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Concise and efficient asymmetric synthesis of (*S*)-2-ethylphenylpropanoic acid derivatives: Dual agonists for human peroxisome proliferator-activated receptor α and δ

Jun-ichi Kasuga, Yuichi Hashimoto and Hiroyuki Miyachi*

Institute of Molecular and Cellular Biosciences, University of Tokyo, Japan

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Abstract—Optically active (*S*)-2-ethylphenylpropanoic acid derivatives, dual agonists for human peroxisome proliferator-activated receptor (PPAR) α and δ, were efficiently prepared by using Evans's chiral oxazolidinone technique and reductive amide N-alkylation as key steps.

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor family, which includes steroid, thyroid, retinoid, vitamin D, and other receptors.[1] To date, three subtypes of PPARs, termed PPARα [officially NR1C1], PPARδ (also known as PPARβ, NUCI, FAAR) [NR1C2], and PPARγ [NR1C3], have been identified in various species, including humans.[2] Each PPAR subtype appears to be differentially expressed in a tissue-specific manner and to play a pivotal role in lipid, lipoprotein, and glucose homeostasis.[3] PPARα is mostly expressed in the tissues involved in lipid oxidation, such as liver, kidney, skeletal muscle, cardiac muscle, and adrenal glands. PPARγ is expressed in adipose tissue, macrophages, and vascular smooth muscles. In contrast to the specific distributions of PPARα and PPARγ, PPARδ is ubiquitously expressed in almost all mammalian tissues.

PPARγ was first identified as a master regulator of adipocyte differentiation, but more recent molecular–biological studies have indicated that PPARγ activation is also linked to the expression of many important genes that affect energy production, such as the TNF-α, leptin, and adiponectin genes.[4]

PPARα regulates the expression of genes encoding for proteins involved in lipid and lipoprotein homeostasis.[5] For example, it regulates genes involved in fatty acid uptake (such as fatty acid binding protein, FABP), β-oxidation (acyl-CoA oxidase), and ω-oxidation (cytochrome P450). It down-regulates apolipoprotein C-III, a protein that inhibits triglyceride hydrolysis by lipoprotein lipase,[6] and it also regulates genes involved in reverse cholesterol transport, such as apolipoprotein A-I and apolipoprotein A-II.[5]

Based on the findings that antidiabetic thiazolidine-2,4-diones (glitazones), and antidyslipidemic fibrates are ligands of PPARγ and PPARα, respectively, much research has been focused on these metabolic nuclear receptor subtypes as therapeutic targets for the treatment of metabolic syndrome, and compounds such as GW-9578 (**4**)[6] and KCL (**5**)[7] (Fig. 1) have been developed.

Although PPARδ is ubiquitously distributed in a wide range of tissues and cells, research interest in PPARδ has been limited. However, the availability of selective ligands, such as GW-501516 (**7**)[8] and L-165041 (**8**)[9] (Fig. 1), prompted us to examine the roles of PPARδ in fatty acid metabolism, reverse cholesterol transport, and other disease states. Considering the positive contributions of PPARα and PPARδ to lipid, lipoprotein, and cholesterol homeostasis, dual agonists of both PPARα and PPARδ might be candidates of choice for the treatment of metabolic syndrome, by decreasing triglyceride,

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* Corresponding author. E-mail: miyachi@iam.u-tokyo.ac.jp

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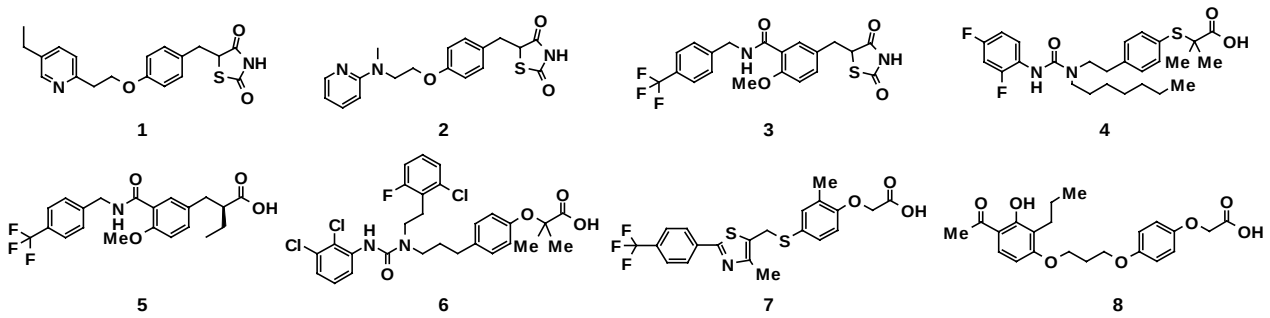


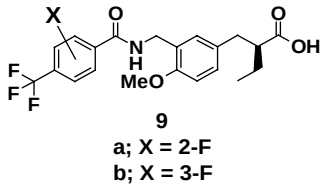
Figure 1. Structures of representative PPARγ (**1** (pioglitazone), **2** (rosiglitazone)), dual PPARα/γ (**3** (KRP-297/MK767), PPARα (**4** (GW-9578), **5** (KCL)), dual PPARα/δ (**6** (GW-2433)), and PPARδ (**7** (GW-501516), **8** (L-165041)) agonists.

free fatty acid, LDL-cholesterol, and increasing HDL cholesterol. But, there have been few reports of such agonists, except for GW-2433 (**6**) (Fig. 1), and its potency is not high.

Recently, we reported the design and synthesis of novel phenylpropanoic acid derivatives as dual PPARα/δ agonists,[10] and we selected the 2-ethylphenylpropanoic acid derivatives (**9a**,**b**; Fig. 2) for further pharmacological study. We also discovered that the agonistic activity depends on the stereochemistry of the α-substituted ethyl group, and the (*S*)-form is more potent than the antipode.[10] In order to establish in detail the in vivo pharmacological profiles of **9a**,**b**, and to evaluate the compounds as candidate drugs for the treatment of metabolic syndrome, a versatile asymmetric synthetic route suitable to prepare large amounts of **9a**,**b** was needed. In this paper, we report an efficient asymmetric synthetic route to **9a**,**b** in excellent enantiomeric excess (Scheme 1).

We previously prepared **9a** and **b** by the method depicted in Scheme 2.[11] However, this route contains multiple steps with chromatographic purification of intermediates, and a low total yield (seven steps, 3% overall yield), and it is unsuitable for scale-up.

In our initial design, we planned the synthesis of **9a**,**b** by the condensation of 2-fluoro-4-trifluoromethylbenzoic acid (or 3-fluoro-4-trifluoromethylbenzoic acid) and an optically active benzylamine derivative (**11**) (Scheme 1). Compound **11** was expected to be obtainable from the corresponding benzoic acid derivative (**12**), used for the synthesis of optically active human PPARα selective agonist KCL (**5**).[7] However, several attempts failed to afford the desired benzylamine derivative (**11**) in good yield with high purity.



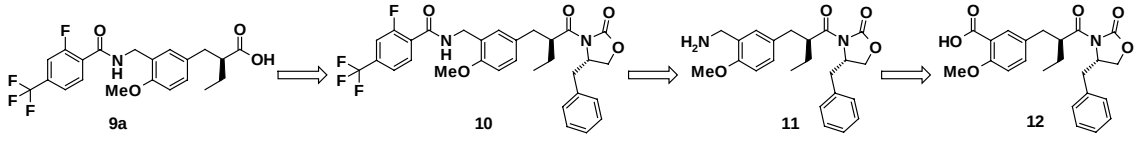
9
a; X = 2-F
b; X = 3-F

Figure 2. Structures of dual PPARα/δ agonists **9a** and **9b**.

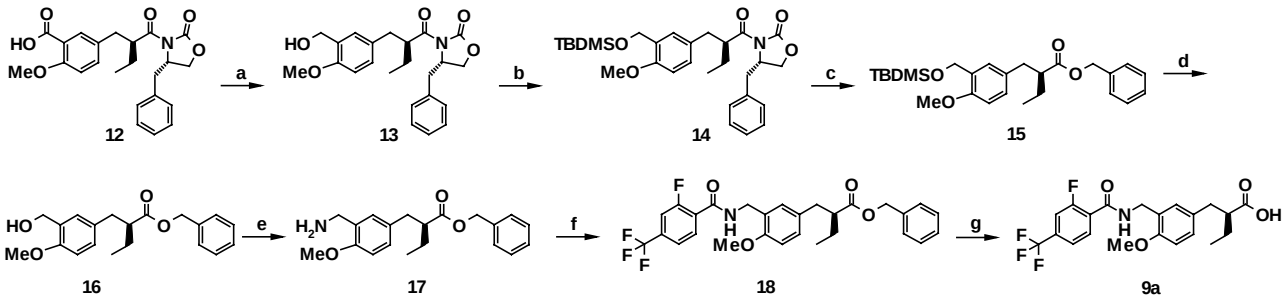
We then planned the synthesis of **9a**,**b** by the N-alkylation of 2-fluoro-4-trifluoromethylbenzamide (or 3-fluoro-4-trifluoromethylbenzamide) with the bromomethyl derivative (**19**) (Scheme 3 step b). Compound **19** was prepared by the reduction of **12** with BH_3–tetrahydrofuran complex and subsequent bromination with PPh_3–CBr_4 (yield 67%, two steps).[12] 3-Fluoro-4-trifluoromethylbenzamide was treated with NaH (or LiHMDS, or *t*-BuOK) and then treated with **19** to afford several compounds, including **20**. After silica gel column chromatography, **20** was isolated in only 15% yield, and a considerable amount of the starting 3-fluoro-4-trifluoromethylbenzamide was recovered. Therefore, direct N-alkylation was also found to be unsuitable in this case.

Recently, Dobe and Scholte reported an efficient reductive N-alkylation of amides using TFA/Et_3SiH with aldehyde.[13] Since the aldehyde (**21**) was readily prepared by the reduction of **12**, followed by oxidation with activated MnO_2 (90% yield, two steps),[14] we examined the application of this methodology to the synthesis of **9a**,**b** (Scheme 3 step e).

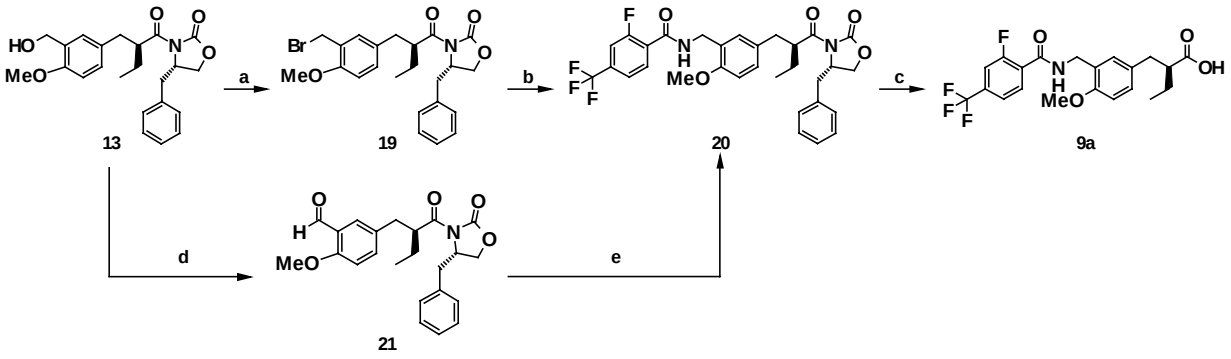
When a mixture of 2-fluoro-4-trifluoromethylbenzamide (1 equiv), the aldehyde (**21**) (3 equiv), triethylsilane (3 equiv), and trifluoroacetic acid (3 equiv) in toluene was heated to reflux for 24 h, the desired N-alkylation product (**20**) was successfully obtained in good (66%) yield after silica gel column chromatography.[15] After deprotection of the chiral oxazolidinone moiety with the LiOH/30% H_2O_2 system,[16] the desired **9a** was



Scheme 1. Retrosynthetic analysis of the preparation of **9a**.



Scheme 2. Initial synthetic route to **9a**. Reagents and conditions: (a) BH_3–tetrahydrofuran, THF, 0 °C, overnight, 90%; (b) TBDMSCl, imidazole, THF, rt, overnight, 65%; (c) benzyl alcohol, *n*-BuLi in tetrahydrofuran, THF, −40 °C, 4 h, quant.; (d) TBAF, THF, rt, overnight, 87%; (e) (1) $P(Ph)_3$-polymer, CBr_4, rt, overnight, 86%, (2) potassium phthalimide, DMF, 100 °C, 2 h, 80%, (3) $NaBH_4$, *i*PrOH–H_2O, rt, overnight then AcOH, 80 °C, 3 h, 37%; (f) ethyl chloroformate, triethylamine, 0 °C, 20 min, then 2-fluoro-4-trifluoromethylbenzoic acid, THF, rt, overnight, 26%; (g) H_2, 10% Pd-C, AcOEt, rt, overnight, 60%.



Scheme 3. Preparation of **9a** by amide N-alkylation or reductive amide N-alkylation. Reagents and conditions: (a) $P(Ph)_3$-polymer, CBr_4, rt overnight, 70%; (b) (1) 60% NaH, THF, 0 °C, then 2-fluoro-4-trifluoromethylbenzamide, THF, rt, overnight, 15%; (c) LiOH H_2O, 30% H_2O_2, THF/H_2O = 4:1 (v/v), 85%; (d) activated MnO_2, rt, quant.; (e) 2-fluoro-4-trifluoromethylbenzamide, triethylsilane, trifluoroacetic acid, toluene, reflux, 66%.

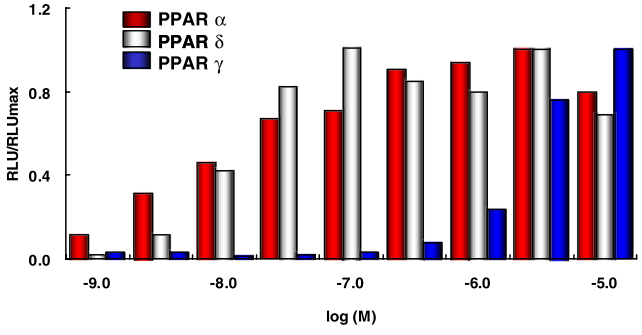


Figure 3. Dose–response of the transactivation of PPARα/δ agonists **9a**.

obtained in 85% yield. Namely, **9a** was obtained from **12** in a total yield of about 50% in only three steps. Similarly, **9b** was obtained from **12** in total yield of about 50%.

In conclusion, we have developed an efficient and practical synthetic route to the optically active 2-ethylphenylpropanoic acid derivatives **9a** and **b**, using Evans's asymmetric alkylation and reductive N-alkylation as key steps. Since **9a** and **b** are very potent and human PPARα/δ dual agonists (Fig. 3),[17] they should not only be useful pharmacological tools to investigate the physiology and pathophysiology of PPARα and PPARδ, but also candidate drugs for the clinical treatment of metabolic syndrome.

Acknowledgments

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References and notes

1. Porte, D., Jr.; Schwartz, M. W. *Science* **1996**, *272*, 699.
2. Staels, B.; Auwerx, J. *Curr. Pharm. Des.* **1997**, *3*, 1.
3. Willson, T. M.; Brown, P. J.; Sternbach, D. D.; Henke, B. R. *J. Med. Chem.* **2000**, *43*, 527.
4. Okuno, A.; Tamemoto, H.; Tobe, K.; Ueki, K.; Mori, Y.; Iwamoto, K.; Umesono, K.; Akanuma, Y.; Ujiwara, T.; Horikoshi, H.; Yazaki, Y.; Kadowaki, T. *J. Clin. Invest.* **1998**, *101*, 1354.
5. Mukherjee, R.; Jow, L.; Noonan, D.; McDonnell, D. P. *J. Steroid Biochem. Mol. Biol.* **1994**, *51*, 157.
6. Brown, P. J.; Winegar, D. A.; Plunket, K. D.; Moore, L. B.; Lewis, M. C.; Wilson, J. G.; Sundseth, S. S.; Koble, C. S.; Wu, Z.; Chapman, J. M.; Lehmann, J. M.; Kliewer, S. A.; Willson, T. M. *J. Med. Chem.* **1999**, *42*, 3785.

7. (a) Nomura, M.; Takahashi, Y.; Tanase, T.; Miyachi, H.; Ide, T.; Tsunoda, M.; Murakami, K.; *PCT Int. Appl.* WO 00/75103; (b) Nomura, M.; Tanase, T.; Ide, T.; Tsunoda, M.; Suzuki, M.; Uchiki, H.; Murakami, K.; Miyachi, H. *J. Med. Chem.* **2003**, *46*, 3581.
8. 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.
9. Lim, H.; Gupta, R. A.; Ma, W. G.; Paria, B. C.; Moller, D. E.; Morrow, J. D.; DuBois, R. N.; Trzaskos, J. M.; Dey, S. K. *Genes Dev.* **1999**, *13*, 1561.
10. Kasuga, J.; Makishima, M.; Hashimoto, Y.; Miyachi, H. *Bioorg. Med. Chem. Lett.* **2005**, accepted for publication.;
11. Nomura, M.; Tanase, T.; Miyachi, H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2101.
12. A mixture of **12** (1.20 g, 2.90 mmol) was dissolved in 30 mL of dehydrated tetrahydrofuran and cooled to 0 °C. 3.50 mL of 1 mol/L borane–tetrahydrofuran complex was added dropwise and stirred overnight at rt. The reaction mixture was poured into satd NH_4Cl solution and extracted with ethyl acetate. The extract was dried, filtered, and evaporated. The residue was purified by silica gel column chromatography (eluant; *n*-hexane/ethyl acetate 1:1 v/v) to obtain 1.10 g (95%) of **13** as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (t, *J* = 7.3 Hz, 3 H), 1.65 (m, 2H), 1.82 (dd, *J* = 13.3, 9.4 Hz, 1H), 2.33 (m, 1H), 2.56 (dd, *J* = 13.3, 6.4 Hz, 1H), 2.80 (dd, *J* = 13.3, 6.9 Hz, 1H), 3.07 (dd, *J* = 13.3, 6.9 Hz, 1H), 3.14 (dd, *J* = 13.3, 6.9 Hz, 1H), 3.89 (s, 3H), 4.13–4.22 (m, 3H), 4.71 (d, *J* = 6.0 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 1H), 7.12 (m, 2H), 7.24–7.34 (m, 5H); MS (FAB$^+$) 397 (M); $[\alpha]_D$ −36.3 (*c* = 0.52, MeCN). A mixture of **13** (958 mg, 2.41 mmol), $P(Ph)_3$ (840 mg, 3.20 mmol), CBr_4 (1.06 g, 3.20 mmol), and 25 mL CH_2Cl_2 was stirred for overnight at rt. The reaction solvent was evaporated and the residue was purified by silica gel column chromatography (eluant; *n*-hexane/ethyl acetate 2:1 v/v) to obtain 720 mg (70%) of **19** as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.3 Hz, 3H), 1.57 (m, 1H), 1.77 (m, 1H), 2.41 (dd, *J* = 13.3, 9.4 Hz, 1H), 2.75 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.97 (dd, *J* = 13.6, 6.4 Hz, 1H), 3.03 (m, 1H), 3.84 (s, 3H), 4.05 (m, 1H), 4.12 (m, 2H), 4.52 (s, 2H), 4.65 (m, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 2H), 7.20 (m, 5H); HRMS (EI$^+$) calcd for $C_{23}H_{27}BO_4{}^{79}Br$ (M + H) 460.1132, found 460.1161. This compound was used without further purification.
13. Dube, D.; Scholte, A. A. *Tetrahedron Lett.* **1999**, *40*, 2295.
14. A mixture of **13** (1.50 g, 3.89 mmol), activated MnO_2 (3.00 g, 42.3 mmol), and 40 mL of dehydrated dichloromethane was stirred overnight at rt. The mixture was filtered through Celite and the filtrate was evaporated. The residue was purified by silica gel column chromatography (eluant; *n*-hexane/ethyl acetate 3:2 v/v) to obtain 1.50 g (quant.) of **21** as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* = 7.3 Hz), 1.51–1.55 (1H, m), 1.72–1.78 (1H, m), 2.51 (1H, dd, *J* = 13.3, 6.8 Hz), 2.74 (1H, dd, *J* = 6.8, 6.8 Hz), 3.03 (1H, dd, *J* = 13.3, 7.3 Hz), 3.09 (1H, dd, *J* = 13.3, 3.0 Hz), 3.87 (3H, s), 4.01–4.15 (3H, m), 4.64 (1H, m), 6.90 (1H, d, *J* = 8.6 Hz), 7.05 (2H, d, *J* = 6.4 Hz), 7.22–7.27 (2H, m), 7.50 (1H, dd, *J* = 8.6, 2.6 Hz), 7.67 (1H, d, *J* = 2.6 Hz), 10.4 (1H, s); $[\alpha]_D$ −68.1 (*c* = 0.356, MeCN).
15. A mixture of **21** (750 mg, 1.95 mmol), 2-fluoro-4-trifluoromethylbenzamide (1.21 g, 5.85 mmol), triethylsilane (0.94 mL, 5.85 mmol), trifluoroacetic acid (0.45 mL, 5.85 mmol), and 30 mL of dehydrated toluene was refluxed for 24 h. The mixture was evaporated, and the residue was purified by silica gel column chromatography (eluant; *n*-hexane/ethyl acetate 2:1 v/v) to obtain 750 mg (66%) of **20** as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (3H, t, *J* = 7.6 Hz), 1.56—1.60 (1H, m), 1.73—1.79 (1H, m), 2.44 (1H, dd, *J* = 13.7, 6.4 Hz), 2.76 (1H, dd, *J* = 13.7, 6.4 Hz), 2.94–3.02 (2H, m), 3.86 (3H, s), 4.03 (1H, dd, *J* = 9.0, 2.6 Hz), 4.09–4.12 (2H, m), 4.57–4.69 (3H, m), 6.84 (1H, d, *J* = 8.1 Hz), 6.94 (2H, s), 7.18–7.31 (6H, m), 7.46 (1H, d, *J* = 8.1 Hz), 8.15 (1H, t, *J* = 8.1 Hz); $[\alpha]_D$ −58.3 (*c* = 0.114, MeCN).
16. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
17. Human embryonic kidney HEK293 cells were cultured in DMEM containing 5% fetal bovine serum and antibiotic–antimycotic at 37 °C in a humidified atmosphere of 5% CO_2 in air. Transfections were performed by the calcium phosphate coprecipitation. Eight hours after transfection, ligands were added. Cells were harvested approximately 16–20 h after the treatment, and luciferase and β-galactosidase activities were assayed using a luminometer and a microplate reader. DNA cotransfection experiments included 50 ng reporter plasmid, 20 ng pCMX-β-galactosidase, 15 ng of each PPAR receptor, and pGEM carrier DNA for a total of 150 ng DNA per well in a 96-well plate. Luciferase data were normalized to an internal β-galactosidase control and represent means (±SD) of triplicate assays.