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Efficient Asymmetric Synthesis of (*S*)-2-Ethylphenylpropanoic Acid Derivative, a Selective Agonist for Human Peroxisome Proliferator-Activated Receptor Alpha

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Abstract—An optically active phenylpropanoic acid derivative, a selective agonist for human peroxisome proliferator-activated receptor alpha, was efficiently prepared in high optical purity by using Evans chiral oxazolidinone technique as a key step.

Introduction

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor family which includes steroid receptor, thyroid receptor, retinoid receptor and others.[1] These receptors are ligand-dependent transcription factors. Upon ligand binding, the activated PPARs heterodimerize with another nuclear receptor, the retinoid X receptor (RXR),[2] and modulate the transcription of the target genes after binding to specific peroxisome proliferator response elements (PPREs), which are a direct repeat of the hexameric AGGTCA recognition motif separated by one nucleotide (DR1).[3] Three subtypes of PPARs, termed PPARα, PPARδ (also known as PPARβ NUCI, FAAR) and PPARγ have been identified so far in various species, including humans.[4] PPARα, the first isoform to be cloned, in 1990,[5] is present at high density in the liver and regulates the expression of genes encoding proteins involved in lipid and lipoprotein metabolism, such as acyl-CoA oxidase, bifunctional enzyme, liver fatty acid binding protein, apo A, apo C, and so on.[6] In addition to the above in vitro results, PPARα-deficient transgenic mouse (PPARα−/−) exhibited massive hepatic and cardiac lipid accumulation owing to inhibition of the cellular fatty acid flux.[7] These results clearly indicate a pivotal role for PPARα in lipid homeostasis in vivo.

Fibrate compounds, such as clofibrate and bezafibrate (Chart 1), have been used for the treatment of hypertriglyceridemia for more than 20 years,[8] and recently fenofibrate (Chart 1) was launched in Japan. Although the molecular target of these drugs remains to be definitively established, recent molecular pharmacological studies have demonstrated that fibrates activate PPARs at high micromolar concentrations, with poor subtype selectivity.[9] We considered that more potent and selective activators of PPARα, especially human PPARα, might have therapeutic utility for the treatment of altered lipid homeostasis in the target organs, especially in the liver. Recently, we have reported the design and the synthesis of some novel phenylpropanoic acid derivatives as subtype-selective PPAR agonists,[10] and we selected the 2-ethylphenylpropanoic acid derivative (**4**; Chart 1) for further pharmacological study. We also examined the enantio-dependency of **4** in peroxisome proliferator-activated receptor α transactivation and binding, and showed that these activities exclusively reside on the (*S*)-isomer.[11] In order to establish in detail the in vivo pharmacological profile of (*S*)-(+)-**4**, and to evaluate the compound as a candidate drug for the treatment of metabolic disorders, such as obesity, diabetes and others, a versatile asymmetric synthetic route suitable to prepare large amounts was needed. In this paper, we report an efficient asymmetric synthetic route to (*S*)-(+)-**4** in excellent enantiomeric excess.

Chemistry

As already reported, we have prepared (*S*)-(+)-**4** by optical resolution of the corresponding imide derivative of **4**, and subsequent removal of the chiral auxiliary.[11]

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However, the yield of (*S*)-(+)-**4** was not high, and the antipodal (*R*)-(−)-**4** could not be racemized easily, so this optical resolution method is not suitable from a practical point of view.

It was anticipated that the chiral α-ethylphenylpropanoic acid derivative **4** could be prepared by using Evans asymmetric alkylation methodology,[12] with subsequent derivatization (Chart 2). Therefore, to test this idea, we first examined the reaction between the acyl oxazolidinone derivative **5** and benzyl 5-bromomethyl-2-methoxybenzoate (which was prepared from methyl 5-formyl-2-methoxy benzoate in four steps) at −78 °C, using an equimolar amount of sodium hexamethyldisilazide (NaHMDS) as a base.[13] The reaction was complete in about 10 h and gave the desired alkylated product **6** in about 64% yield, with 97% diastereomeric excess (see Chart 3).[14] The absolute configuration of the C-2 ethyl group was determined by comparison with the final product **4**, which was prepared both from **6** and from (*R*)-(−)-2-benzylbutanoic acid ((*R*)-(−)-BnBA) (Chart 4).[11] As already reported, (*R*)-**4** that was prepared from known (*R*)-(−)-BnBA exhibited levo rotation. On the contrary, **4** prepared from the alkylated product **6** exhibited antipodal dextro rotation, so the absolute configuration of the C-2 ethyl group of **6** was deduced to be (*S*).[11]

We next examined the effects of the organic base and the reaction temperature, since a very low temperature reaction condition (such as −78 °C) is not convenient from a practical point of view. At a higher temperature of about −30 °C, no reaction took place and the starting materials were recovered. The reason for this is probably the instability of the sodium enolate of the oxazolidinone formed in the medium.[12] Then we tried the reaction at −30 °C using lithium hexamethyldisilazide (LiHMDS) instead of NaHMDS, because the corresponding lithium enolate derivative of the oxazolidinone was expected to be more stable at higher temperature than the sodium enolate derivative.[12] As expected, the reaction proceeded smoothly and gave **6** in

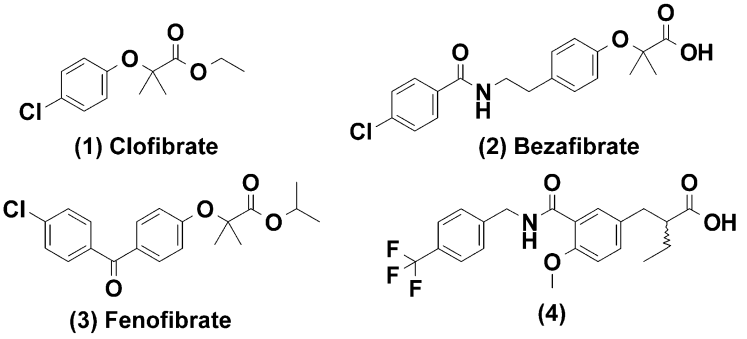


Chart 1. Chemical structures of the known fibrate drugs and **4**.

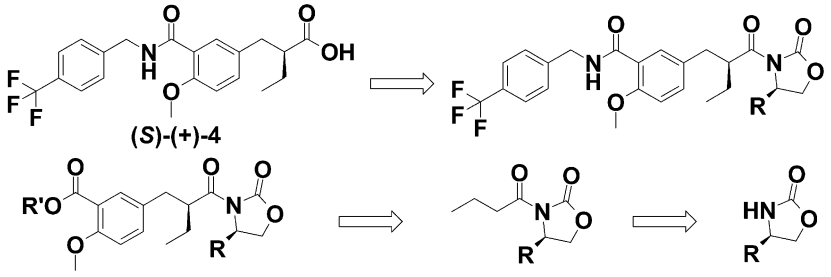


Chart 2. Retro synthetic scheme for (*S*)-(+)-**4**.

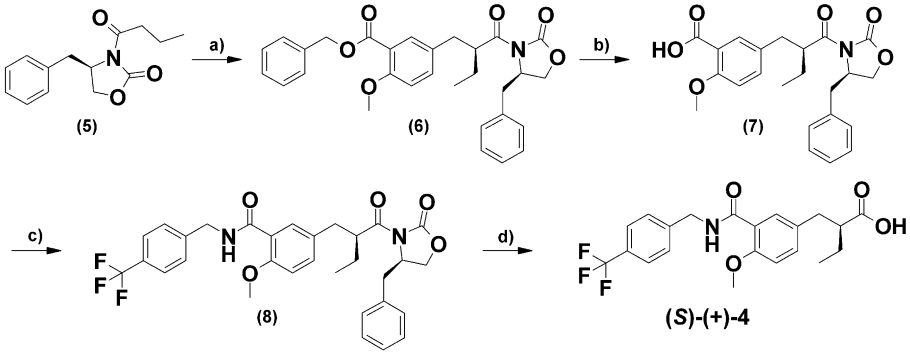


Chart 3. Synthetic route to (*S*)-(+)-**4**. Reagents and conditions: (a) LiHMDS, benzyl 5-bromomethyl-2-methoxybenzoate, THF, −20 °C, 5 h, 80%; (b) H_2, 10% Pd/C, EtOH, quant; (c) $ClCO_2Et$, TEA, 4-(trifluoromethyl)benzylamine, CH_2Cl_2, 90%; (d) $LiOH{\cdot}H_2O$, 30% H_2O_2, 87%.

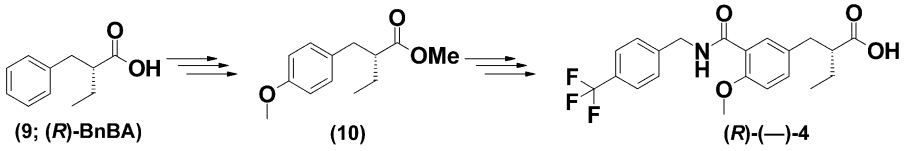
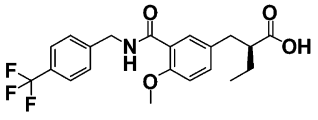


Chart 4. Synthetic route to (*R*)-(−)-**4** starting from known (*R*)-(−)-BnBA.

about 80% yield, with 98% enantiomeric excess. When the reaction was performed at 0 °C, the reaction was incomplete and only a 20% yield of **6** was obtained. Benzyl 5-bromomethyl- 2-methoxybenzoate was important, because no alkylated product was obtained when the corresponding chloromethyl derivative was used as the electrophile, probably due to insufficient reactivity of the electrophile.

Considering these preliminary results, the synthesis of (*S*)-(+)-**4** was performed as follows (Chart 3). (*R*)-*N*-Butyryl-4-benzyloxazolidinone **5** was treated with benzyl 5-bromomethyl- 2-methoxybenzoate at −20 °C for 5 h in the presence of an equimolar amount of LiHMDS as a base to afford 90% yield of the desired alkylated product **6**, with high enentiomeric excess (98% e.e.). Subsequent hydrogenolysis afforded the important versatile synthetic intermediate **7** almost quantitatively. 4-(Trifluoromethyl)benzylamine was condensed with **7** by the mixed anhydride method (90% yield), followed by the removal of the chiral auxiliary of **8** by alkaline hydrolysis to afford the desired (*S*)-(+)-**4** with high retention of enantiomeric excess (98% e.e.).[15]

In conclusion, we have developed an efficient and practical asymmetric synthetic route to an optically active 2-ethylphenylpropanoic acid derivative (*S*)-(+)-**4**, using Evans's asymmetric alkylation methodology as a key step. Since (*S*)-(+)-**4** is a very potent and subtype-selective human PPARα agonist,[10,11] it not only represents a useful pharmacological tool to investigate the physiology and pathophysiology of PPARα, but is also a candidate drug for the clinical treatment of metabolic disorders, such as dyslipidemia, obesity, and diabetes (Fig. 1).



	hPPARα	hPPARγ	hPPARδ
EC_{50}(nM)	76	23000	1300

Figure 1. A PPARα selective agonist (*S*)-(+)-**4**.

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13. (*R*)-3-(1-Butyryl)-4-benzyloxazolidin-2-one (3.37 g, 13.6 mmol) and 70 mL of dehydrated tetrahydrofuran were mixed under an atmosphere of argon, and cooled to −78 °C. Under stirring, a 1 mol/L solution of NaHMDS in dehydrated tetrahydrofuran (15.0 mL, 15.0 mmol) was added dropwise. After completion of the addition, the mixture was stirred for 1 h at −78 °C and then a solution of benzyl 5-bromomethyl-2-methoxybenzoate (5.04 g, 15.0 mmol) in dehydrated tetrahydrofuran (20 mL) was added dropwise. After the addition, the mixture was stirred for 6 h at −78 °C. Saturated aqueous ammonium chloride was added, and the whole was extracted with ethyl acetate. The organic solution was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluant; *n*-hexane/ethyl acetate = 4:1v/v) to obtain 4.38 g (64%) of **6** as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.51–1.63 (1H, m), 1.71–1.82 (1H, m), 2.43 (1H, dd, J = 13.2, 9.8 Hz), 2.75 (1H, dd, J = 13.7, 6.3 Hz), 2.99–3.08 (2H, m), 3.86 (3H, s), 4.03–4.15 (3H, m), 4.64 (1H, m), 5.27 (1H, d, J = 12.2 Hz), 5.31 (1H, d, J = 12.7 Hz), 6.91 (1H, d, J = 8.8 Hz), 7.03 (2H, dd, J = 7.8, 2.0 Hz), 7.20–7.42 (9H, m), 7.72 (1H, d, J = 2.0 Hz); low-resolution MS (EI^+) m/e 501(M^+).
14. Analysis of the enantiomeric excess was performed by HPLC with a CHIRAPAC OD column (0.0046×0.25 m, flow rate 1.00 mL/min, UV 254 nm, *n*-hexane/*i*-PrOH: TFA = 95:5:0.2 v/v/v as the eluant).

15. Physicochemical properties of (*S*)-(+)-**4** were as follows; mp 128–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.3 Hz), 1.54–1.69 (2H, m), 2.58–2.65 (1H, m), 2.77 (1H, dd, J = 13.7, 6.3 Hz), 2.96 (1H, dd, J = 13.7, 8.3 Hz), 3.92 (3H, s), 4.38 (1H, br s), 4.72 (2H, d, J = 5.9 Hz), 6.90 (1H, d, J = 8.3 Hz), 7.29 (1H, dd, J = 8.3, 2.4 Hz), 7.46 (2H, d, J = 7.8 Hz), 7.58 (2H, d, J = 7.8 Hz), 8.07 (1H, d, J = 2.4 Hz), 8.34 (1H, t, J = 5.9 Hz); low-resolution MS (EI$^+$) m/e 451 (M^+); $[\alpha]_D$ +25° (*c* 0.8, MeOH). Anal. calcd for $C_{21}H_{22}F_3NO_4$: C, 61.61; H, 5.42; N, 3.42. Found: C, 61.41; H, 5.44; N, 3.41.