Organic Process Research & Development **2007,** *11,* 1010–1014

Synthesis of a 5-((Aryloxy)methyl)-3-(4-(trifluoromethyl)phenyl)[1,2,4]thiadiazole Derivative: A Promising PPARα,δ Agonist

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Abstract:

The preparation of the PPARα,δ agonist 2-methyl-2-(2-methyl-4-(3-(4-(trifluoromethyl)phenyl)[1,2,4]thiadiazol-5-ylmethoxy)phenoxy)propionic acid sodium salt (17) is described and compared with earlier in-house preparations of this important target compound. Key concerns around a large-scale synthesis of this thiadiazole derivative were a large number of purification steps, the use of dichlorobenzene as a solvent, and a possible large-scale Baeyer–Villiger oxidation. This paper describes a straightforward preparation of the target agonist using methylhydroquinone (MHQ) as an inexpensive precursor that eliminates the need of an oxidation step.

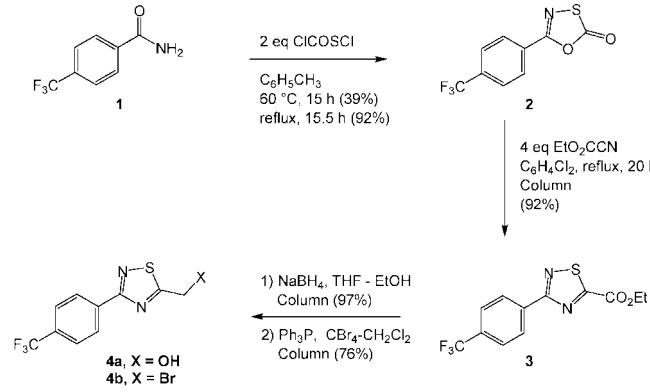
Introduction

2-Methyl-2-(2-methyl-4-(3-(4-(trifluoromethyl)phenyl)[1,2,4]thiadiazol-5-ylmethoxy)phenoxy)propionic acid sodium salt (**17**) is a potent and selective PPARα/δ dual agonist with PPARα EC_{50} = 94 nM and PPARδ EC_{50} = 3 nM.[1] Compounds with PPARα,δ agonist activity are important in the possible treatment of metabolic disorders such as diabetes, hyperlipidemia, and atherosclerosis.[2] The discovery and synthesis of this key target compound **17**, initially carried out by our Discovery team, is a convergent synthesis requiring the preparation and coupling of the thiadiazole **4b** (Scheme 1) and phenol **8** (Scheme 2). The initial preparation has drawbacks that were of concern in a large-scale preparation: these include the large number of chromatographic separations, the use of dichlorobenzene (because of its toxicity) as the solvent for the thiadiazole preparation, and the Baeyer–Villiger (peracid) oxidation step. An additional restriction that we faced was to limit the reaction temperature of the dipolar addition step to 130−140 °C because of the heat transfer medium and temperature capabilities in our local pilot plant facilities.

Results and Discussion

The primary concerns for the scale-up of the thiadiazole portion of our target was to eliminate the chromatographic purifications and, due to its toxicity, to avoid the use of *o*-dichlorobenzene as a solvent in the dipolar addition step. The latter issue was easily addressed by changing from *o*-dichlorobenzene (bp 178–180 °C) to *o*-xylene (bp 142 °C) at the cost of a longer reaction time. To partially offset the longer reaction time, the sequence of steps could be made more efficient by combining the preparation of **2** and **3**; therefore, the solvent switch to *o*-xylene was also included in the first step. An additional concern was the use of excess (2 equiv) of chlorocarbonylsulfenyl chloride (ClCOSCl) for the initial preparation of **2**. This reagent presents a potential hazard, and the excess reagent may have unexpected consequences if significant residual amounts are carried over to the next operation. The amount of this reagent was reduced to 1.2 equiv; to minimize loss of ClCOSCl to the scrubber, the reaction temperature was reduced from 110 °C (reflux in toluene) to 80 °C. With these modifications at hand, amide **1** was prepared[3] from the acid chloride and NH_4OH (100%) and converted to oxothiazolone **2** (Scheme 3) (xylene, 80 °C, 1.2 equiv of ClCOSCl); after this step was complete (HPLC), 70% of the solvent volume was removed by vacuum distillation to ensure removal of residual ClCOSCl (bp 98 °C). Next, ethyl cyanoformate was added and the temperature was increased to enable the dipolar addition to occur.[4] After this step was complete (5 days, determined by HPLC and ^1H NMR), the *o*-xylene was removed under vacuum. The weight of the crude thiadiazole **3** indicated a 93% yield, with a purity of 91.5% (area % at 210 nm). As this product was of high purity, this material was converted directly to alcohol **4a** ($NaBH_4$, THF–EtOH) in 85% yield from amide **1**. The $NaBH_4$ reduction step required a much larger volume of

Scheme 1. **Discovery Chemistry Route: Thiadiazole 4b**



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(1) Shen, L.; Zhang, Y.; Wang, A.; Sieber-McMaster, E.; Chen, X.; Pelton, P.; Xu, J. Z.; Yang, M.; Zhu, P.; Zhou, L.; Reuman, M.; Hu, Z.; Russell, R.; Gibbs, A. C.; Ross, H.; Demarest, K.; Murray, W. V.; Kuo, G.-H. *J. Med. Chem.* **2007**, *50*, 3954.

(2) (a) Leibowitz, M. D.; Fievet, C.; Hennuyer, N.; Peinado-Onsurbe, J.; Duez, H.; Berger, J.; Cullinan, C. A.; Sparrow, C. P.; Baffic, J.; Berger, G. D.; Santini, C.; Marquis, R. W.; Tolman, R. L.; Smith, R. G.; Moller, D. E.; Auwerx, J. *FEBS Lett.* **2000**, *473*, 333. (b) Shi, Y.; Hon, M.; Evans, R. M. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 2613. (c) Oliver, W. R., Jr.; Shenk, J. L.; Snaith, M. R.; Russell, C. S.; Plunket, K. D.; Bodkin, N. L.; Lewis, M. C.; Winega, D. A.; Sznaidman, M. L.; Lambert, M. H.; Xu, H. E.; Sternbach, D. D.; Kliewer, S. A.; Hansen, B. C.; Willson, T. M *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 5306.

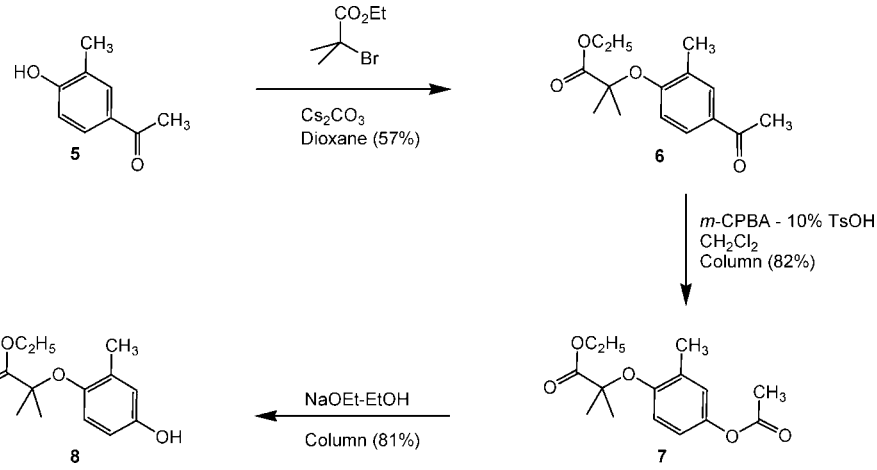
(3) Suzuki, H.; Kimura, Y. *J. Fluorine Chem.* **1991**, *52*, 341 (describes this method applied to a similar amide).

(4) The dipolar addition reaction of nitrile sulfides and ethyl cyanoformate has been described in: Howe, R. K.; Franz, J. E. *J. Org. Chem.* **1974**, *39*, 962.

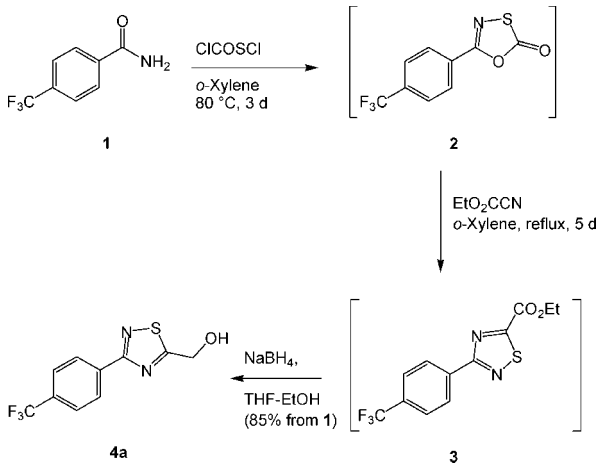
Published on Web 11/16/2007

10.1021/op700141u CCC: $37.00

Scheme 2. **Discovery Chemistry Route: Phenol 8**



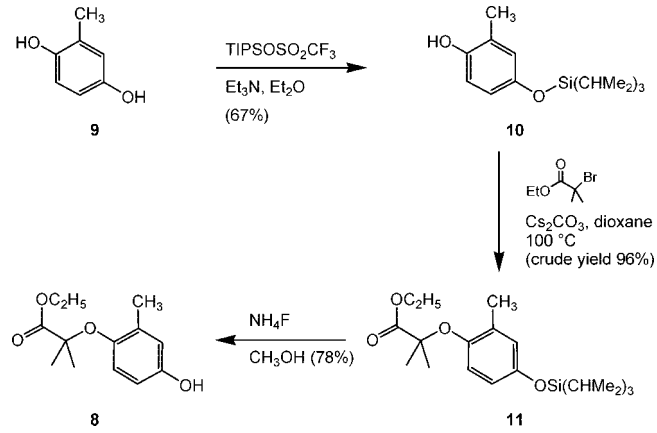
Scheme 3. **Improved Thiadiazole Preparation**



solvent than the prior step, and this necessitated a switch to a larger flask. These modifications effectively compressed three discrete steps and their respective workups into nearly a one-pot sequence and gave 353 g of intermediate **4a** in one campaign *without* any chromatographic purification to this point. A potential issue ahead was the possible preparation of **4b** (Scheme 1), as this was initially prepared using CBr_4-Ph_3P to generate the bromide, thus mandating a purification step. It seemed reasonable to consider an alternate coupling method, not needing **4b**; to this end the thiadiazole alcohol **4a** was converted into its mesylate derivative **4c**. The mesylate was easily prepared (MsCl, Et_3N) in high purity (99%, HPLC), needing no additional purification of any kind.

The next concern was the preparation of phenol intermediate **8**. While the Baeyer–Villiger oxidation provides a direct synthesis to **8** from **6**, an approach that avoided *m*-CPBA or any related oxidation on a large scale was important from a safety standpoint.[5] The most expeditious approach was to use a published route starting from readily available methylhydroquinone (MHQ).[6] Without any attempt to improve this method,[7] the less hindered phenol of MHQ was converted to the triisopropylsilyl derivative **10** using TIPS triflate (67%); this was alkylated with ethyl bromoisobutyrate to give the ether **11** (96%). Finally, removal of the TIPS blocking group (NH_4F) gave **8**, which was identical with the material prepared by the initial route and avoided a large-scale oxidation step (Scheme 4).

Scheme 4. **Preparation of Phenol 8**



It was important to confirm the structure of **8** prepared by the MHQ alternate method. To accomplish this, both isomers were prepared on a small scale by unambiguous routes as their acetates **14** and **15** (Scheme 5). The commercially available acetophenone **12** was alkylated (ethyl bromoisobutyrate, Cs_2CO_3) and subjected to Baeyer–Villiger conditions to provide acetate **14**. For comparison, phenol **8** was converted to acetate **15** (Ac_2O, DMAP). These isomers were readily distinguished by chemical shift differences in the ^1H NMR. For example, the aromatic CH_3 groups for **14** and **15** had chemical shifts of δ 2.11 and 2.22 ppm in $CDCl_3$, respectively.

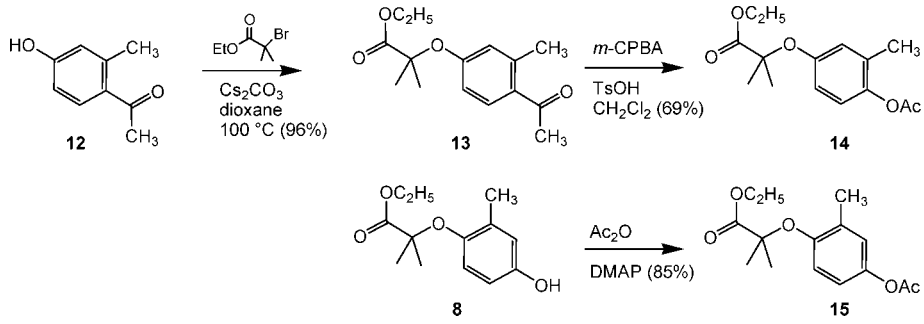
The coupling of the phenol and thiadiazole parts was accomplished using the mesylate derivative **4c**. This was

(5) (a) Kubota, A.; Takeuchi, H. *Org. Process Res. Dev.* **2004**, *8*, 1076. (b) Gillespie, J. S., Jr.; Acharya, S. P.; Shamblee, D. A.; Davis, R. E *Tetrahedron* **1975**, *31*, 3. (c) Brand, W. W. *Chem. Eng. News* **1978**, *56*, 88. (d) For another alternative to the conventional Baeyer-Villiger reaction see: Yoshida, A.; Hao, X.; Yamazaki, O.; Nishikido, J. *QSAR Comb. Sci.* **2006**, *25*, 697 and references cited therein.

(6) (a) Stanton, J. L.; Cahill, E.; Dotson, R.; Tan, J.; Tomaselli, H. C.; Wasvary, J. M.; Stephan, Z. F.; Steele, R. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1661. (b) Mazzinni, F.; Alpi, E.; Salvadori, P.; Netscher, T. *Eur. J. Org. Chem.* **2003**, 2840.

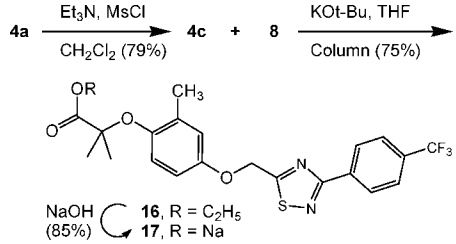
(7) (a) Other phenol blocking methods can be considered:Masada, H., Oishi, Y. *Chem. Lett.* **1978**, 57. (b) Stern, A.; Swenton, J. S. *J. Org. Chem.* **1987**, *52*, 2763. (c) Schmid, H. *Monatsh. Chem.* **1911**, *32*, 435.

Scheme 5. **Structure Proof of Phenol 8**



achieved by the addition of the potassium salt of **8** (KO*t*-Bu in THF) in THF to a chilled (0–5 °C) solution of **4c** in THF. After extractive workup the ester **16** was obtained in 89% purity with three impurities >1%. Crude **16** was subjected to flash chromatography to provide the ester in 75% yield and 97% purity. The target sodium salt **17** was obtained (NaOH, EtOH) by hydrolysis (85%) in high purity (99% HPLC) (Scheme 6).

Scheme 6. **Coupling of Thiadiazole 4a and Phenol 8**



Conclusion

An efficient, streamlined process was developed for the preparation of thiadiazole **4a** by conducting three steps sequentially without the need for isolation. A safety concern was addressed by the adoption of a literature method for the selective blocking of MHQ, providing an alternative to a large-scale Baeyer–Villiger oxidation. Finally, a coupling route for our target precursor **16** was developed that avoided a potentially difficult chromatographic purification of bromide **4b** employed in the initial synthesis. In this campaign, the preparations of phenol **8** and its TIPS precursor **10** were not optimized and these intermediates were subjected to column chromatography. Outside of this, our target **17** was prepared in seven steps in 43% overall yield with only one chromatographic purification after the preparation of ester **16**.

Experimental Section

4-(Trifluoromethyl)benzoyl chloride was obtained from SynQuest Laboratories., Inc., Alachua, FL. All other starting materials, reagents, and solvents were obtained from commercial suppliers and used without any purification. ^{1}H NMR spectra were recorded at 300 or 400 MHz on a Bruker Avance instrument in the solvent noted in this section. Mass spectra were obtained on an Agilent Series 180 LC/MS instrument. Chemical purity was determined on an Agilent Series 1100 system at 210 nm using the following methods: for ester **16** and salt **17** a Zorbax XDB C18 column (4.6 mm i.d. × 150 mm × 3.5 μM) at 35 °C using 80/20 MeCN/water (w/0.05% TFA) with a flow rate of 1 mL/min; for compounds **2**, **3**, and **4a** the solvent was changed to 60/40 MeCN/water (w/0.05% TFA); for benzamide **1** a Phenomenex Luna C18 column (4.6 mm × 50 mm × 5 μM) using 30/70 MeCN/water (w/0.05% TFA) with detection at 215 nm, for this method a gradient starting at 30% MeCN (time = 0), reaching 40% MeCN at 1 min, 90% MeCN at 4–8 min, and 30% MeCN at 10 min.

Preparation of 4-(Trifluoromethyl)benzamide (1). A 5 L four-neck Morton flask equipped with an overhead stirrer, thermocouple, addition funnel, and condenser was charged with concentrated NH_4OH (324.8 g, 5.35 mol) and water (2.0 L). The mixture was stirred, and the acid chloride (360.0 g, 1.73 mol) was added portionwise from the addition funnel over 45 min. The reaction mixture was stirred at 20 °C for an additional 3 h. The solid was filtered, washed with water (2 × 1 L), and air-dried followed by oven drying at 50 °C under house vacuum (200 ± 50 mmHg) to provide amide **1** (325.4 g, 100%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.2 (s, 1H, N*H*), 8.07 (m, 2H), 7.82 (m, 2H), 7.62 (s, 1H, N*H*).

Preparation of Thiadiazole 4a. *Oxothiazolone* ***2.*** A 5 L four-neck Morton flask was equipped with an overhead stirrer, a condenser, a nitrogen inlet adapter, a thermocouple, and a nitrogen bubbler, and a scrubber (Büchi Model B-414) was connected to the end of the nitrogen bubbler. The reaction flask was charged with amide **1** (300 g, 1.59 mol), *o*-xylene (2 L), and ClCOSCl (249 g, 1.90 mol), followed by an additional portion of *o*-xylene (1 L). The stirred mixture was slowly heated to 80 °C, and the reaction progress was followed by HPLC. After the reaction was determined to be complete (3 days), the mixture was cooled, the condenser was replaced by a distillation head, and the excess reagent and a portion of the solvent were removed by vacuum distillation (60–70 °C, <120 mmHg). The volume of all the distillate in any flasks used and the dry ice traps was 2.1 L. The reaction mixture was used in the next step without isolation. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.12 (d, 2H, J = 8.5 Hz), 7.94 (d, 2H, J = 8.5 Hz).

Thiadiazole ***3.*** Additional fresh *o*-xylene (1 L) was added back to the reaction mixture to bring the concentration to approximately 0.8 M. The mixture was charged with ethyl cyanoformate (453.2 g, 4.51 mol), placed under nitrogen, and heated to reflux. The reaction was followed by HPLC, and after the reaction was judged complete (5 days), the solvent and excess reagent was removed by distillation. The crude material was used without purification in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.50 (d, 2H, J = 8.2 Hz), 7.76 (d, 2H, J = 8.2 Hz), 4.57 (q, 2H, J = 7.2 Hz), 1.49 (t, 3H, J = 7.2 Hz).

Preparation of Thiadiazole Alcohol 4a. A 12 L four-neck Morton flask equipped with an overhead stirrer, a nitrogen inlet adapter, and a thermocouple was charged with ester **3** (448 g, 1.48 mol), THF (1.5 L), and EtOH (2.7 L). This mixture was stirred to dissolve the substrate, and then $NaBH_4$ (37.1 g, 0.98 mol) was added in portions at a rate that kept the internal temperature ≤40 °C. After complete addition of $NaBH_4$, the reaction mixture was stirred overnight. The reaction was quenched by the addition of acetone (60 mL) to consume excess $NaBH_4$ followed by HCl (500 mL, 20% v/v). The mixture was concentrated on a rotary evaporator to remove most of the solvents; the residue was suspended in water, filtered, and rinsed with water (4 L) to give a tan solid. The product was air-dried and dried under vacuum (40 °C, 200 ± 50 mmHg) to give alcohol **4a** (353 g, 85% based on amide **1**). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.40 (d, 2H, J = 8.1 Hz), 7.74 (d, 2H, J = 8.1 Hz), 5.19 (s, 2H), 2.0 (br s, 4H, OH + water). LCMS: $[MH]^+$ m/z 261. Anal Calcd for $C_{10}H_7F_3N_2OS$: C, 46.15; H, 2.71; F, 21.90; N, 10.76; S, 12.32. Found: C, 45.94; H, 2.78; F, 21.56; N, 10.49; S, 12.22; residual B, 0.05.

Preparation of Thiadiazole Mesylate 4c. A 12 L four-neck Morton flask equipped with an overhead stirrer, thermocouple, nitrogen inlet adapter, and addition funnel was charged with thiadiazole alcohol **4a** (300 g, 1.15 mol), CH_2Cl_2 (5.25 L), and Et_3N (241 mL, 1.73 mol). The mixture was cooled to −20 °C, methanesulfonyl chloride (89.6 mL, 1.15 mol) was added dropwise over 30 min, and the mixture was stirred at −20 °C for 1 h and then allowed to warm to room temperature. The mixture was washed with 1N HCl solution (4 L), saturated $NaHCO_3$ (4 L), brine (4 L) and dried over Na_2SO_4 and concentrated to 700 mL on a rotary evaporator. The precipitate was filtered, rinsed with CH_2Cl_2 (50 mL), and dried (50 °C, 200 ± 50 mmHg) to give 307 g (79% yield, 99% purity) of mesylate **4c** as yellow needles. This material was used in the next step without further purification. LCMS: $[MH]^+$ m/z 339, $[M + Na]^+$ m/z 361. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.40 (d, 2H, J = 8.2 Hz), 7.75 (d, 2H, J = 8.2 Hz), 5.69 (s, 2H), 3.21 (s, 3H).

Preparation of TIPS-Blocked Methylhydroquinone 10. A 12 L four-neck flask equipped with a thermocouple controller, an overhead stirrer, and a nitrogen inlet adaptor was charged with methylhydroquinone (500.0 g, 4.0 mol), ether (7.0 L), and Et_3N (650 mL, 4.66 mol). The reaction mixture was cooled to −78 °C, and $TIPSOSO_2CF_3$ (885 mL, 4.0 mol) was added dropwise over 30 min. The reaction mixture was warmed to 22 °C and stirred for 24 h. The reaction mixture was concentrated in vacuo to yield 2.30 kg of crude product. Purification by column chromatography (silica gel (2 kg), 90/10 hexane/acetone (v/v)) provided hydroquinone **10** (767.85 g, 68%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.65 (d, 1H, $J \approx$ 2.5 Hz), 6.61 (d, 1H, $J \approx$ 8.5 Hz), 6.57 (dd, 1H, $J \approx$ 8.5 Hz, $J \approx$ 2.5 Hz), 2.19 (s, 3H), 1.2 (complex m, 3H), 1.09 (two singlets, 18 H).

Alkylation of 10 with Ethyl Bromoisobutyrate. A 12 L four-neck flask equipped with a thermocouple controller, an overhead stirrer, condenser, and a nitrogen inlet adaptor was charged with **10** (400.0 g, 1.43 mol), dioxane (6.0 L), ethyl 2-bromoisobutyrate (320 mL, 2.18 mol), and Cs_2CO_3 (736 g, 2.26 mol). The reaction mixture was heated to 100 °C and stirred for 24 h. The reaction mixture was quenched with H_2O (4.0 L) and extracted with EtOAc (3.0 L × 2). The organic layer was concentrated in vacuo to give the crude product **11** (539 g). ^{1}H NMR for crude **11** ($CDCl_3$, 400 MHz): δ 6.69–6.52 (m, 3H), 4.25 (q, 2H, J = 7.1 Hz), 2.18 (s, 3H), 1.35–1.15 (complex m, 6H (impure), this contains a triplet at δ 1.28, J = 7.1 Hz), 1.08 (m, 20 H (impure)).

Preparation of Phenol 8. A 5 L four-neck flask equipped with a thermocouple controller, an overhead stirrer, and a nitrogen inlet adaptor was charged with **11** (538 g, 1.36 mol), MeOH (1.0 L), and 0.50 M NH_4F in MeOH (1.60 L, 0.8 mol). The reaction mixture was stirred at 22 °C for 24 h. The reaction mixture was quenched with H_2O (4.0 L) and extracted with CH_2Cl_2 (1.0 L × 3). The organic layer was concentrated in vacuo to yield 499 g of crude product. Purification by column chromatography (silica gel (2 kg), 60/40 hexane/EtOAc (v/v)) produced phenol **8** (252 g, 78%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.61 (d, 1H, $J \approx$ 8.7 Hz), 6.62 (overlapping d, 1H), 6.49 (dd, 1H, $J \approx$ 8.7 Hz, $J \approx$ 3 Hz), 5.0 (br s, 1H), 4.25 (q, 2H, J = 7.2 Hz), 2.17 (s, 3H), 1.53 (s, 6H), 1.28 (t, 3H, J = 7.2 Hz).

Coupling of Mesylate 4c and Phenol 8. A 12 L four-neck Morton flask equipped with an overhead stirrer, thermocouple, nitrogen inlet adapter, and stopper was charged with the thiadiazole mesylate **4c** (232 g, 0.686 mol) and THF (6 L). The mixture was cooled to 0–5 °C using ice–water. A 5 L four-neck Morton flask equipped with an overhead stirrer, thermocouple, nitrogen inlet adapter, and addition funnel was charged with phenol **8** (180 g, 0.755 mol) and THF (1.5 L). The mixture was cooled to 0–5 °C, and then *t*-BuOK (755 mL, 1.0 M solution in THF) was added over 30 min while the temperature was maintained at 0–5 °C. After the addition, the mixture was stirred at 0–5 °C for 30 min and then transferred to the mesylate solution via cannula over 30 min. This resulting mixture was stirred for 6 h while the temperature changed from 5 to 18 °C. The mixture was diluted with EtOAc (5 L), washed with 1 N HCl (6 L) and brine (6 L), and dried over Na_2SO_4. The solvent was evaporated via rotary evaporation to afford a tar-like residue (327 g, 89% purity) that was purified by a flash column (5% EtOAc in heptane, 3.5 kg of silica gel). There was obtained 246.5 g (75% yield, 97% purity) of **16** as a light yellow solid. LCMS: $[MH]^+$ m/z 481, $[M + Na]^+$ m/z 503. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.42 (d, 2H, J = 8.2 Hz), 7.75 (d, 2H, J = 8.2 Hz), 6.86 (s, 1H), 6.71 (two nearly superimposed s, 2H), 5.46 (s, 2H), 4.26 (q, 2H, J = 7.1 Hz), 2.25 (s, 3H), 1.56 (s, 6H), 1.28 (t, 3H, J = 7.1 Hz).

Preparation of 2-Methyl-2-(2-methyl-4-(3-(4-(trifluoromethyl)phenyl)[1,2,4]thiadiazol-5-ylmethoxy)phenoxy)propionic Acid Sodium Salt 17. A 5 L four-neck Morton flask equipped with an overhead stirrer, thermocouple, condenser with a nitrogen inlet adapter, and stopper was charged with ester **16** (245 g, 0.51 mol) and EtOH (2.5 L). A portion of 2 N NaOH solution (255 mL, 0.51 mol) was added, and then the mixture was heated at 40 °C overnight. A precipitate was isolated by filtration and rinsed with EtOH (300 mL). The filtrate was concentrated to 1 L via rotary evaporation, and the second precipitate was isolated by filtration and rinsed with EtOH (100 mL). The combined precipitate was dried in a vacuum oven

(60 °C, 200 ± 50 mmHg) for 2 days to afford **17** as a white solid: 206 g (85% yield, 99% purity). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.44 (d, 2H, J = 8.3 Hz), 7.93 (d, 2H, J = 8.3 Hz), 6.93 (d, 1H, J = 8.9 Hz), 6.88 (d, 1H, J = 3.1 Hz), 6.72 (dd, 1H, J = 8.9 Hz, J = 3.1 Hz), 5.62 (s, 2H), 2.11 (s, 3H), 1.35 (s, 6H). LCMS: $[MH]^+$ m/z 453, $[M + Na]^+$ m/z 475. Anal. Calcd for $C_{21}H_{18}N_2O_4F_3SNa$: C, 52.46; H, 3.87; F, 11.94; N, 5.87; S, 6.72; Na, 4.81. Found: C, 52.94; H, 3.64; F, 12.29; N, 5.82; S, 6.67; Na, 4.78; water (KF) 0.63%.

Structure Proof of Phenol 8 by Acetate Derivatives 14 and 15. *Preparation of Acetophenone **13**.* To a 500 mL four-neck flask equipped with a thermocouple controller, an overhead stirrer, a condenser, and a nitrogen inlet adaptor was charged with 4-hydroxy-2-methylacetophenone (5.5 g, 0.036 mol), dioxane (100 mL), ethyl 2-bromoisobutyrate (6.50 g, 0.033 mol), and Cs_2CO_3 (17.0 g, 0.052 mol). The reaction mixture was heated to 100 °C and stirred for 24 h. The reaction mixture was quenched with H_2O (400 mL) and extracted with EtOAc (100 mL × 2) to yield 10.32 g of crude product. Purification by column chromatography (silica gel (300 g), 80/20 (v/v) hexane/EtOAc) produced acetophenone **13** (8.50 g, 90%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.69 (d, 1H, J = 6.8 Hz), 6.68 (2, 1H, J = 2.6 Hz), 6.63 (dd, 1H, J = 2.6 Hz, J = 8.6 Hz), 4.24 (q, 2H, J = 7.1 Hz), 2.54 (s, 3H, (C═O)CH_3), 2.52 (s, 3H, ArCH_3), 1.23 (t, 3H, J = 7.1 Hz).

*Preparation of Acetate **14**.* A 500 mL four-neck flask equipped with a thermocouple controller, an overhead stirrer, condenser, and a nitrogen inlet adaptor was charged with **13** (8.0 g, 0.05 mol), CH_2Cl_2 (100 mL), *m*-CPBA (12.30 g, 0.05 mol), and *p*-TsOH (0.60 g, 0.003 mol). The reaction mixture was heated to 40 °C and stirred for 24 h. The reaction mixture was quenched with H_2O (100 mL) and extracted with EtOAc (100 mL × 2) to yield 10.79 g of crude product. Purification by column chromatography (silica gel (300 g), 90/10 (v/v) hexane/EtOAc) produced acetate **14** (5.38 g, 69%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.86 (d, 1H, J = 8.8 Hz), 6.73 (d, 1H, J = 2.9 Hz), 6.66 (dd, 1H, J = 8.8 Hz, J = 2.9 Hz), 4.23 (q, 2H, J = 7.1 Hz), 2.29 (s, 3H, O(C═O)CH_3), 2.11 (s, 3H, ArCH_3), 1.25 (t, 3H, J = 7.1 Hz).

*Preparation of Acetate **15** by Acetylation of Phenol **8**.* A 100 mL single-neck flask was charged with phenol **8** (1.0 g, 4.2 mmol), acetic anhydride (4 mL), and DMAP (12 mg). After the solution was briefly warmed to reflux with a heat gun, it was cooled and condensed in vacuo on a rotary evaporator at 50 °C (5 mmHg). The residue was dissolved in a minimal amount of CH_2Cl_2 and passed through a small bed of SiO_2 (~30 mL) using 85/15 (v/v) heptane/EtOAc. Solvent removal afforded **15** (1.0 g, 85%) as a clear liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.87 (d, 1H, J = 2.9 Hz), 6.77 (d, 1H, J = 2.9 Hz), 6.75 (d, 1H, J = 2.9 Hz), 4.23 (q, 2H, J = 7.1 Hz), 2.25 (s, 3H, O(C═O)CH_3), 2.22 (s, 3H, ArCH_3), 1.25 (t, 3H, J = 7.1 Hz).

Received for review June 19, 2007.

OP700141U