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A highly efficient synthesis of antiobestic ligand GW501516 for the peroxisome proliferator-activated receptor δ through in situ protection of the phenol group by reaction with a Grignard reagent

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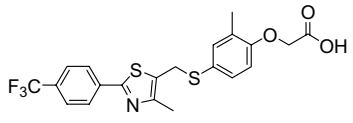
Abstract—A new synthesis of an agonist for the peroxisome proliferator-activated receptor δ (PPARδ) GW501516 as a potential antiobesity drug is described. The synthetic route involves the in situ protection of the phenol group with a Grignard reagent and a regio-controlled one-pot reaction for the formation of a sulfide bond as the key step. Starting from commercially available 4-iodo-2-methylphenol, this approach affords GW501516 with an overall yield of 87%.

Obesity is a devastating medical condition, which is associated with type II diabetes, hyperlipidemia, cardiovascular disease, and hypertension.[1] Many medical strategies have been devised to treat obesity, such as the manipulation of food intake centrally or peripherally, blocking of fat absorption by inhibition of a pancreatic lipase, modulation of fat metabolism, and control of adaptive thermogenesis.[2] Although, very successful in the market, the drugs currently available are either facing serious problems such as unpleasant side effects and even patient deaths, or their efficacies are modest: a 5–10% loss of initial body weight in less than 50% of patients.[3] Stimulation of thermogenesis (the regulated production of heat) has thus long been pursued to treat obesity.[4] Recently, the uncoupling of oxidative phosphorylation through uncoupling proteins (UCPs) has become an attractive process in the development of antiobesity drugs.[5] Direct control of UCPs has become a promising strategy to treat obesity in humans. We have identified that PPARδ is a key regulator of UCPs in peripheral tissue in collaboration with Evans' group at the Salk Institute.[6] Targeted activation of PPARδ in adipocytes and muscles in combination with a chemical tool GW501516 showed that it selectively activates genes responsible for fatty acid oxidation and energy uncoupling and causes an adaptive muscle switch and an increase in mitochondrial biogenesis.[6,7] These findings suggest that PPARδ serves as a widespread regulator of fat burning and as a key transcriptional factor regulating muscle fiber plasticity. Overall PPARδ is a novel target for developing drugs to treat obesity and its associated diseases.[8]

Recently, the research group of GlaxoSmithKline discovered GW501516 (**1**) to be the most effective and selective ligand for PPARδ over the other PPAR subtypes through structure-based drug design and combinatorial chemistry (Fig. 1).[9] Treatment for two months with a PPARδ-selective agonist GW501516 of mice on a high-fat diet (35%) showed that the treated mice gained much less body weight and fat mass



GW501516 (1)

Figure 1. Chemical structure of GW501516 as a PPARδ synthetic agonist.

Keywords: PPARδ; Antiobestic drug; GW501516; Grignard reagent; One-pot synthesis; Sulfide.
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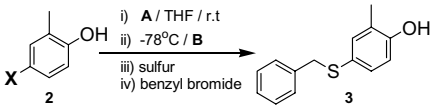
(one-third) than controls.[7] Therefore, compound **1** is an indispensable tool in efforts to reveal the underlying biology of ubiquitously expressed PPARδ and a potential drug in the treatment of obesity and its associated disorders, such as type II diabetes[10] and atherosclerosis.[11]

The synthesis of **1** and its derivatives was first reported by the GlaxoSmithKline group, and involved the coupling of thiazole chloride with aryl thiol prepared from *o*-cresol in more than eight steps with an overall yield of 7%.[9a] Later on Wei and Kozikowski reported a more efficient method for the synthesis of **1** with a 78% overall yield.[12] Although this method shows an improvement in both the number of synthetic steps and the overall yield, there are still a few limitations in the production of **1**.

For example, it is still difficult to prepare 4-mercapto-2-methylphenol from *o*-cresol, which can easily form a disulfide under oxidative and low pH conditions, or with free radicals, causing a lower overall yield. Thus, a much simpler, safer, and more efficient synthesis of **1** is in demand. Herein, we wish to report a simple preparation of **1** through in situ protection of the phenol group by reaction with a Grignard reagent and through an extension of the one-pot methodology used for alkyl aryl sulfides published in a previous report.[13]

We first attempted to find the reaction conditions for the preparation of 4-benzylsulfanyl-2-methylphenol (**3**) through a one-pot reaction without any special steps to protect the phenol group on the starting material (Table 1). First, we tried *n*-butyllithium (2.0 equiv)[13] and *tert*-butyllithium (2.0–3.0 equiv) for in situ protection of the phenol and for lithium–halogen exchange. However, these reactions produced low yields (entries 1–3), and so were hardly applicable for the synthesis of the intermediate compound **8**. However, Grignard reagent (1.0 equiv), used instead of *n*- or *tert*-butyllithium, proved effective at in situ protection of the phenol group (1.0 equiv) from reaction at room temperature. As a result, we were able to obtain the desired compound **3** at 42% and 96% yields (entries 4 and 5), respectively. Concerning the reactivity of halide on **2** (entries 5–7), 4-iodo- and 4-bromo-2-methylphenols were good starting materials for the preparation of the targeted sulfide compound (**3**), while 4-chloro-2-methylphenol did not undergo lithium–halogen exchange at all under the same conditions used for the other starting materials.

Table 1. Optimization of the one-pot reaction for compound **3**[a]



Entry	X	A (equiv)	B (equiv)	% Yield[b]
1	I	None	*n*-BuLi (2)	33
2	I	None	*t*-BuLi (2)	Trace
3	I	None	*t*-BuLi (3)	26
4[c]	I	^{i}PrMgCl (1)	*n*-BuLi (1)	42
5	I	^{i}PrMgCl (1)	*t*-BuLi (2)	96
6	Br	^{i}PrMgCl (1)	*t*-BuLi (2)	73
7	Cl	^{i}PrMgCl (1)	*t*-BuLi (2)	No reaction

[a] All reactions were performed using 4-halo-2-methylphenol (0.5 mmol), sulfur (1.0 equiv), and benzyl bromide (1.0 equiv).

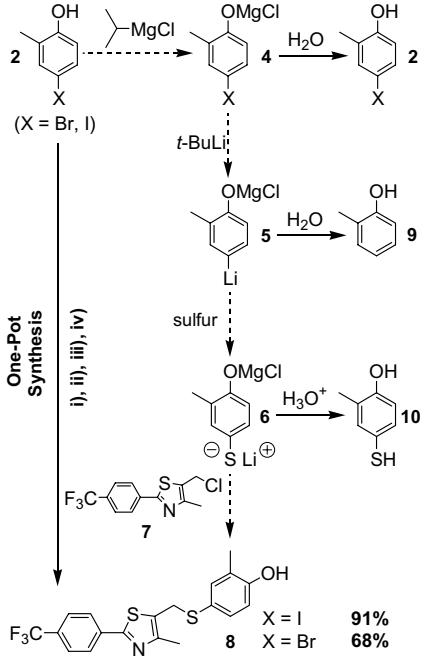
[b] Yields were given for isolated products and average values of triplicate reactions.

[c] 4-Butylsulfanyl-2-methylphenol as a side product was obtained in 36% yields.

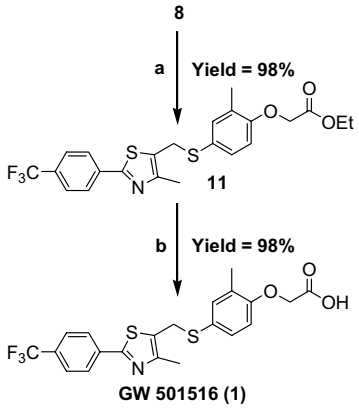
Based on the results of the model reactions, we were able to prepare the intermediate sulfide **8** at 91% yields, from 4-iodo-2-methylphenol as a starting material, via a one-pot reaction that included the in situ protection of phenol with isopropylmagnesium chloride, lithium–halogen exchange by *tert*-butyllithium, thiolate formation, and quenching the resultant thiolate with chloromethyl thiazole **7**[9b] (Scheme 1).

The starting material **2** is commercially available or easily prepared from *o*-cresol by general methods.[14] Although we could not detect the intermediates **4**–**6** directly during the reaction, we could infer their formation from the target compound **8** (68–91%).[15] Quenching each step—from phenol protection, lithium–halogen exchange to thiolate formation—with water or mild acid yielded the desired compounds **2**, **9**, and **10**, respectively, thus proving the formation of the reaction intermediates **4**–**6**.

We found that the in situ protecting group (–OMgCl, from ^{i}PrMgCl on the starting material **2**) was free from lithium–halogen exchange and lithium thiolate formation. In addition, the nucleophilicity of sulfur anion in



Scheme 1. Reagents and conditions: (i) 4-halo-2-methylphenol (5.0 mmol), isopropylmagnesium chloride (1.0 equiv), THF, 0 °C, 10 min; (ii) *tert*-butyllithium (2.0 equiv), −78 °C, 0.5 h; (iii) sulfur powder, THF, −78 to 0 °C, 0.5 h; (iv) compound **7**, THF, 0 °C, 0.5 h.



Scheme 2. Reagents and conditions: (a) ethyl bromoacetate, K_2CO_3, aq DMSO, 50 °C, 1 h; (b) 3 N NaOH, aq EtOH, rt, 0.5 h, then 1 N HCl.

the intermediate **6** was found to be much higher than that of oxygen anion toward chloromethyl thiazole **7**. Although 4-mercapto-2-methylphenol (**10**) was obtained more easily and with better yields (93%)[16] by our method than by any other known method,[12] compound **10** was readily converted into its disulfide under oxidative and acidic conditions or with free radicals. Thus, we chose a one-pot synthesis of compound **8** instead of using a step-by-step process, which gave the target compound at good yields.

In the second step, treatment of **8** with K_2CO_3 and ethyl bromoacetate in 5% aqueous DMSO at 50 °C for 1 h gave the ester **11** with a 98% yield (Scheme 2).[17] In previous reports, the compound **8** was reacted with the same reagents in THF or CH_3CN for 16 h or 5 h.[9b,12] However, our synthesis enabled the reaction time to be reduced to 1 h when a 5% aqueous DMSO with mild heating was used.

As the final step, the saponification of ester **11** with 3 N NaOH afforded the target compound **1** at a 98% yield (Scheme 2).[18]

In conclusion, we have developed a simple route for the synthesis of an antiobestic ligand GW501516 for PPARδ (**1**) from commercially available 4-iodo- or 4-bromo-2-methylphenol (**2**). Our method has accomplished the synthesis of **1** in 87% overall yields. Moreover, the in situ protection of phenol with a Grignard reagent and the regio-controlled one-pot synthesis of the central sulfide is a very useful protocol for the preparation of other pharmaceutical drugs that include the alkyl aryl sulfides.

Acknowledgments

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15. For the synthesis of 4-{{2-[4-(trifluoromethyl)phenyl]-4-methylthiazol-5-yl}methylthio}-2-methylphenol **8**: To a solution of 4-iodo-2-methylphenol (**2**) (1.17 g, 5.0 mmol) in THF (50 mL) was added isopropylmagnesium chloride (2.5 mL, 2.0 M in THF solution, 5.0 mmol) at 0 °C and the mixture was stirred for 10 min under N_2 atmosphere. After the mixture was cooled to −78 °C, *tert*-butyllithium (5.88 mL, 1.7 M solution in pentane, 10.0 mmol) was introduced dropwise and stirred for 0.5 h at the same temperature. A solution of sulfur (160 mg, 5.0 mmol) in THF (5 mL) was slowly added and then the reaction mixture warmed to room temperature for 0.5 h. After the mixture was cooled to 0 °C again, a solution of **7** (1.46 g, 5.0 mmol) in THF (5 mL) was added and stirred at room temperature for additional 0.5 h. The reaction was monitored by thin-layer chromatography. After the reaction was completed, it was quenched with aqueous NH_4Cl (40 mL). The organic layer was separated and then the aqueous layer was extracted with ethyl acetate (2 × 25 mL). The combined extract was washed with water, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude product. The crude compound was purified by column chromatography on silica gel with hexane–ethyl acetate (3/1, v/v) to obtain **7** as an ivory solid (1.62 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, 2H, $J = 8.1$ Hz), 7.65 (d, 2H, $J = 8.2$ Hz), 7.18 (d, 1H, $J = 1.5$ Hz), 7.03 (dd, 1H, $J = 8.2$, 2.0 Hz), 6.63 (d, 1H, $J = 8.2$ Hz), 5.48 (br s, 1H), 4.08 (s, 2H), 2.19 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.1, 155.6, 151.6, 137.5, 136.8, 133.6, 131.9 (q, $J = 32.6$ Hz), 131.8, 126.9, 126.3 (q, $J = 3.7$ Hz), 125.9, 124.3 (q, $J = 272.3$ Hz), 123.8, 115.6, 33.2, 16.2, 14.7. HREIMS *m*/*z* 395.0622 (calcd for $C_{19}H_{16}F_3NOS_2$: 395.0625).
16. Certification of 4-mercapto-2-methylphenol **10**: To a solution of 4-iodo-2-methylphenol (**2**) (234 mg, 1.0 mmol) in THF (15 mL) was added isopropylmagnesium chloride (0.5 mL, 2.0 M in THF solution, 1.0 mmol) at 0 °C and the mixture was stirred for 10 min under N_2 atmosphere. After the mixture was cooled to −78 °C, *tert*-butyllithium (1.18 mL, 1.7 M solution in pentane, 2.0 mmol) was introduced dropwise and stirred for 0.5 h at the same temperature. A solution of sulfur (32 mg, 1.0 mmol) in THF (1.5 mL) was slowly added and then the reaction mixture warmed to room temperature for 1 h. After that, the reaction mixture was quenched with aqueous NH_4Cl (10 mL) and then acidified with 1 N HCl. The mixture was extracted with ethyl acetate (3 × 20 mL). The combined extract was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude product. The crude compound was purified by column chromatography on silica gel with hexane/ethyl acetate (3/1, v/v) to obtain **10** as a white solid (1.4 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, 1H, $J = 1.8$ Hz), 7.05 (dd, 1H, $J = 8.2$, 1.8 Hz), 6.66 (d, 1H, $J = 8.2$ Hz), 4.68 (s, 1H), 3.33 (s, 1H), 2.20 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 153.1, 134.2, 130.4, 124.9, 119.6, 116.1, 15.9. CIMS *m*/*z* 141 $[M+H]^+$.
17. For the synthesis of ethyl 2-{4-{{2-[4-(trifluoromethyl)phenyl]-4-methylthiazol-5-yl}methylthio}-2-methylphenoxy}acetate **11**: To a solution of **8** (1.2 g, 3.0 mmol) in 5% aqueous DMSO (25 mL) was added K_2CO_3 (622 mg, 4.5 mmol), followed by ethyl bromoacetate (2.02 mL, 3.6 mmol) at room temperature. The reaction mixture was warmed to 50 °C and then vigorously stirred for 1 h. After the reaction was completed, the mixture was poured into water (30 mL) and extracted with ethyl acetate (3 × 35 mL). The combined extract was washed with water, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude product. The crude compound was purified by column chromatography on silica gel with hexane/ethyl acetate (v/v = 5/1) to obtain **11** as an ivory solid (1.4 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, 2H, $J = 8.1$ Hz), 7.65 (d, 2H, $J = 8.3$ Hz), 7.21 (d, 1H, $J = 2.0$ Hz), 7.12 (dd, 1H, $J = 8.4$, 2.0 Hz), 6.59 (d, 1H, $J = 8.4$ Hz), 4.61 (s, 2H), 4.24 (q, 2H, $J = 7.1$ Hz), 4.11 (s, 2H), 2.24 (s, 3H), 2.21 (s, 3H), 1.28 (t, 3H, $J = 7.1$ Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.1, 163.5, 156.8, 151.8, 137.2, 136.5, 132.5, 131.6 (q, $J = 32.8$ Hz), 131.1, 128.8, 126.8, 126.2 (q, $J = 3.9$ Hz), 125.7, 124.3 (q, $J = 272.3$ Hz) 111.9, 65.9, 61.7, 32.9, 16.5, 15.2, 14.5. HREIMS *m*/*z* 481.0993 (calcd for $C_{23}H_{22}F_3NO_3S_2$, 481.0993).
18. For the synthesis of 2-{4-{{2-[4-(trifluoromethyl)phenyl]-4-methylthiazol-5-yl}methylthio}-2-methylphenoxy}acetic acid **1**: To a solution of **11** (1.0 g, 2.1 mmol) in ethyl alcohol (40 mL) was slowly added 3 N NaOH (1.1 mL) at room temperature. After the reaction mixture was stirred for 0.5 h to complete the reaction, the reaction mixture was acidified with 1 N HCl to pH 2–3 and ethyl alcohol was removed. The residue was dissolved into ethyl acetate (60 mL) and washed with brine (2 × 30 mL), dried over $MgSO_4$, and evaporated under reduced pressure to give the crude product. The crude compound was purified by LH-20 column chromatography with methyl alcohol to obtain GW501516 (**1**) as a white solid (932 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8,98 (br s, 1H), 7.93 (d, 2H, $J = 8.1$ Hz), 7.65 (d, 2H, $J = 8.2$ Hz), 7.21 (d, 1H, $J = 1.6$ Hz), 7.10 (dd, 1H, $J = 8.4$, 2.1 Hz), 6.61 (d, 1H, $J = 8.5$ Hz), 4.66 (s, 2H), 4.09 (s, 2H), 2.22 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.2, 164.1, 156.6, 151.6, 136.8, 136.7, 132.6, 131.9 (q, $J = 32.8$ Hz), 131.4, 128.8, 126.9, 126.3 (q, $J = 3.8$ Hz), 125.8, 124.3 (q, $J = 272.2$ Hz), 111.9, 65.5, 32.8, 16.5, 14.9. HREIMS *m*/*z* 453.0679 (calcd for $C_{21}H_{18}F_3NO_3S_2$: 453.0680).