after separation of the phases the organic solution contained **12** of ~97% purity. This organic solution was used directly in the next step.

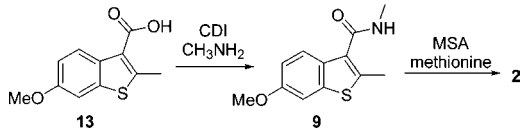
The remaining step in the benzothiophene formation was the dehydrative cyclization of **12**. Initially, this transformation was effected in neat methanesulfonic acid (MSA). Further optimization led to a more streamlined approach whereby the crude heptane/$CH_2Cl_2$ solution obtained from the previous step was stirred with concentrated $H_2SO_4$ (~0.5 mL/g **12**) to effect the desired cyclization. The ratio of isomers of **13**:**14** from the dehydrative cyclization was 5.5:1. The heptane/$CH_2Cl_2$ solvent system was chosen to work up the previous step since it cleanly dissolves **12**, but during the cyclization reaction **13** will crystallize from this solution. The workup consisted of addition of water to dilute the sulfuric acid and complete crystallization of **13** followed by filtration. The crude product wet cake was then reslurried in $CH_3CN$ to provide **13** isomerically pure in 55% yield over the two steps from **5**.

**Scale-Up of the Benzothiophene Synthesis.** The sequence described above was transferred to kilo-lab facilities for scale-up, and a few comments on the initial campaign are warranted. The reaction to convert **11** to **10** required heating to initiate the radical reaction, and the reaction was typically heated to 75−80 °C to drive to completion. However, the reaction was best executed with a gentle heating ramp past ~60 °C to account for the heat generated by the exothermic bromination reaction. Our Engineering Technologies group ran this reaction in an RC1 calorimeter without incident, and concluded that the heat evolved from the reaction exotherm should be controlled by solvent reflux if the external temperature control failed to sufficiently moderate the internal temperature. To minimize potential problems of self-heating on large-scale runs, it was decided to dose-control the bromination reaction. The total volume of starting material and solvent were charged with one-third the original stoichiometry of NBS and AIBN, and the reaction was heated to >75 °C for initiation and reaction procession. Once the majority of the NBS was consumed, the solution was cooled, charged with another one-third of NBS and AIBN, heated to react, and the whole sequence repeated a third time. This procedure successfully provided the product in the expected purity with an easily controlled exotherm, and a dose-controlled process is suggested for further scale-up.

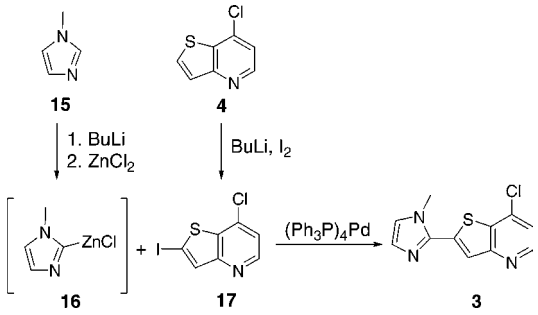
In the second part of the procedure, the crude solution of **10** was combined with $K_2CO_3$ and acetone, followed by the addition of thiol **5**. It was known that bromide **10** could not be stirred with base for prolonged periods (>1 h) without noticeable degradation. On laboratory scale, this operation was complete relatively quickly as the alkylation was nearly instantaneous. However, on multikilogram scale bromide **10** might be in contact with the base over an extended period due to equipment limitations. To alleviate this issue, the addition order was reversed. Thiol **5** was thus mixed with the $K_2CO_3$ prior to addition of the solution of **10**. It was important to exclude oxygen, which facilitates oxidative thiol

(4) Titus, R. L.; Titus, C. F. *J. Heterocycl. Chem.* **1973**, *10*, 679−681.
(5) Compound **10** has been reported via an alternate method: Sprinson, D. B.; Chargaff, E. *J. Biol. Chem.* **1946**, *164*, 417−432.

**Scheme 5**




**Scheme 6**




coupling to produce the disulfide dimer of **5** under basic conditions. The large-scale synthesis starting with 4.46 kg of 3-methoxythiol (**5**) thus produced 3.39 kg (48%) of **13**.

**Completion of Fragment 2.** To complete the synthesis of **2** (Scheme 5), the carboxylic acid of **13** was first activated with CDI to form the acylimidazole, followed by reaction with aq methylamine to produce amide **9**. This reaction was carried out in THF, and upon completion, water was added to crystallize the product. The isolation yield was further improved by removal of most of the THF via distillation. Filtration provided the purified product in high yield. This procedure was run starting with 3 kg of **13** to produce 2.9 kg of **9** (92%).

Completion of fragment **2** required unmasking the protected phenol. The methyl group was removed under acidic conditions using methionine as a stoichiometric methyl scavenger.[6] The reaction was carried out in neat MSA (10 mL/g **9**) with 4 equiv of methionine. For kilogram scale, the methionine was added in portions to mediate the exotherm of dissolution/protonation followed by heating the homogeneous mixture. Upon reaction completion, quench into water crystallized the product **2** in high yield. Using this method, 2.4 kg of **2** (89%) were produced.

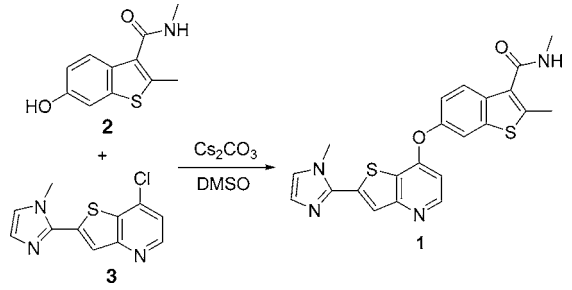
**Synthesis of Imidazole/Thienopyridine Subunit 3.** The syntheses of **4** and **17** have been previously reported, and these fragments were available on multikilogram scale.[7] The previously disclosed method to synthesize **3** (Scheme 6) utilized metalation at the 2-position on 1-methyl imidazole, followed by a Pd-mediated coupling with iodide **17**.[8]

Difficulties in performing robust Pd-mediated couplings on a closely related heterocyclic system have been reported.[7] Upon screening various Pd catalysts and utilizing several coupling partners akin to the examples outlined by Ragan, we found similar limitations to this imidazole/thienopyridine coupling. Although the reaction often worked via the previously published Negishi-coupling procedure, variable results were obtained, and reproducibility was not as high as one would require for a multikilogram synthesis. Lacking readily available alternatives, we chose to further optimize this coupling for the initial campaign.

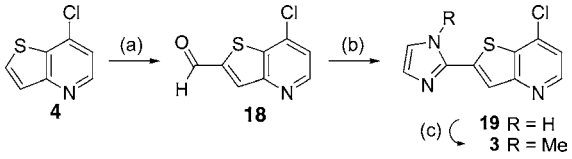
Utilizing the previously published procedure to form **16** led to significant precipitation of the zinc species. Observation of the solids thus formed indicated the precipitation did not provide material of consistent quality, often producing gummy material. The poor physical properties of the precipitate were viewed as one possible culprit to the reaction variability. Alternate solvents were sought that might fully dissolve the zincate **16**, but solvent choice was limited because both **16** and **17** have poor solubilities in many organic solvents. Screens of several solvents led to identification of $CH_3CN$ as a promising solvent for dissolution of **16** and compatibility with the subsequent Pd-mediated coupling. Unfortunately, the procedure to metalate 1-methylimidizole via the lithium reagent was not amenable to $CH_3CN$ incorporation; therefore, $CH_3CN$ had to be added after zincate generation. Since THF dilution led to poor solubility and lower reactivity in the Pd-mediated coupling, the amount of this solvent used during the deprotonation was minimized. Thus, a concentrated 1-methylimidizole solution in THF was deprotonated with BuLi between −20 and −10 °C. Solid $ZnCl_2$ was added to the anion solution, which was significantly exothermic, causing a rapid temperature spike as high as 48 °C on laboratory scale. Due to the low volume of solvent, this zincate generation procedure is not suggested for large-scale manufacture without adequate temperature control. However, the addition of solid $ZnCl_2$ was reliable and well-controlled on 5-L scale using typical laboratory bath cooling. After the zinc reagent **16** was formed, $CH_3CN$ was added to provide a solution. Iodide **17** was added, followed by rigorous subsurface purging with Ar. Addition of catalytic $Pd(PPh_3)_4$ (∼3%) was followed by heating at 50 °C for several hours. This procedure was repeated over seven batches to process 2.85 kg of **17** to crude **3**. At this point the main issue remaining was isolation of the product from the excess zinc reagent and salts. The insolubility of **3** in most organic solvents limited the usefulness of extractive workups. Using the poor solubility of **3** to our advantage, the majority of the product from the crude reaction mixture was precipitated by direct addition of water to dilute the $CH_3CN$. Filtration then removed most of the product from the crude mixture; however, the product was still contaminated with a large amount of insoluble inorganics and was typically isolated in ∼50% potency. This crude solid was purified via dissolution in hot DMSO, addition of Celite, and filtration. The Celite was added to adsorb the solids that do not dissolve in DMSO, as direct filtration was very slow. After the hot filtration, water was added to the DMSO, the solution was cooled, and the solids were filtered. To produce the required bulk material, the crude material was purified in eight batches to provide a total of 1.5 kg of **3** that was >95% pure and >95% potency in a 63% overall yield of **3** from **17**. A drawback to this procedure was that **3** was difficult to purify from residual Pd, and this bulk material contained an average of 5650 ppm Pd even after the recrystallization. The

(6) Fujii, N.; Irie, H.; Yajima, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2288−2289.
(7) Ragan, J. A.; Raggon, J. W.; Hill, P. D.; Jones, B. P.; McDermott, R. E.; Munchhof, M. J.; Marx, M. A.; Casavant, J. M.; Cooper, B. A.; Doty, J. L.; Lu, Y. *Org. Process Res. Dev.* **2003**, *7*, 676−683.
(8) Munchhof, M. J.; Sobolov-Jaynes, S. B. PCT Int. Appl. WO 99/24440, 1999.

**Scheme 7**




**Scheme 8**[a]




[a] Reagents and conditions: (a) i. BuLi, THF ii. DMF; (b) glyoxal trimer dihydrate, $NH_4OAc$, HOAc; (c) MeOTs, NaOtBu.

insolubility of **3** in most solvents led to low yields when extractive or chromatographic purifications were attempted. As a result, the material was carried forward with the high Pd content with plans to lower the metal impurities at a later stage in the synthesis.

**Coupling To Produce AG-28262 (1).** To complete the synthesis, the fragments **2** and **3** were coupled under basic conditions ($Cs_2CO_3$) in hot DMSO (Scheme 7). The product was precipitated by the addition of water to the mixture. The dried product was dissolved in a warm $CH_2Cl_2$/EtOH mixture and filtered to remove any trace insoluble material. The resulting filtrate solution was distilled under atmospheric pressure to remove the $CH_2Cl_2$ and crystallize the product (**1**) from the EtOH solution. This procedure was utilized to produce 2.1 kg of **1** (75% yield). Conversion to the benzenesulfonic acid (BsOH) salt provided drug substance **1**·BsOH with >99% purity in 88% yield.

Unfortunately, the **1**·BsOH thus produced was not pure enough for clinical use due to high Pd content. The aforementioned difficulty in removing Pd from **3** produced AG-28262 (**1**) with >2100 ppm Pd content. After formation of the besylate salt, the material still contained 783 ppm Pd. To reduce the Pd content below the target 100 ppm, three successive recrystallizations of the salt were required, each proceeding in ~84% yield. This translated into a disappointing loss of 40% of the final material. Although most of **1** was recovered via reworking the filtrates, a more desirable procedure was sought for future scale-up.

**Second-Generation Synthesis of 3.** Due to the capricious coupling to produce **3** combined with the difficulty in removing Pd from the intermediates and final product as described above, we chose to revise the synthetic strategy to this fragment. We planned to synthesize the imidazole, utilizing the classic Radziszewski procedure followed by nitrogen methylation to provide the desired fragment **3** (Scheme 8). The ease of lithiation at the 2-position of thienopyridine **4** was utilized as an analogous entry to the desired substitution. Deprotonation with BuLi under cryogenic conditions followed by reaction with DMF successfully formylated the ring to provide aldehyde **18**,[9] which provided the regiospecific handle for imidazole synthesis. Using this procedure, 9.5 kg of **18** was produced in 75% overall yield. Condensation of **18** with aq glyoxal and ammonium acetate initially provided **19** in only trace amounts. A large screen of conditions was conducted, varying glyoxal source (40% glyoxal in $H_2O$, glyoxal trimer-dihydrate, glyoxal bis-diallylacetal, glyoxal sodium sulfite bis-addition complex), ammonia source [$NH_4OH$, $NH_3$/MeOH, $NH_4Cl$, $NH_4OAc$, $NH(TMS)_2$], and solvent (NMP, MeOH, acetone, THF, $CH_3CN$, HOAc, DMF, DMAC, DMSO, $CH_2Cl_2$, EtOH, IPA, toluene). From this data set, several key parameters were outlined for production of **19**: (1) glyoxal trimer dihydrate was superior to the other glyoxal sources for most conditions explored; (2) many reactions were limited by poor solubilities of aldehyde **18**, glyoxal trimer, and ammonia salts; (3) aldehyde **18** was unstable in the presence of ammonia sources in a variety of solvents, leading to significant byproducts (mainly dimeric); (4) methanol added considerable stability to **18** in solution, presumably via a methanol hemiacetal; (5) glyoxal trimer and ammonia sources produced polymeric black material in the absence of any other reagents; and (6) the reaction was often sluggish at room temperature, and most reactions were heated to 50 °C to increase the reaction rate. Acetic acid and methanol were the solvents that consistently produced reasonable conversions. An improved procedure was realized by combination of these two solvents which provided higher solubility of reagents, resulted in faster and cleaner reaction, and also improved the stability of the aldehyde **18**. In fact, the use of acetic acid as a cosolvent in methanol allowed enough solubility of reagents that the transformation could be carried out at ambient temperature, further decreasing the amount of polymeric material formed.

Unfortunately, the yield was still modest (50−60%) due to formation of the polymeric material and losses due to purification of **19** from these byproducts. Addition of water precipitated most of the desired product **19**, and rinsing the cake with methanol/water followed by $CH_2Cl_2$ removed most impurities. Despite the moderate yield, the new procedure was not sensitive to variations due to scale and could reliably provide bulk material. Using this method, 5.2 kg of **19** were produced in 47% isolated yield.

To complete the synthesis of **3**, the imidazole nitrogen was methylated using methyl tosylate and NaOtBu in THF. After reaction completion, addition of water was followed by distillation to remove excess THF and fully precipitate the product. Filtration provided the desired product in >95% purity. Using this straightforward methylation method, 4.8 kg of **3** (87%) were produced.

The yield of the sequence to produce **3** via **18** was lower than the Pd-mediated coupling. However, the reliability and increased robustness of the procedure was a clear improvement for multikilogram synthesis. Using this route, 4.8 kg of **3** were produced in 30% overall yield from **4**. In addition, the synthesis utilized no Pd, thereby eliminating the need to remove it. Compound **3** produced via this route was of

(9) Luzzio, M. J.; Yang, B. V.; Marx, M. A. Pat. Appl. U.S. 2002/0004511, 2002.

comparable purity (>98%) and slightly lower potency (~90%) but has been successfully utilized in couplings to produce **1** in high quality.

## Conclusions

We have utilized a convergent alkylation/cyclization strategy to assemble benzothiophene **2**. An enabled synthesis of **3** via a Pd-mediated Negishi coupling followed by reaction with **2** produced the first cGMP bulk material of **1**. Unfortunately, Pd removal from **1** proved difficult. A second-generation synthesis of **3** was developed to replace the capricious Pd-mediated coupling with a more scalable route. All procedures have been demonstrated on kilogram scale.

## Experimental Section

All materials were purchased from commercial suppliers and used without further purification. Palladium tetrakis-(triphenylphosphine) was ordered from Strem Chemicals. ACS reagent grade $ZnCl_2$ (>98%) was ordered from Aldrich Chemical Co. and used as-received. All reactions were conducted under an atmosphere of nitrogen unless noted otherwise.

**3-(3-Methoxyphenylthio)-2-oxobutanoic acid (12).** *Method A (Laboratory Pilot).* A flask was sequentially charged with 2-ketobutyric acid (**11**) (100.0 g, 0.9798 mol) and 1,2-dichloroethane (DCE, 700 mL). To the solution was added *N*-bromosuccinimide (NBS, 226.9 g, 1.275 mol) in one portion. 2,2′-Azobis(isobutyronitrile) (AIBN, 4.02 g, 0.025 mol) was then added to the mixture. The reaction solution was heated quickly to an internal temperature of 60 °C, and the internal temperature raised to 70 °C over the next 20 min. The reaction was then heated to maintain the internal temperature between 75 and 80 °C. The reaction was monitored by $^1$H NMR analysis of aliquots. After a total heating time of 65 min, $^1$H NMR of a sample showed ~16:1 ratio of **10**:**11**, and the reaction was cooled to room temperature by immersion in an ice/water bath. To the room temperature solution was added acetone (350 mL), and the reaction flask was held in the ice/water bath. To the reaction solution was added $K_2CO_3$ (154.4 g, 1.117 mol) in portions to control bubbling. The solution was stirred in the ice bath an additional 5 min after $K_2CO_3$ addition. 3-Methoxybenzenethiol (**5**, 110 mL, 0.887 mol) was added via an addition funnel. After a total reaction time of 15 min after thiol addition, the reaction solution was added to a separatory funnel followed by water (700 mL) and heptane (600 mL). The solution was mixed well, and the layers were allowed to settle. The lower aqueous phase (containing **12**) was added back to the reaction flask. The upper organic phase was discarded. To the aqueous solution in the reaction flask was added heptane (350 mL) and $CH_2Cl_2$ (350 mL) and the solution cooled to 15 °C. Concentrated aq HCl (97 mL) was slowly added ($CO_2$ evolution) until the pH of the aqueous phase was 1.9. The solution was added back to a separatory funnel, and the layers were separated. The lower aqueous phase was discarded, and the upper organic phase containing crude **12** was further extracted with saturated aqueous NaCl solution (200 mL). The phases were separated, and the organic layer was used directly in the subsequent reaction.

*Method B (Bulk Campaign).* A 75-L Hastelloy reactor was sequentially charged with 1,2-dichloroethane (DCE, 16 L) and **11** (3.5 kg, 34 mol). To the solution was added NBS (2491 g, 14.0 mol) and AIBN (46 g, 0.28 mol). The reaction solution was slowly heated to an internal temperature of 60 °C over 1.5 h. The reaction was further heated to 80 °C over 45 min. The reaction was cooled back down to 41 °C over 1 h and then charged with NBS (2496 g, 14.02 mol), AIBN (45 g, 0.27 mol), and DCE (2 L) rinse. The reaction was heated back to 60 °C over 30 min, up to 80 °C over another 30 min, and held at 80 °C for 30 min. The reaction was then cooled to 60 °C over 1 h and then charged with NBS (2500 g, 14.04 mol), AIBN (45 g, 0.27 mol), and DCE (2 L) rinse. The reaction was heated to 80 °C and held for 1 h. An aliquot was removed and analyzed by $^1$H NMR showing no **11**. A separate reactor was charged with $K_2CO_3$ (5.412 kg, 39.15 mol) and acetone (13 L) at ambient temperature. The reaction was cooled to 9 °C and then charged with **5** (4464 g, 31.84 mol). To the reaction solution was slowly charged the solution of **10** via vacuum over 30 min. The addition rate of the solution of **10** was adjusted to maintain the internal reaction temperature <15 °C. After an additional 15 min, the reactor was charged with water (24 L) and heptane (20 L). The solution was mixed well, and the layers were allowed to settle. The lower aqueous phase (containing **12**) was added back to the reactor. The upper organic phase was discarded. To the aqueous solution in the reactor was added heptane (12 L), $CH_2Cl_2$ (12 L), and the solution was cooled to <15 °C. Concentrated aq HCl (3800 mL) was added while the internal pH of the aqueous phase was monitored at such a rate that the moderate bubbling and exotherm were controllable. After the complete addition of HCl the pH of the aqueous phase was 1.64. The solution was transferred to an extractor, and the layers were separated. The lower aqueous phase was discarded, and the upper organic phase containing crude **12** was further extracted with saturated aqueous NaCl solution (8 L). The phases were separated, and the organic layer was used directly in the subsequent reaction. $^1$H NMR of the crude sample of **12** (quickly dried to remove most solvents): (300 MHz, $d_6$-acetone) 1.37 (d, 3H, $J$ = 6.9), 3.81 (s, 3H), 4.56 (q, 1H, $J$ = 6.9), 6.96 (dd, 1H, $J$ = 1.0, 2.5), 7.00−7.05 (m, 2H), 7.29 (t, 1H, $J$ = 8.2), ~9.90 (v br s, 1H).

**6-Methoxy-2-methylbenzo[*b*]thiophene-3-carboxylic Acid (13).** *Method A (Laboratory Pilot).* The crude solution of **12** (from Method A, theoretical amount: 213.0 g; 0.8865 mol, in ~700 mL of 1:1 $CH_2Cl_2$/heptane solution) was cooled to 5 °C. While stirring vigorously, $H_2SO_4$ (115 mL) was added at such a rate that the internal temperature remained between 10 and 13 °C. After complete $H_2SO_4$ addition, the cooling bath was removed and replaced with a 20 °C water bath. After 15 min, there were significant solids in the reaction solution, and the internal temperature was up to 25 °C. Due to slow self-heating during the reaction, the bath temperature was periodically readjusted to 19 °C. After a total reaction time of 6 h after acid addition, the reaction solution was cooled to an internal temperature of 10 °C. Cold water (500 mL, 5 °C) was added in one portion, causing an

increase in internal temperature to 19 °C. The mixture was stirred at room temperature for 20 min, and the bilayer was filtered. The crude solids were rinsed with $H_2O$ (2 × 200 mL). The wet cake was added back to the reaction flask followed by $CH_3CN$ (350 mL) and the slurry stirred at room temperature for 1 h. The slurry was filtered and the off-white cake rinsed with $CH_3CN$ (2 × 175 mL) and dried to provide 108.69 g (55% over two steps) of **13**.

*Method B (Bulk Campaign).* The crude solution of **12** (from Method B, theoretical amount: 7487 g, 31.16 mol, in 24 L of 1:1 $CH_2Cl_2$/heptane solution) was charged to a 75-L Hastelloy reactor and was cooled to 5 °C. While stirring vigorously, $H_2SO_4$ (4.1 L) was added in four portions at such a rate that the internal temperature remained between 10 and 13 °C. After complete $H_2SO_4$ addition, the reactor was warmed to room temperature. Due to the presence of solids out of solution after 2 h, the reaction was not stirring efficiently. After 3 h, additional portions of $H_2SO_4$ (2 L), heptane (2 L), and $CH_2Cl_2$ (4 L) were charged to the reactor to aid in stirring the mixture. After an additional 30 min the reactor was charged with water (30 L). During the water addition the internal temperature was kept <30 °C. After 1 h at 10 °C the reaction mixture was filtered and washed with water (4 L). The wet cake was added back to the reactor followed by $CH_3CN$ (16 L) and the slurry stirred at room temperature for 1 h. The slurry was filtered and the off-white cake rinsed with $CH_3CN$ (12 L), and the solids were dried to provide 3389 g (48% over two steps) of **13**. Mp = 225.2−226.8 °C. $^1$H NMR (300 MHz, $d_6$-DMSO): 2.75 (s, 3H), 3.81 (s, 3H), 7.03 (dd, 1H, $J$ = 2.5, 9.0), 7.51 (d, 1H, $J$ = 2.4), 8.22 (d, 1H, $J$ = 9.0), ∼12.9 (v br s, 1H). $^{13}$C NMR (75 MHz, $d_6$-DMSO): 16.4, 55.4, 104.7, 114.7, 122.7, 124.8, 132.2, 137.9, 148.8, 156.8, 164.8. Anal. Calcd for $C_{11}H_{10}O_3S$: C, 59.44; H, 4.53. Found: C, 59.66; H, 4.43.

**6-Methoxy-N,2-dimethylbenzo[*b*]thiophene-3-carboxamide (9).** A 75-L Hastelloy reactor was sequentially charged with THF (27 L) and **13** (3010 g, 13.54 mol) at room temperature. To the slurry was added 1,1′-carbonyldiimidazole (CDI, 2632 g, 16.23 mol) in one portion. After 1 h, the reaction solution was cooled to 10 °C. The $CH_3NH_2$ solution (2.34 L, 40% by wt in $H_2O$, 67.6 mol) was slowly added to the reaction. After complete addition of the $CH_3NH_2$ solution, the reaction solution was warmed to room temperature. After a reaction time of 3 h (post-amine addition), water (27 L) was added to the reaction solution. The mixture was distilled under atmospheric pressure down to an approximate volume of 30 L and a distillation head temperature of 71 °C. The reaction mixture was seeded with **9** at 60 °C, then the heat was turned off and the solution allowed to cool to room temperature overnight with continued stirring. After 18 h, the solution was filtered, and the solids were rinsed with a 5:1 $H_2O$/THF mixure (27 L). The white solids were dried to provide 2919 g (92%) of **9**. Mp = 157.9−159.0 °C. $^1$H NMR (300 MHz, $CDCl_3$): 2.66 (s, 3H), 3.07 (d, 3H, $J$ = 4.9), 3.88 (s, 3H), 5.93 (br s, 1H), 6.99 (dd, 1H, $J$ = 2.4, 8.9), 7.23 (d, 1H, $J$ = 2.4), 7.75 (d, 1H, $J$ = 8.9). $^{13}$C NMR (75 MHz, $d_6$-DMSO): 14.7, 26.0, 55.4, 104.8, 114.2, 123.3, 129.6, 132.1, 137.6, 138.6, 156.8, 164.5. Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: C, 61.25; H, 5.50; N, 5.92.

**6-Hydroxy-*N*,2-dimethylbenzo[*b*]thiophene-3-carboxamide (2).** A 75-L Hastelloy reactor was sequentially charged with **9** (2901 g, 12.32 mol) and methanesulfonic acid (MSA, 29 L) at 23 °C. To the solution was added the first portion of methionine (2000 g, 13.40 mol), and an exotherm to 27 °C was observed. The solution was cooled to 24 °C. To the reaction, the second portion of methionine (3000 g, 20.10 mol) was added. After 25 min, the internal temperature had cooled to 25 °C, and the third portion of methionine (2374 g, 15.91 mol) was added. The reaction was heated to 60 °C. After a total reaction time of 19 h, heating was discontinued, and the reaction solution was cooled to room temperature. In a separate reactor, water (29 L) was cooled to 6 °C. In portions the reaction solution was slowly added to the water at such a rate that the internal temperature of the water solution remained below 25 °C. After complete addition, the mixture was stirred at room temperature overnight. The slurry was filtered and the cake washed with water (2 × 5.8 L). The wet cake was dried to provide 2438 g (89%) of **2** as a white solid. Mp = 209.1−210.8 °C. $^1$H NMR (300 MHz, $d_6$-acetone): 2.58 (s, 3H), 2.95 (d, 3H, $J$ = 4.7), 6.91 (dd, 1H, $J$ = 2.3, 8.8), 7.22 (d, 1H, $J$ = 2.2), 7.25 (br s, 1H), 7.70 (d, 1H, $J$ = 8.8). $^{13}$C NMR (75 MHz, $d_6$-DMSO): 14.6, 26.0, 106.9, 114.5, 123.4, 129.6, 131.0, 136.3, 138.6, 154.8, 164.7. Anal. Calcd for $C_{11}H_{11}NO_2S$: C, 59.71; H, 5.01; N, 6.33. Found: C, 59.74; H, 5.02; N, 6.37.

**7-Chloro-2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-*b*]-pyridine (3).** *Method A (from **17**).* A flask was sequentially charged with THF (400 mL) and 1-methylimidazole (140 mL, 1.76 mol) followed by a rigorous Ar purge. The solution was cooled to −20 °C. A solution of BuLi (2.5 M in hexanes, 700 mL, 1.76 mol) was slowly added to the flask, maintaining the internal temperature between −20 and −10 °C. After the addition was complete, the cooling bath was removed and the solution warmed to 0 °C. Solid $ZnCl_2$ (277.8 g, 2.038 mol) was added in one portion, which resulted in a temperature spike to 48 °C, and then the solution was recooled with an ice bath to room temperature. $CH_3CN$ (1000 mL) and **17** (401.72 g, 1.35 mol) were added to the solution followed by additional $CH_3CN$ (1000 mL). The solution was purged with a subsurface Ar stream for 1 h. With careful exclusion of air, $Pd(PPh_3)_4$ (49.62 g, 0.0432 mol) was added and the mixture heated to 50 °C. After 5 h, water (1.5 L) was added to the hot reaction, and then the solution was cooled to room temperature. After stirring overnight the solids were filtered and washed with 1.3:1 $CH_3CN$/water (350 mL) to provide 625.63 g of **3** as a yellow solid (this material was ∼42% potency). The solids were combined with six other lots synthesized using the same general procedure above (total of 4779.10 g, ranging in potency 39−50%), and the combined solids were heated in water (48 L) containing sodium thiosulfate (500.60 g) up to a temperature of 50 °C and then cooled to room temperature over 14 h. After cooling, the slurry was filtered and dried to provide 4076 g of crude **3**. A total of 3915 g of this material was taken forward in eight batches into the recrystallization below.

**Recrystallization of Crude 3.** Crude **3** (412.24 g) was charged to a flask with DMSO (2000 mL) and heated to 80 °C. After 1 h of heating, Celite (200.77 g) was added and the mixture stirred for 1 h at 80 °C. The solution was then filtered over a pad of Celite and washed with DMSO (800 mL); the filtrate was transferred to a clean flask and heated back to 80 °C. Water (700 mL) was slowly added to the flask and the solution heated for 4 h, then cooled to room temperature overnight. The solution was filtered, and the solids were washed with 4:1 DMSO/water (250 mL) followed by water (1 L). The solids were dried to yield 197.69 g of **3** (97% purity, 98% potency). This general procedure was repeated for the remaining material in seven batches. After all the lots were purified, a total of 1.48 kg of **3** was produced for an overall yield of 63% from **17**. Mp = 216.9−218.2 °C. $^1$H NMR (300 MHz, $d_6$-DMSO): 4.01 (s, 3H), 7.08 (d, 1H, $J$ = 1.0), 7.44 (d, 1H, $J$ = 1.0), 7.57 (d, 1H, $J$ = 5.1), 7.95 (s, 1H), 8.65 (d, 1H, $J$ = 5.1). $^{13}$C NMR (75 MHz, $d_6$-DMSO): 34.8, 119.1, 120.9, 125.8, 128.6, 131.6, 136.1, 138.5, 139.9, 148.8, 157.7. Anal. Calcd for $C_{11}H_8ClN_3S$: C, 52.91; H, 3.23; N, 16.83. Found: C, 52.92; H, 3.25; N, 16.85.

***N*,2-Dimethyl-6-(2-(1-methyl-1H-imidazol-2-yl)thieno-[3,2-*b*]pyridin-7-yloxy)benzo[*b*]thiophene-3-carboxamide (1).** An Ar-purged 75-L Hastelloy reactor was sequentially charged with DMSO (10 L), **3** (1643 g, 6.58 mol), **2** (1468 g, 6.63 mol), $Cs_2CO_3$ (3625 g, 11.12 mol), and additional DMSO (2.5 L) rinse. While stirring, the slurry was heated to 80 °C. After 27 h, water (32.7 L) was added to the hot reaction mixture, causing precipitation of the product. After 15 min, the solution was cooled to room temperature. After 1 h, the mixture was filtered, and the solids were rinsed with water (3 × 6 L), and pulled dry on the filter. The cake was charged to a 75-L Hastelloy reactor, and $CH_2Cl_2$ (42.5 L) and EtOH (28.6 L) were added. The slurry was heated to 40 °C with stirring to dissolve the crude **1**. The solution was cooled (<25 °C) and filtered through Celite. The Celite cake was rinsed with the solvent mixture (4.1 L of 3:2 $CH_2Cl_2$/EtOH). The filtrate was added back to a clean reactor. The solution was distilled under atmospheric pressure to remove $CH_2Cl_2$. The distillation was continued until the internal temperature reached 75 °C and was held at this temperature for 15 min. The slurry was cooled to below 70 °C and seeded with **1** (300 mg) to initiate crystallization. The slurry was cooled to room temperature and filtered, and the solids were rinsed with EtOH (3 × 4L). The solids were dried to provide 1774 g (62%) of **1**. The filtrate contained a large amount of uncrystallized product, so that the filtrate was concentrated to ∼10 L, cooled, filtered, and dried to provide 229 g (8%) of a second crop of **1**. The filtrate from the second crop was further concentrated to ∼4 L and filtered, and the solids were dried to provide a third crop of 132 g of **1**. The three portions of **1** were combined to provide 2122 g (75% overall yield) of **1** in >99% overall purity by HPLC analysis. Mp = 249.5−250.4 °C. $^1$H NMR (300 MHz, $d_6$-DMSO): 2.61 (s, 3H), 2.84 (d, 3H, $J$ = 4.6), 3.99 (s, 3H), 6.71 (d, 1H, $J$ = 5.4), 7.03 (d, 1H, $J$ = 1.0), 7.33 (dd, 1H, $J$ = 2.3, 8.8), 7.41 (d, 1H, $J$ = 1.0), 7.86 (d, 1H, $J$ = 8.8), 7.89 (s, 1H), 7.95 (d, 1H, $J$ = 2.3), 8.28 (br q, 1H, $J$ = 4.6), 8.53 (d, 1H, $J$ = 5.4). $^{13}$C NMR (75 MHz, $d_6$-DMSO): 14.8, 26.0, 34.8, 105.6, 114.2, 118.4, 120.9, 121.3, 124.1, 125.5, 128.4, 129.7, 136.1, 137.8, 138.4, 140.2, 141.2, 149.8, 150.1, 159.0, 159.4, 164.2. Anal. Calcd for $C_{22}H_{18}N_4O_2S_2$: C, 60.81; H, 4.18; N, 12.89. Found: C, 60.62; H, 4.03; N, 12.75.

**Benzenesulfonic Acid (BsOH) Salt of 1.** A 75-L Hastelloy reactor was sequentially charged with EtOH (19 L) and **1** (2095 g, 4.82 mol), and the slurry was heated to 55 °C. In a separate container, benzenesulfonic acid hydrate (925.05 g, 5.25 mol) was dissolved in water (2.1 L) and EtOH (4.2 L). The acid solution was added to the reaction slurry in one portion and rinsed over with EtOH (2.1 L). The solution was seeded with **1**·BsOH. After stirring for 20 min, significant solids were present. After a total of 30 min, THF (21 L) was added slowly via addition funnel. After all the THF was added, the solution was held at 53 °C for 15 min and then cooled to room temperature over 2 h. The solution was stirred at room temperature for 1.25 h and filtered, and the solids were rinsed with solvent (9.2 L of solution containing 5 L of EtOH and 4.2 L THF). The solids were dried to provide 2511 g (88%) of **1**·BsOH in >99% purity by HPLC analysis. Mp = 237.3−239.2 °C. $^1$H NMR (300 MHz, $d_6$-DMSO): 2.63 (s, 3H), 2.85 (d, 3H, $J$ = 4.5), 4.04 (s, 3H), 6.90 (d, 1H, $J$ = 5.7), 7.23−7.35 (m, 3H), 7.37 (dd, 1H, $J$ = 2.3, 8.8), 7.58−7.62 (m, 3H), 7.79 (d, 1H, $J$ = 1.5), 7.91 (d, 1H, $J$ = 8.8), 8.02 (d, 1H, $J$ = 2.3), 8.22 (s, 1H), 8.27 (br q, 1H, $J$ = 4.4), 8.70 (d, 1H, $J$ = 5.7). $^{13}$C NMR (176 MHz, $d_6$-DMSO): 14.9, 26.0, 35.6, 106.1, 114.4, 118.3, 123.1, 123.9, 124.3, 125.5, 126.1, 127.6, 128.3, 129.7, 136.6, 137.7, 138.4, 138.5, 141.5, 148.4, 149.7, 156.1, 160.3, 164.1. Anal. Calcd for $C_{28}H_{24}N_4O_5S_3$: C, 56.74; H, 4.08; N, 9.45. Found: C, 56.67; H, 4.00; N, 9.35.

**7-Chlorothieno[3,2-*b*]pyridine-2-carbaldehyde (18).** A 5-L, Ar-purged flask was sequentially charged with **4** (150.0 g, 0.8843 mol) and THF (750 mL). The mixture was stirred until the starting material dissolved. The flask was cooled in a dry ice/acetone bath to an internal temperature of −46 °C. A solution of BuLi (390 mL, 2.5M in hexanes, 0.975 mol) was added via addition funnel at such a rate that the internal temperature remained between −43 and −46 °C. After base addition, the solution was allowed to stir for 10 min, and the internal temperature had dropped to −66 °C. Anhydrous DMF (86.0 mL, 1.11 mol) was added via addition funnel at such a rate that the internal temperature was held at −56 to −57 °C. The internal temperature was held at ∼-62 °C for 1 h and then the reaction was quenched by the addition of MeOH (285 mL), followed by immediate removal of the cooling bath. To the solution was slowly added aq HCl (∼1.5 M, 160 mL concn HCl added to 1150 mL $H_2O$). The solution was stirred at room temperature for 30 min. Aqueous sat. $NaHCO_3$ (60 mL) was added until the pH stablilized at 7. The slurry was stirred for 5 min and filtered, and the cake was rinsed with solvent mixture (2 × 530 mL soln containing 430 mL $H_2O$ and 100 mL MeOH). The solids were given a final rinse with MTBE (2 × 250 mL), and the solids were dried to provide 122.8 g (70%) of **18** as a white powder.

Mp = 173.1−174.1 °C. $^1$H NMR (300 MHz, $d_6$-DMSO): 7.80 (d, 1H, $J$ = 5.0), 8.63 (s, 1H), 8.83 (d, 1H, $J$ = 5.0), 10.25 (s, 1H). $^{13}$C NMR (75 MHz, $d_6$-DMSO): 121.7, 135.1, 135.7, 137.7, 145.8, 150.2, 155.6, 186.4. Anal. Calcd for $C_8H_4ClNOS$: C, 48.62; H, 2.04; N, 7.09. Found: C, 48.43; H, 1.87; N, 7.05.

**7-Chloro-2-(1H-imidazol-2-yl)thieno[3,2-*b*]pyridine (19).** A 3-L flask was charged with aldehyde **18** (110.07 g, 0.5569 mol) and MeOH (1250 mL). The slurry was stirred for ∼5 min followed by sequential charge of acetic acid (250 mL), glyoxal trimer dihydrate (117.34 g, 1.675 mol equiv glyoxal), and $NH_4OAc$ (258.07 g, 3.348 mol). The mixture was stirred at room temperature for 24 h. Water (625 mL) was slowly added via addition funnel over 30 min, and the resulting slurry was stirred an additional 15 min at room temperature. The slurry was filtered, and the smoothed cake was rinsed (2:1 MeOH/$H_2O$, 2 × 600 mL). After the filtration was pulled down to a smooth, packed cake, it was given a final rinse with $CH_2Cl_2$ (600 mL). The solids were dried to provide 78.33 g (60%) of **19** as a brown powder. Mp = 233.0−234.0 °C. $^1$H NMR (300 MHz, $d_6$-DMSO): 7.12 (br s, 1H), 7.45 (br s, 1H), 7.55 (d, 1H, $J$ = 5.1), 8.00 (s, 1H), 8.62 (d, 1H, $J$ = 5.1), 13.1 (br s, 1H). $^{13}$C NMR (75 MHz, $d_6$-DMSO): 118.9, 119.7, 129.9, 131.5, 136.4, 139.25, 139.34, 140.2, 148.9, 157.5. Anal. Calcd for $C_{10}H_6ClN_3S$: C, 50.96; H, 2.57; N, 17.83. Found: C, 50.63; H, 2.57; N, 17.43.

**7-Chloro-2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-*b*]-pyridine (3).** *Method B (From **19**).* A 3-L flask was sequentially charged with **19** (85.18 g, 0.3614 mol), THF (1275 mL), and methyl tosylate (65.0 mL, 0.431 mol). The reaction flask was cooled in an ice/water bath to an internal temperature of 6 °C. The NaOtBu solid was added in two portions to allow control of the exotherm. The first addition of NaOtBu (21.28 g, 0.221 mol) caused the internal temperature to rise to 9 °C. After 5 min, the second portion of NaOtBu (21.25 g, 0.221 mol) was added, causing the internal temp to rise to 11 °C. After an additional 5 min, the cooling bath was removed and the solution allowed to warm to room temperature. After 50 min, water (1275 mL) was added to the reaction solution and the flask set up for distillation. The solution was distilled at atmospheric pressure to remove most of the THF, the distillation deemed complete when the internal temperature held at a steady 75 °C. The solution was allowed to cool to room temperature over 3 h. The slurry was filtered, and the solids were rinsed with water (400 mL) and then dried to provide 79.06 g (87%) of **3** as a brown powder.

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