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Process Development for Sodelglitazar: A PPAR Panagonist

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Abstract:

Three efficient syntheses of sodelglitazar (1) have been developed. In particular, the third synthesis avoids the use of zinc and eliminates the resulting heavy metal waste stream as well as the potential genotoxic methanesulfonate in the two earlier syntheses. This process produces sodelglitazar in 74% overall yield from readily available thiophenol (8) and thiazole alcohol (3).

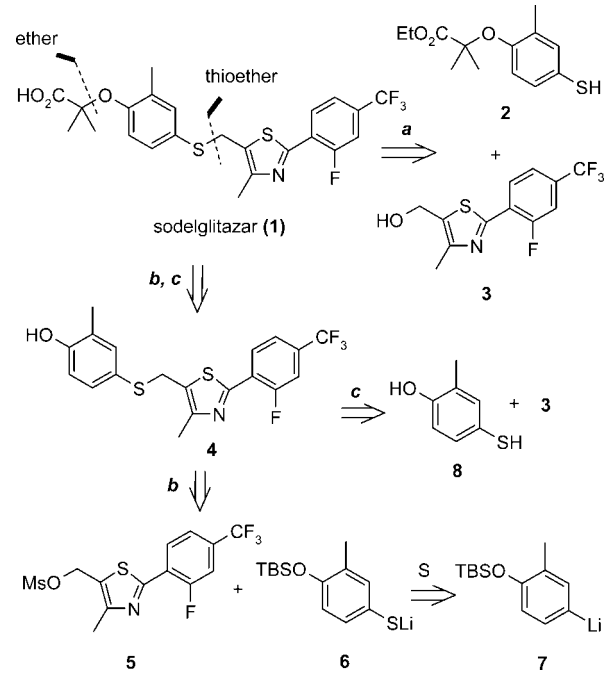
Introduction

Sodelglitazar (**1**) is a panagonist active towards all three peroxisome proliferator-activated receptors (PPAR).[1] Sodelglitazar (**1**) had been in the phase II clinical development for the treatment of type 2 diabetes and metabolic syndrome. To supply drug substance for the development studies, a robust and efficient synthesis of sodelglitazar (**1**) was needed. Herein, we detail our efforts on the process development for sodelglitazar (**1**).

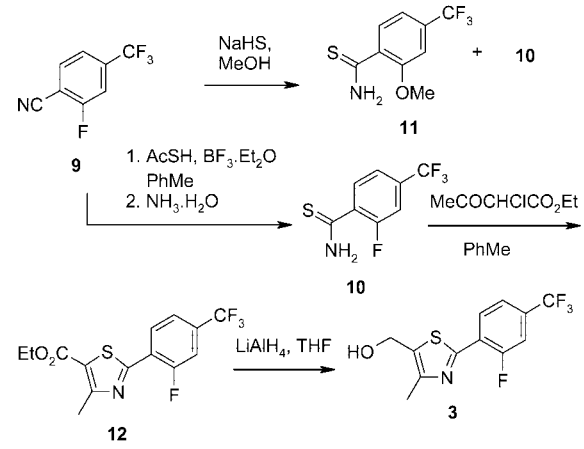
Retrosynthetic analysis of sodelglitazar (**1**) suggested that disconnections of ether and thioether are the most accessible (Scheme 1). Our first approach to sodelglitazar (**1**), a slight modification of the medicinal chemistry routes,[1a] was to make the ether linkage first followed by thioether formation through coupling of thiophenol **2** with thiazole alcohol **3** (pathway a). Our second approach to sodelglitazar was to construct the ether linkage at the last stage of synthesis from phenol **4** (pathway b). The phenol **4** was prepared from substitution of thiazole alcohol methanesulfonate **5** by lithium thiolate **6** that was obtained from aryl lithium **7** and elemental sulfur.[2] Our third approach to sodelglitazar was a slight variation of the second synthesis. The phenol **4** was prepared from the direct coupling of thiazole alcohol **3** with thiophenol **8** (pathway c).

Synthesis of Starting Intermediate (3). For all syntheses under consideration, the thiazole alcohol **3** was a key intermediate. This was efficiently prepared from readily available benzonitrile **9** (Scheme 2). Reaction of benzonitrile **9** with sodium hydrogen sulfide in methanol at 50 °C gave thioamide **10** in 32% yield along with 19% of methoxy substituted thioamide **11**. Column chromatography was required for purification as recrystallization failed to provide the clean thioamide **10**. To eliminate the substitution reaction, we screened different thionation agents such as NaHS in different solvents,

Scheme 1. **Retrosynthetic analysis of sodelglitazar**



Scheme 2. **Preparation of thiazole alcohol 3**



P_2S_5, thioacetamide, and thioacetic acid,[3] and found that thioacetic acid as a thionation agent worked best to convert nitrile into thioamide without the undesired substitution reaction. Thus, treatment of benzonitrile **9** with thioacetic acid and boron trifluoride diethyl etherate followed by ammonia gave thioamide **10** in greater than 95% conversion. After aqueous workup and azeotropic distillation to remove water, the crude thioamide **10**

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(1) (a) Cadilla, R.; Gosmini, R. L. M.; Lambert, M. H., III; Sierra, M. L. PCT WO 2002062774, 2002. (b) Evans, J. L.; Lin, J. J.; Goldfine, I. D. *Curr. Diabetes Rev.* **2005**, *1*, 299–307.

(2) (a) Ingold, K.; Liu, B. PCT WO 2003074504, 2003. (b) Ko, J.; Ham, J.; Yang, I.; Chin, J.; Nam, S.-J.; Kang, H. *Tetrahedron Lett.* **2006**, *47*, 7101–7106.

(3) Gauthier, J. Y.; Lebel, H. *Phosphorus Sulfur* **1994**, *95 and 96*, 325–326.

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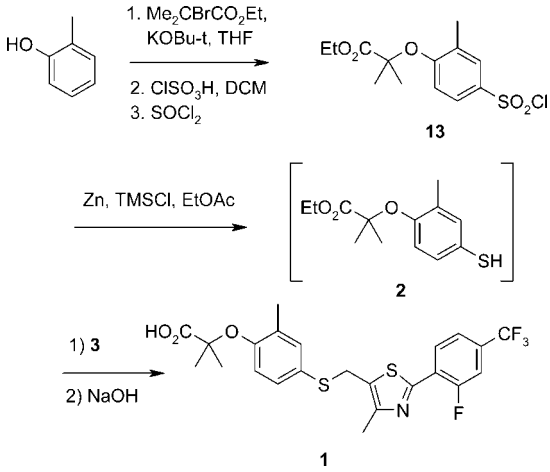
Scheme 3. **First synthesis of 1**



reacted with 2-chloroacetoacetate in toluene at 100 °C to give thiazole ester **12** in 70% yield in one pot. Ester **12** was reduced with $LiAlH_4$ to give thiazole alcohol **3** in 91% yield.

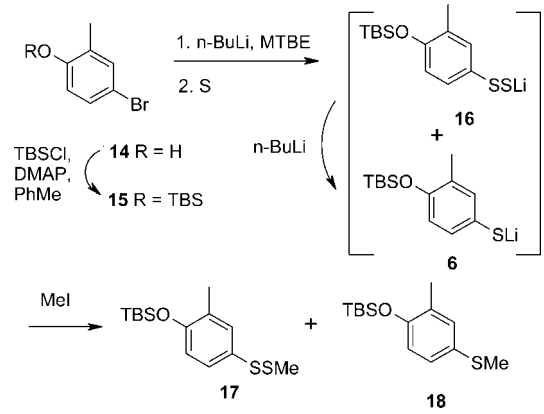
First Synthesis. In our first synthesis of **1**, we required thiophenol **2**. This was prepared through alkylation of 2-methylphenol with 2-bromo-2-methylpropanoate in the presence of t-BuOK in THF followed by sulfonation with chlorosulfonic acid (Scheme 3). Subsequent reaction with thionyl chloride gave sulfonyl chloride **13** in 74% yield, which was reduced using zinc and TMSCl in ethyl acetate with acetic acid and water to provide thiophenol **2**. $ZnCl_2$ generated in situ from zinc and TMSCl facilitated the coupling of thiophenol **2** with thiazole alcohol **3** followed by saponification to give **1** in 78% yield in one pot on the multigram scale.[4] The scalability of this process was of concern due to the use of zinc, which tended to settle on the bottom of the reactor, causing agitation issues on scale. In addition, generation of a heavy metal waste stream was not desirable. The one-pot process also lacked an isolation step prior to the formation of **1**, considered important for control of the final drug substance quality. To address these issues, we designed the second approach to sodelglitazar (**1**) (Scheme 1).

Second Synthesis. Our second synthesis of **1** started with the readily available 4-bromo-2-methylphenol (**14**). Silylation of **14** with TBSCl and DMAP in toluene gave silyl ether **15** in quantitative yield. The crude bromide **15** in *tert*-butyl methyl ether (TBME) at −20 °C was treated with n-BuLi to generate aryllithium **7** that further reacted with elemental sulfur to form the lithium arylthiolate intermediate **6**. The lithium bromine exchange reaction of bromide **14** was unsuccessful without protection of the phenol as its *tert*-butyldimethylsilyl ether. In one scale-up run of the coupling, the sulfenation of aryllithium **7** was incomplete as treatment of an aliquot of the reaction mixture with MeI generated a significant amount of disulfide **17**. Mechanistically, the disulfide **16** is the intermediate en route to the sulfide **6** in the sulfenation reaction. The high residual disulfide observed was a result of a probable process error caused by a sulfur overcharge.

To better understand the sulfenation reaction, we studied the effects of order of addition and the stoichiometry of organolithium **7** to sulfur. As measured by the amount of disulfide in

(4) Martin, M. T.; Thomas, A. M.; York, D. G. *Tetrahedron Lett.* **2002**, *43*, 2145–2147.

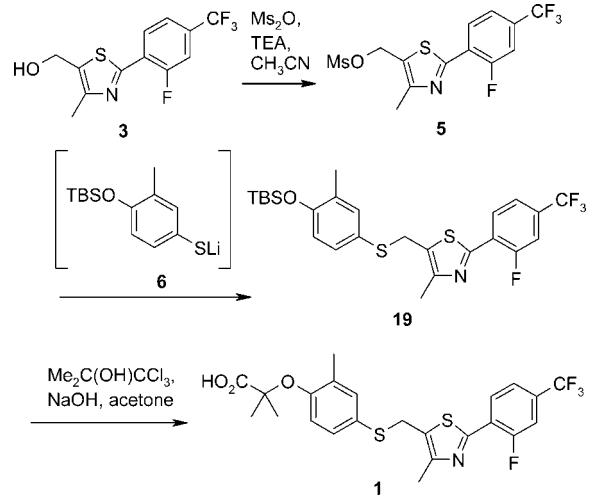
Table 1. **Sulfenation of organolithium 7**



run	equiv of **15**:n-BuLi:S	ratio of **17**:**18**[a]
1	1:1:0.9	0.4:99.6
2	1:1:0.9 (inverse addition)	3:97
3	1:1:1.2	23:77
4	1:1:1.2 followed by 0.2 equiv of n-BuLi	**17** not detected

[a] The ratio was determined by HPLC.

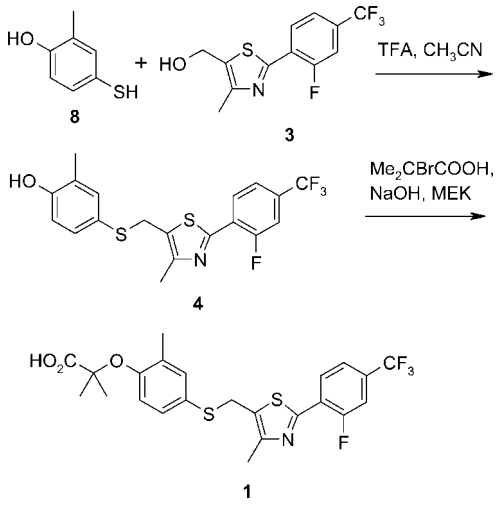
Scheme 4. **Second synthesis of 1**



the sulfenation reaction, the order of addition has no major impact (Table 1). The normal addition of sulfur to the aryl lithium mixture (run 1) left an insignificant amount of disulfide. The inverse addition, adding aryl lithium to a slurry of elemental sulfur in TBME, led to a slight increase in the amount of disulfide. However, the sulfenation process was highly dependent upon the stoichiometry of organolithium **7** and elemental sulfur in the reaction mixture. Excess sulfur resulted in incomplete conversion of disulfide **16** to sulfide **6**, generating 23% of disulfide **17** upon derivatization with MeI (run 3). Gratifyingly, the addition of additional n-BuLi brought about complete conversion of disulfide **16** to sulfide **6** (run 4).

Once the sulfenation reaction was complete as determined by MeI derivatization, the lithium arylthiolate intermediate **6** was treated with thiazole alcohol methanesulfonate **5** prepared from thiazole alcohol **3** and methanesulfonic anhydride to give sulfide **19** in 74% yield (Scheme 4). Desilylation and alkylation were carried out in one pot. Introduction of the isobutyric acid moiety was first achieved with ethyl 2-bromo-2-methylpro-

Scheme 5. **Third synthesis of 1**



panoate. However, a significant amount of methacrylate formed, and its polymerization presented a scale-up issue from a quality perspective since polymer coating of reactors was observed. The alternative method to make α-phenoxyisobutyric acid was the Bargellini reaction that involves the condensation of phenol with chloroform and acetone in the presence of sodium hydroxide.[5] Thus, the Bargellini reaction using 1,1,1-trichloro-2-methyl-2-propanol, the condensation product of $CHCl_3$ and acetone, introduced the isobutyric acid segment, producing sodelglitazar **1** in 65% yield. The use of the Bargellini reaction avoided the formation of methacrylate and therefore the polymerization issue. The second synthesis of sodelglitazar was efficient and had been scaled up in 50-L reactors. However, the process still had several issues that made it less than ideal as a manufacturing route. The route involved the use of potentially genotoxic methanesulfonate **5** which needed to be controlled at low levels in the drug substance. In addition, the sulfenation of organolithium **7** with elemental sulfur required careful control to minimize the residual disulfide **16**. Finally, the Bargellini reaction was highly exothermic and involved the use of polyhalogenated compounds that are a safety concern. For these reasons, an alternative synthesis to address these issues was desired.

Commercial Synthesis. Fortunately, during our work on sodelglitazar, thiophenol **8** became available as a potential starting material, and thus we opted to develop the third process for sodelglitazar from **8** (Scheme 5). Selective coupling of thiophenol **8** with thiazole alcohol **3** was achieved successfully using strong acids such as trifluoroacetic acid in acetonitrile. Strong inorganic acids such as sulfuric acid and sulfonic acids such as methanesulfonic acid were less selective, leading to the formation of ether **20** from the homocoupling of thiazole alcohol **3**, and ether **21** from the further reaction of phenol **4** with thiazole alcohol **3** (Figure 1). During the coupling of thiazole alcohol **3** and thiophenol **8** in the mixture of trifluoroacetic acid and acetonitrile, a transient intermediate determined by LC/MS to be thiazole alcohol trifluoroacetate formed first and then

(5) (a) Bargellini, G. *Gazz. Chim. Ital.* **1906**, *36*, 329–339. For a recent example, see: (b) Bose, A. K.; Manhas, M. S.; Ganguly, S. N.; Pednekar, S.; Mandadi, A. *Tetrahedron Lett.* **2005**, *46*, 3011–3013. (c) Caution! The mixture of chloroform and acetone in the presence of sodium hydroxide has been reported as explosive and an exothermic hazard.

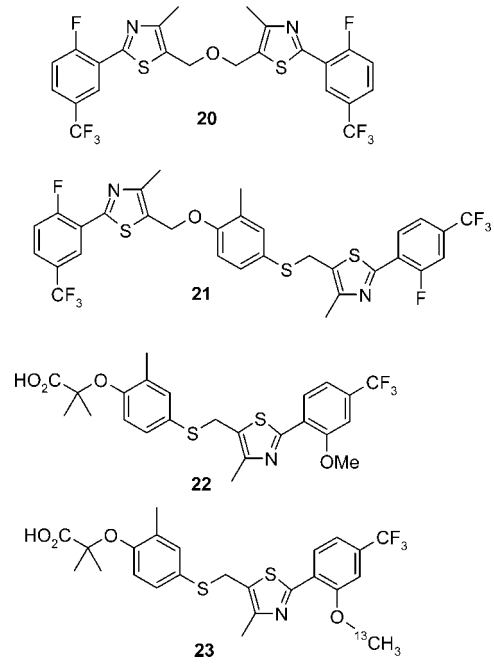


Figure 1. **Structures of process impurities.**

reacted with thiophenol **8** to give phenol **4**. When the reaction was complete, the product phenol **4** was precipitated from the reaction mixture by addition of water.

Alkylation of phenol **4** was carried out under heterogeneous conditions in the presence of sodium hydroxide using 2-bromo-2-methylpropanoic acid instead of the Bargellini reaction described in the second process (Scheme 4). The alkylation using 2-bromo-2-methylpropanoic acid is less exothermic than the Bargellini reaction.[6] We next studied the process in more detail to get the process ready for manufacturing scale. Screens of different carbonate bases, hydroxides, and organic bases confirmed solid sodium hydroxide as the optimal base for the alkylation. No alkylation occurred with carbonate bases or organic bases such as DBU as decomposition of 2-bromo-2-methylpropanoic acid appeared to be the major pathway. Soluble bases such as t-BuOLi and Me_3SiOK failed to bring the alkylation to completion. Attempts to run the alkylation in the presence of 50% NaOH under phase transfer conditions proved fruitless. 2-Butanone (MEK) was the preferred solvent for the alkylation reaction over toluene and ether solvents such as THF, DME, and 1,4-dioxane. Alcoholic solvents were unsuitable for the alkylation as the fluorine in the phenol was susceptible for substitution by alkoxide. Adequate agitation was essential for the heterogeneous reaction to go to completion as solid NaOH agglomerated as the reaction progressed. Different forms of solid NaOH such as pellets, flakes, and beads had no impact on the alkylation outcome once adequate agitation was applied. After the reaction was complete, a water quench of the reaction mixture and a 2-h hold at 50 °C destroyed the excess 2-bromo-2-methylpropanoic acid to less than 10 ppm that was the control specification for 2-bromo-2-methylpropanoic acid in the final drug substance. Water wash of the MEK suspension removed salts and excess hydroxide. The sodium salt of the product remained in the organic layer during the

(6) Davis, R. D.; Fitzgerald, R. N.; Guo, J. *Synthesis* **2004**, 1959–1962.

water wash. Acidification of the organic layer followed by solvent exchange to heptane gave **1** in 75% yield.

There was about 0.1% of methoxy impurity **22** detected in the isolated drug substance (Figure 1). From a quality perspective, we needed to understand the origin of this impurity as no methanol source was employed in the synthesis. The starting phenol was confirmed to be free from any methoxy containing contaminants. Analysis of the solvent MEK showed there were 43 ppm of methanol and 90 ppm of methyl propanoate in MEK. It was interesting to note that treatment of MEK with solid NaOH at 50 °C for 2 h increased the amount of methanol to 56 ppm and the amount of methyl propanoate to 1300 ppm. It should be noted that the amount of methyl propanoate did not increase significantly with extended reaction time in the open air. Methyl propanoate could be hydrolyzed under the alkylation conditions to methanol that caused the formation of methoxy-substituted impurity **22** observed in the isolated product. Alkylation in acetone-1,3-$^{13}C_2$ (C-13 methanol not present to any extent) formed ^{13}C-labeled methoxy impurity **23**. This suggested that methanol was derived from the hydrolysis of methyl ester formed from 2-butanone through a Baeyer−Villiger oxidation.[7]

The third synthesis of sodelglitazar (**1**) was a two-step synthesis that eliminated potential genotoxic intermediate sulfonate **5** and the potentially nonrobust sulfenation reaction in the second synthesis. This synthetic route was selected as the manufacturing route for sodelglitazar.

In summary, we have developed three efficient syntheses of sodelglitazar. The third synthesis avoids the use of zinc and eliminates the resulting heavy metal waste stream as well as the potential genotoxic methanesulfonate in the two earlier syntheses. The process produces sodelglitazar in 74% overall yield from readily available thiophenol **8** and thiazole alcohol **3**.

Experimental Section

^{1}H NMR spectra were obtained with 300 or 400 MHz instruments. All reagents and solvents were purchased from commercial sources and were used without further purification. HPLC purity was determined on a Hewlett Packard series 1100 system using Agilent Eclipse XDB C18 columns (150 mm × 4.6 mm, 3.5 μm), and a mixture of water and acetonitrile as mobile phase (gradient at a flow rate of 1.0 mL/min and UV detector at 220 nm). Mass spectral data were collected on an Agilent quadrupole ion trap mass spectrometer using electron-spray ionization (ESI) in positive ion mode.

2-(4-Chlorosulfonyl-2-methylphenoxy)-2-methylpropionic Acid Ethyl Ester (13). A solution of 1 M t-BuOK (325 mL, 0.325 mol) was stirred and cooled to between −10 and 0 °C. 2-Cresol (35.1 g, 0.325 mol) in THF (70 mL) was added dropwise over 10 min, keeping the temperature below 0 °C. The main exotherm occurred during the first half of addition. The mixture was then cooled to −5 °C, and ethyl 2-bromo-2-methylpropanoate (50.7 g, 0.28 mol) was added at once. The mixture was warmed to 55−65 °C. During the warm-up, a dark pink/magenta color formed. The mixture was stirred at 62−65 °C for 50 min. The mixture was concentrated to half-volume at 40−50 °C, and water (200 mL) was added. Isooctane (200 mL) was added, and the layers were allowed to separate. The organic phase was extracted with 1 N NaOH (200 mL) to remove excess 2-methylphenol. The organic phase was dried over Na_2SO_4 and concentrated at 40−50 °C to one-quarter volume.

The 2-methyl-2-(*o*-tolyloxy)propionic acid ethyl ester in isooctane (from above) was dissolved in dichloromethane (330 mL), stirred, and cooled to −5 °C. Neat chlorosulfonic acid (32.3 g, 0.28 mol) was added dropwise over 15−20 min, controlling the temperature below 0 °C. The mixture was stirred at −5 °C for 60 min. *N*,*N*-Dimethylformamide (57.9 g, 0.79 mol) was added over 15 min, while controlling the temperature below 10 °C. The solution was cooled to −5 °C, and thionyl chloride (35.3 g, 0.30 mol) was added over 5 min, with no temperature rise. The reaction was allowed to warm to ambient and to stir at ambient for 1.5 h. The mixture was cooled to 0 °C, and H_2O (330 mL) was added. The layers were separated, and the organic (lower) phase was washed with 0.1 N HCl (2 × 330 mL). The organic phase was dried over Na_2SO_4. Solvent was exchanged at 40−50 °C to isooctane until distillation had ceased. Upon cooling to ambient, a solid precipitated. The solid was collected by filtration, washed with isooctane (25 mL), and dried under vacuum at 25 °C to constant weight to give 60.0 g of 2-(4-chlorosulfonyl-2-methylphenoxy)-2-methylpropionic acid ethyl ester (**13**) as an amber solid in 74% yield over two steps. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, 1 H, J = 2.4 Hz), 7.78 (dd, 1 H, J = 8.9, 2.4 Hz), 6.70 (d, 1 H, J = 8.9 Hz), 4.26 (q, 2 H, J = 7.1 Hz), 2.34 (s, 3 H), 1.73 (s, 6 H), 1.25 (t, 3 H, J = 7.1 Hz). HPLC purity: 96.3% AUC.

2-[2-Fluoro-4-(trifluoromethyl)phenyl]-4-methyl-5-thiazolecarboxylic Acid Ethyl Ester (12). To a solution of thioacetic acid (320 mL, 4.48 mol) and boron trifluoride diethyl etherate (550 mL, 4.34 mol) in toluene (1.5 L), was added slowly a solution of 2-fluoro-4-trifluoromethylbenzonitrile (**9**) (303 g, 1.6 mol) in toluene (300 mL) over 60 min at 20 °C. After the addition was complete, the mixture was allowed to stir for 3 h. The mixture was cooled to 5 °C, and water (300 mL) was added over 30 min to quench boron trifluoride. Once the quenching was complete, water (900 mL) was added to dilute the reaction mixture. The aqueous layer was separated. To the organic layer was added 10% ammonia solution (1.2 L) over 30 min while maintaining the temperature below 5 °C. The mixture was heated to 20 °C where it was maintained for an additional 30 min. The aqueous layer (basic) was separated. The organic layer was washed with water (2 × 1.2 L) and concentrated under reduced pressure to ∼900 mL. To the mixture was added ethyl 2-chloroacetoacetate (241 mL, 1.74 mol), and the mixture was heated at 100 °C until the reaction was complete (∼16 h). The reaction mixture was cooled to 50 °C, and toluene was removed under reduced pressure. Ethanol (1.5 L) was added followed by adding water (0.6 vol). The mixture was allowed to cool to ambient over 1 h and maintained at ambient for 1 h. The solid was collected by filtration, washed with cold 90% ethanol (300 mL), and dried under vacuum at 40 °C to a constant weight to give 370 g of thiazole ester **12** as a white solid in 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (t, 1 H, J = 7.7 Hz), 7.54 (d, 1 H, J = 8.5 Hz), 7.50 (d,

(7) Fermin, M. C.; Bruno, J. W. *Tetrahedron Lett.* **1993**, *34*, 7545–7548.

1 H, J = 12.1 Hz), 4.39 (q, 2 H, J = 7.1 Hz), 2.82 (s, 3 H), 1.43 (q, 3 H, J = 7.1 Hz). HPLC purity: 96.9% AUC. MS: MH^+ = 334.

2-[2-Fluoro-4-(trifluoromethyl)phenyl]-4-methyl-5-thiazolemethanol (3). A dry nitrogen purged vessel was charged with THF (1.26 L) and 1 M $LiAlH_4$ in THF (0.67 L, 0.670 mol), and the solution was cooled to −15 °C. A solution of thiazole ester **12** (360 g, 1.08 mol) dissolved in THF (0.72 L) was added over 1.5 h at a rate as to maintain the reaction mixture temperature between −10 and −15 °C. The mixture was allowed to stir at −15 °C for 0.5 h. The reaction was consecutively quenched with a mixture of water and THF (1/1, 54 mL) over 30 min, a 20% NaOH solution (20.2 mL) over 15 min, and water (93.6 mL) over 15 min. During the quenching process, the reaction temperature was maintained at −10 and −15 °C with vigorous stirring. The quenched mixture was warmed to ambient over 30 min where it was maintained for an additional 0.5 h The granular aluminum salts were filtered and washed with THF (3 × 0.36 L). The combined filtrate was concentrated under reduced pressure to ∼1.44 L. Water (2.88 L) was added to the mixture over 30 min while maintaining the solution temperature at 50 °C. The resultant slurry was cooled to 20 °C over 1 h, cooled further to 10 °C, and stirred at 10 °C for 30 min. The solid was filtered, washed with heptane (2 × 0.72 L), and dried under vacuum at 50−55 °C to a constant weight to give 286.3 g of thiazole alcohol **3** as a slightly yellow solid in 91%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (t, 1 H, J = 7.8 Hz), 7.49 (d, 1 H, J = 8.5 Hz), 7.44 (d, 1 H, J = 10.8 Hz), 4.88 (s, 2 H), 2.49 (s, 3 H). HPLC purity: 98.2% AUC. MS: MH^+ = 272.

2-[4-[[[2-[2-Fluoro-4-(trifluoromethyl)phenyl]-4-methyl-1,3-thiazol-5-yl]methyl]sulfanyl]-2-methylphenoxy]-2-methylpropanoic Acid (1). A stirred suspension of zinc (15.7 g, 0.24 mol) in ethyl acetate (220 mL) was heated at 40 °C, and then acetic acid (7.87 mL, 0.137 mol) and water (2.47 mL, 0.137 mol) were added. To the resultant suspension was added sulfonyl chloride **13** (22.0 g, 0.0687 mol) in small portions over 15 min while keeping the temperature below 60 °C. After the addition was complete, the mixture was stirred for one hour. HPLC showed a complete conversion to sulfinic acid. To the mixture was added TMSCl (52.3 mL, 0.412 mol) over 1 h while keeping the temperature below 55 °C. After the addition was complete, the mixture was heated to gentle reflux (about 77 °C) for 3 h. Then thiazole alcohol **3** (20.0 g, 0.0687 mol) was added in one portion. No obvious exotherm occurred. The mixture was maintained at about 77 °C for 15 h or until the reaction was complete. The mixture was cooled to ambient, washed with water (2 × 100 mL), dilute NaCl solution (2 × 100 mL), and concentrated under reduced pressure to ∼40 mL. Ethanol (120 mL) was added, and the mixture was concentrated to ∼40 mL. The solvent exchange process was repeated once. To the mixture was added ethanol (120 mL), followed by water (40 mL), and 50% sodium hydroxide (5.0 mL, 0.094 mol). The cloudy mixture was heated to 60 °C for 2 h. A brown solution was afforded. The mixture was cooled to 40 °C, and concentrated hydrochloric acid (15.0 mL, 0.175 mol) was added over 10 min. The resultant mixture was stirred at 60 °C for 15 min. A slurry with yellow solid formed. The mixture was allowed to cool to room temperature. The solid was collected by filtration, washed with ethanol/water (2:1, 40 mL), and dried under vacuum at 60 °C to a constant weight to give 26.9 g of **1** as a slightly yellow solid in 78% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.02 (br s, 1 H), 8.32 (t, 1 H, J = 7.9 Hz), 7.86 (d, 1 H, J = 10.4 Hz), 7.67 (d, 1 H, J = 8.4 Hz), 7.20 (d, 1 H, J = 1.8 Hz), 7.10 (dd, 1 H, J = 8.4, 2.2 Hz), 6.60 (d, 1 H, J = 8.4 Hz), 4.35 (s, 2 H), 2.20 (s, 3 H), 2.07 (s, 3 H), 1.46 (s, 6 H). HPLC purity: 95.6% AUC. MS: MH^+ = 500.

4-*tert*-Butyldimethylsilyloxy-3-methylbromobenzene (15). To a solution of 4-bromo-2-methylphenol (149.6 g, 0.80 mol), 4-N,N-dimethylaminopyridine (102.6 g, 0.84 mol) and toluene (450 mL) was added a solution of tert-butyldimethylsilyl chloride (126.6 g, 0.84 mol) in toluene (280 mL), at such a rate that the temperature was maintained between 20 and 25 °C (about 20 min). The resulting slurry was stirred at ambient overnight, then quenched with water (115 mL). The organic layer was washed with 1 N HCl (100 mL) followed by 2 N NaOH (100 mL). The organic layer was concentrated under vacuum to give 241 g of silyl ether **15** as a colorless oil in quantitative yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.35 (s, 1 H), 7.24 (d, 1 H, J = 8.4 Hz), 6.75 (d, 1 H, J = 8.4 Hz), 2.30 (s, 3 H), 0.98 (s, 9 H), 0.20 (s, 6 H).

5-[[[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-methylphenyl]thio]methyl]-2-[2-fluoro-4-(trifluoromethyl)phenyl]-4-methylthiazole (19). A solution of silyl ether **15** (3.16 kg, 10.5 mol) and TBME (12.6 kg) was stirred and cooled to −20 °C. A solution of 2 M n-BuLi in cyclohexane (4.70 kg, 12.7 mol) was added over 15 min. The solution was allowed to warm to 0 °C for 1 h. The clear pale yellow solution was cooled to −10 °C, and sulfur (0.335 kg, 10.5 mol) was added in small portions to maintain the temperature at −10 to −5 °C. The solution containing lithium thiolate **6** was stirred at −10 °C for 1 h and held there for subsequent use.

Meanwhile, a separate reactor was charged with thiazole alcohol **3** (2.65 kg, 9.1 mol), acetonitrile (7.6 kg), TBME (4.7 kg), and methanesulfonic anhydride (1.67 kg, 9.56 mol). The slurry was stirred and cooled to 0 °C, and then treated dropwise with Et_3N (1.00 kg, 9.9 mol) while maintaining the mixture below 5 °C. The mixture of mesylate **5** was held at 0 °C for 1 h and cooled to −20 °C.

The TBME solution of lithium thiolate **6** was added to the acetonitrile solution of mesylate **5** at such a rate that the temperature was maintained between −10 and −5 °C. The resulting mixture was held at −5 °C for 45 min and then warmed to ambient. The mixture was quenched with water (20 kg). The organic layer was washed with water (14 kg). The organic layer was concentrated to ∼9 L and then treated with 95% ethanol (20 kg) to effect crystallization at 15−20 °C. The solid was filtered, washed with cold ethanol (6 kg), and dried under vacuum at 55 °C to a constant weight to give 3.53 kg of sulfide **19** as a yellow solid in 74% yield. ^{1}H NMR (300 MHz, CDCl3): δ 8.40 (t, 1 H, J = 7.4 Hz), 7.51 (d, 1 H, J = 8.1 Hz), 7.45 (d, 1 H, J = 11.3 Hz), 7.19 (s, 1 H), 7.08 (d, 1 H, J = 8.2 Hz), 6.68 (d, 1 H, J = 8.2 Hz), 4.14 (s, 2 H), 2.26 (s, 3 H), 2.16 (s, 3 H), 1.02 (s, 9 H), 0.21 (s, 6 H). HPLC purity: 97.1% AUC. MS: MH^+ = 528.

2-[4-[[[2-[2-Fluoro-4-(trifluoromethyl)phenyl]-4-methyl-1,3-thiazol-5-yl]methyl]sulfanyl]-2-methylphenoxy]-2-methylpropanoic Acid (1). A slurry of silyl ether **19** (3.16 kg, 6.0 mol) and 20−40 mesh sodium hydroxide (2.4 kg, 6.0 mol) in acetone (25 kg) was stirred at ∼33 °C for 1 h. A solution of 1,1,1-trichloro-2-methyl-propanol hydrate (2.0 kg, 11.4 mol) in acetone (4 kg) was added over at least 60 min, while maintaining the temperature at 36−38 °C. The reaction mixture was cooled to ambient temperature over approximately 1 h. The reaction volume was reduced under vacuum to 1/4 to 1/2 of the total volume, at a temperature below 40 °C. TBME (22 kg) and 1 N hydrochloric acid (26 kg) were added, keeping the temperature under 35 °C. After separation, the organic layer was washed with water (2 × 20 kg) and concentrated to ∼16 L. The solution was heated to approximately 50 °C and heptane (26 kg) was added. The mixture was concentrated at atmospheric pressure until the head temperature reached 83−85 °C. The solution was cooled slowly at <1 °C/min, during which time crystallization began (typically 60 °C). The slurry was further chilled to below 15 °C and stirred for at least 1 h. The solid was collected by filtration, washed with heptane (10 kg), and dried under vacuum at 45−55 °C to a constant weight to give 1.95 kg of **1** as a slightly yellow solid in 65% yield. HPLC purity: 97.3% AUC.

4-[[[2-[2-Fluoro-4-(trifluoromethyl)phenyl]-4-methyl-5-thiazolyl]methyl]thio]-2-methylphenol (4). To a mixture of thiazole alcohol **3** (48.6 kg, 166.8 mol), thiophenol **8** (26.3 kg, 187.6 mol), and acetonitrile (98.5 kg) was added trifluoroacetic acid (185 kg). The mixture was stirred under nitrogen until the exotherm was realized, ∼15 min. The mixture was heated to ∼65 °C over 45 min and maintained at that temperature for 6 h. To the mixture was added water (400 kg) while maintaining the mixture above 40 °C. The mixture was held at 40 °C with good stirring for one hour. The mixture was cooled to ambient over 30 min. The solid was filtered, washed with a mixture of acetonitrile (19.6 kg) and water (37.5 kg) followed by a heptane (68 kg) wash, and dried under vacuum at 60 °C to a constant weight to give 63.1 kg of phenol **4** as a slightly yellow solid in 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (t, 1 H, J = 7.7 Hz), 7.47 (d, 1 H, J = 7.3 Hz), 7.43 (d, 1 H, J = 9.9 Hz), 7.18 (s, 1 H), 7.03 (d, 1 H, J = 8.2 Hz), 6.62 (d, 1 H, J = 8.2 Hz), 4.10 (s, 2 H), 2.18 (s, 3 H), 2.17 (s, 3 H). HPLC purity: 97.6% AUC. MS: MH^+ = 414.

2-[4-[[[2-[2-Fluoro-4-(trifluoromethyl)phenyl]-4-methyl-1,3-thiazol-5-yl]methyl]sulfanyl]-2-methylphenoxy]-2-methylpropanoic Acid (1). A mixture of 2-butanone (313.6 kg), phenol **4** (56.0 kg, 135.4 mol), and 20−40 mesh NaOH (29.7 kg, 742.5 mol) was heated to 50 °C with good stirring over approximately 30 min under nitrogen. The mixture was stirred at 50 °C for 1 h. To the mixture was added a solution of 2-bromo-2-methylpropanoic acid (39.2 kg, 230.2 mol) in 2-butanone (44.8 kg) over approximately 1 h at 50 °C. After the addition, the mixture was held at 50 °C for 2 h with stirring. Water (224 kg) was added, and the mixture was held at 50 °C for 1 h. The mixture was cooled to 20−25 °C. The layers were separated, and the organic layer was washed with 1 N HCl (170 kg). The organic layer was filtered through a 30 μm in line filter and concentrated to ∼112 L under reduced pressure. Heptane (191.5 kg) was added, and the mixture was heated to 65−70 °C. The mixture was cooled to 10−15 °C over 2 h. The solid was filtered, washed with heptane (57.4 kg), and dried under vacuum at 50−55 °C to a constant weight to give 56.0 kg of **1** as a slightly yellow solid in 83% yield. HPLC purity: 98.5% AUC.

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