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A Short and Efficient Synthesis of the Pharmacological Research Tool GW501516 for the Peroxisome Proliferator-Activated Receptor δ

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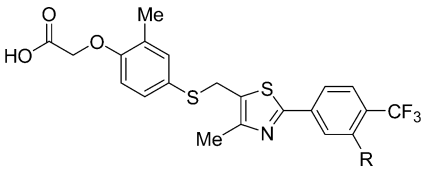
Abstract: The most potent and selective peroxisome proliferator-activated receptor δ (PPARδ) agonist GW501516 (**1**) was synthesized in 4 steps and 78% overall yield starting from *o*-cresol by using a one-pot regiocontrolled dialkylation of mercaptophenol **5** as the key step.

The peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear receptor gene family that function as heterodimers with the 9-*cis*-retinoic acid receptor (RXR).[1,2] Three closely related isoforms, PPARα, -γ, and -δ (or -β), have been identified in organisms ranging from *Xenopus* to humans. Each PPAR subtype appears to be differentially expressed in a tissue-specific manner, with PPARα and PPARγ predominating in the liver and adipocytes, respectively, and PPARδ being ubiquitously expressed. Since the first discovery of PPARα as an orphan receptor,[3] the biology of the PPARs has been driven, in large part, by the availability of potent and selective ligands for the receptors.[1] PPARα, which was recognized to be the target receptor for the fibrate class of anti-hyperlipidemic drugs, regulates the expression of genes involved in lipid metabolism. PPARγ, which was shown to function as the cellular receptor of the thiazolidinedione (TZD) class of insulin-sensitizing drugs, is an important regulator of adipogenesis, lipid metabolism, and glucose homeostasis. In contrast to PPARα and -γ, there are no marketed drugs that target PPARδ, and the physiological role of PPARδ remains largely mysterious due, in part, to the lack of selective ligands as chemical tools to study its pharmacology.[4] Thus, identification of potent and selective ligands for use as chemical tools is essential to elucidating the function of PPARδ. However, all of the ligands published to date either have low affinity for PPARδ or lack selectivity over the other PPAR isoforms,[5] except GW501516 (**1**) and its analogue GW0742 (**2**) which were recently discovered by combinatorial chemistry and structure-based drug design.[6] These two compounds were shown to be the most potent and selective PPARδ agonists known with an EC_{50} of 1.1 nM against PPARδ and 1000-fold selectivity over the other human subtypes, PPARα and -γ. Thus, these two ligands could be used as ideal chemical tools to study the function of the ubiquitously expressed PPARδ.[7]

However, the reported synthesis of **1** and **2** involved more than eight steps with about 7% overall yield, respectively.[6] Thus, a more efficient synthesis of these compounds is needed. Herein, we present a short and efficient method to synthesize GW501516 (**1**).



GW501516 (**1**), R = H
GW0742 (**2**), R = F

Our synthesis of **1** is illustrated in Scheme 1. Treatment of *o*-cresol (**3**) with NaSCN and bromine afforded the thiocyanate **4** in 97% yield,[8] which was reduced to the mercaptophenol **5** with $LiAlH_4$.[9] Treatment of **5** with Cs_2CO_3 and chloromethyl thiazole **6**[6] in acetonitrile at room temperature for 4 h followed by adding more Cs_2CO_3 and methyl bromoacetate (**7**) provided **8** in 96% yield. The ester **8** was saponified with aqueous LiOH to give GW501516 (**1**) in 98% yield.

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(1) Willson, T. M.; Brown, P. J.; Sternbach, D. D.; Henke, B. R. *J. Med. Chem.* **2000**, *43*, 527.

(2) Shearer, B. G.; Hoekstra, W. J. *Curr. Med. Chem.* **2003**, *10*, 267.

(3) Issemann, I.; Green, S. *Nature* **1990**, *347*, 645.

(4) (a) Wang, Y.-X.; Lee, C.-H.; Tiep, S.; Yu, R. T.; Ham, J.; Kang, H.; Evans, R. M. *Cell* **2003**, *113*, 159. (b) Di-Poï, N.; Tan, N. S.; Michalik, L.; Wahli, W.; Desvergne, B. *Mol. Cell* **2002**, *10*, 721. (c) Vosper, H.; Patel, L.; Graham, T. L.; Khoudoli, G. A.; Hill, A.; Macphee, C. H.; Pinto, I.; Smith, S. A.; Suckling, K. E.; Wolf, C. R.; Palmer, C. N. A. *J. Biol. Chem.* **2001**, *276*, 44258. (d) Tan, N. S.; Michalik, L.; Noy, N.; Yasmin, R.; Pacot, C.; Heim, M.; Flühmann, B.; Desvergne, B.; Wahli, W. *Genes Dev.* **2001**, *15*, 3263. (e) Leibowitz, M. D.; Fiévet, 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.

(5) (a) Forman, B. M.; Chen, J.; Evans, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 4312. (b) Brown, P. J.; Smith-Oliver, T. A.; Charifson, P. S.; Tomkinson, N. C. O.; Fivush, A. M.; Sternbach, D. D.; Wade, L. E.; Orband-Miller, L.; Parks, D. J.; Blanchard, S. G.; Kliewer, S. A.; Lehmann J. M.; Willson, T. M. *Chem. Biol.* **1997**, *4*, 909. (c) Berger, J.; Leibowitz, M. D.; Doebber, T. W.; Elbrecht, A.; Zhang, B.; Zhou, G.; Biswas, C.; Cullinan, C. A.; Hayes, N. S.; Li, Y.; Tanen, M.; Ventre, J.; Wu, M. S.; Berger, G. D.; Mosley, R.; Marquis, R.; Santini, C.; Sahoo, S. P.; Tolman, R. L.; Smith, R. G.; Moller, D. E. *J. Biol. Chem.* **1999**, *274*, 6718. (d) Johnson, T. E.; Holloway, M. K.; Vogel, R.; Rutledge, S. J.; Perkins, J. J.; Rodan, G. A.; Schmidt, A. *J. Steroid Biochem. Mol. Biol.* **1997**, *63*, 1. (e) Brooks, C. D. W.; Summers, J. B. *J. Med. Chem.* **1996**, *39*, 2629.

(6) Sznaidman, M. L.; Haffner, C. D.; Maloney, P. R.; Fivush, A.; Chao, E.; Goreham, D.; Sierra, M. L.; LeGrumelec, C.; Xu, H. E.; Montana, V. G.; Lambert, M. H.; Willson, T. M.; Oliver, W. R., Jr.; Sternbach, D. D. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1517.

(7) Oliver, W. R., Jr.; Shenk, J. L.; Snaith, M. R.; Russell, C. S.; Plunket, K. D.; Bodkin, N. L.; Lewis, M. C.; Winegar, 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. U.S.A.* **2001**, *98*, 5306.

(8) Boyer, F. E.; Vara Prasad, J. V. N.; Domagala, J. M.; Ellsworth, E. L.; Gajda, C.; Hagen, S. E.; Markoski, L. J.; Tait, B. D.; Lunney, E. A.; Palovsky, A.; Ferguson, D.; Graham, N.; Holler, T.; Hupe, D.; Nouhan, C.; Tummino, P. J.; Urumov, A.; Zeikus, E.; Zeikus, K.; Gracheck, S. J.; Sanders, J. M.; VanderRoest, S.; Brodfuehrer, J.; Iyer, K.; Sinz, M.; Gulnik, S. V.; Erickson, J. W. *J. Med. Chem.* **2000**, *43*, 843.

(9) Robillard, B.; Hughes, L.; Slaby, M.; Lindsay, D. A.; Ingold, K. U. *J. Org. Chem.* **1986**, *51*, 1700.

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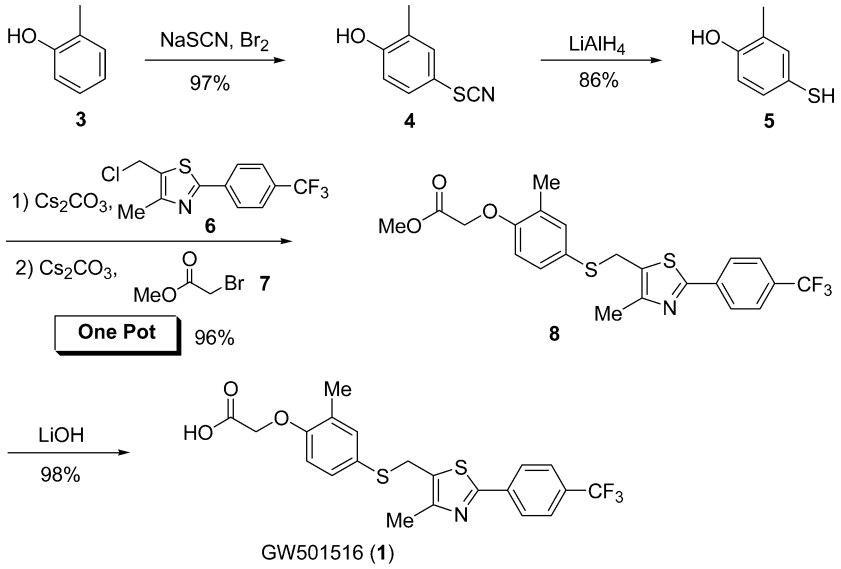
SCHEME 1



In summary, a practical synthesis of **1** was accomplished in 78% overall yield by using a one-pot regiocontrolled dialkylation of mercaptophenol **5** as the key step. Our synthetic route not only is short and efficient but also provides an alternative strategy to procure the mercaptophenol core structure, thus enabling the preparation of additional analogues for further structure−activity relationship studies.

Experimental Section

General Methods. All reactions were performed under an inert atmosphere (Ar or N_2) unless otherwise noted. ^{1}H, ^{13}C, and ^{19}F NMR spectra were obtained at 300, 75, and 282 MHz, respectively. ^{1}H chemical shifts (δ) were reported in ppm with Me_4Si (δ 0.00 ppm) or $CHCl_3$ (δ 7.26 ppm) as internal standards, ^{13}C chemical shifts with $CDCl_3$ (δ 77.0 ppm) or TMS (δ 0.0 ppm) as internal standards, and ^{19}F chemical shifts with $CFCl_3$ (δ 0.0 ppm) as an external standard. Melting points are uncorrected. TLC analysis was performed on silica gel sheets containing a fluorescent indicator. Column chromatography was carried out on silica gel (35−75 mesh).

2-Methyl-4-thiocyanatophenol (4). To a stirred solution of *o*-cresol (**3**) (10.8 g, 0.10 mmol), sodium thiocyanate (26.0 g, 0.32 mmol), and methanol (70 mL) at 0 °C was added a solution of sodium bromide (10.3 g, 0.10 mmol) and bromine (5.3 mL, 0.10 mmol) in methanol (100 mL). The mixture was stirred for 3 h and then diluted with saturated $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (3 × 120 mL), and the organic phases were combined, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (4:1) to give **3** as a light yellow solid (16.0 g, 97%). Mp 70−71 °C (lit.[10] mp 70.5−71 °C); ^{1}H NMR ($CDCl_3$) δ 7.33 (d, 1H, J = 2.4 Hz), 7.26 (dd, 1H, J = 8.4, 2.4 Hz), 6.79 (d, 1H, J = 8.4 Hz), 6.00 (br s, 1H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.3, 135.1, 131.5, 126.9, 116.6, 112.6, 112.5, 15.8.

4-Mercapto-2-methylphenol (5). A solution of **4** (6.0 g, 36.3 mmol) in anhydrous THF (100 mL) was added cautiously to a mixture of $LiAlH_4$ (1.4 g, 36.8 mmol) and anhydrous THF (200 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. After that time, unreacted $LiAlH_4$ was destroyed by adding moist THF, water, and 1.0 M HCl. The mixture was extracted with EtOAc (3 × 100 mL). The organic layers were combined, washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (4:1) to give **5** as a white solid (4.4 g, 86%). Mp 41−42 °C (lit.[11] mp 39−42 °C); ^{1}H NMR ($CDCl_3$) δ 7.12 (d, 1H, J = 2.1 Hz), 7.05 (dd, 1H, J = 8.1, 2.1 Hz), 6.66 (d, 1H, J = 8.1 Hz), 4.89 (s, 1H), 3.33 (s, 1H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.7, 133.8, 129.9, 124.9, 119.6, 115.6, 15.6.

Methyl [2-Methyl-4-[[[4-methyl-2-[4-(trifluoromethyl)-phenyl]thiazol-5-yl]methyl]sulfanyl]phenoxy]acetate (8). To a stirred solution of **5** (1.40 g, 10.0 mmol) in CH_3CN (80 mL) was added Cs_2CO_3 (3.25 g, 10.0 mmol), followed by the chloromethylthiazole **6** (2.60 g, 8.91 mmol).[6] The reaction mixture was stirred at room temperature for 4 h. Then additional Cs_2CO_3 (4.89 g, 15.0 mmol) was added, followed by methyl bromoacetate (1.23 mL, 13.0 mmol). The reaction mixture was stirred at room temperature for a further 5 h. After that time, the mixture was poured into water and extracted with EtOAc (3 × 100 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (5:1) to give **8** as a white solid (4.0 g, 96% relative to **6**). ^{1}H NMR ($CDCl_3$) δ 7.97 (d, 2H, J = 8.4 Hz), 7.65 (d, 2H, J = 8.4 Hz), 7.21 (d, 1H, J = 2.4 Hz), 7.13 (dd, 1H, J = 8.4, 2.4 Hz), 6.58 (d, 1H, J = 8.4 Hz), 4.63 (s, 2H), 4.11 (s, 2H), 3.78 (s, 3H), 2.24 (s, 3H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.2, 163.0, 156.3, 151.3, 136.8, 136.1, 132.1, 131.2 (q, J = 32 Hz), 130.6, 128.4, 126.3, 125.8 (q, J = 4 Hz), 125.3, 122.1, 111.4, 65.4, 52.2, 32.4, 16.1, 14.8; ^{19}F NMR ($CDCl_3$) δ 115.5 (s).

[2-Methyl-4-[[[4-methyl-2-[4-(trifluoromethyl)phenyl]-thiazol-5-yl]methyl]sulfanyl]phenoxy]acetic Acid (1). To a stirred solution of **8** (4.5 g, 9.63 mmol) in 150 mL of THF and 100 mL of H_2O at 0 °C was added slowly 6.0 mL (12.0 mmol) of 2.0 M LiOH. The reaction mixture was stirred at 0 °C until TLC indicated the completion of the reaction (about 1 h), diluted with water (100 mL), acidified with 0.5 M $NaHSO_4$ (25 mL), and extracted with a mixed solvent of EtOAc and THF (3:1, 4 × 150 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel with CH_2Cl_2/MeOH (10:1) to give **1** as a white solid (4.3 g, 98%). Mp 133−134 °C dec; ^{1}H NMR (DMSO-d_6) δ 8.02 (d, 2H, J = 8.4 Hz), 7.79 (d, 2H, J = 8.4 Hz), 7.20 (s, 1H), 7.13 (d, 1H, J = 8.1 Hz), 6.70 (d, 1H, J = 8.1 Hz), 4.46 (s, 2H),

(10) Fujio, M.; Mishima, M.; Tsuno, Y.; Yukawa, Y.; Takai, Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2127.

(11) Hotelling, E. B.; Windgassen, R. J.; Previc, E. P.; Neuworth, M. B. *J. Org. Chem.* **1959**, *24*, 1598.

4.31 (s, 2H), 2.20 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.3, 161.6, 156.4, 150.9, 136.4, 134.1, 131.6, 130.7, 129.5 (q, J = 32 Hz), 126.7, 126.2, 126.0 (q, J = 4 Hz), 123.4, 111.9, 66.2, 30.6, 15.9, 14.6; ^{19}F NMR (DMSO-d_6) δ 115.5 (s).

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