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Synthesis of 2-methoxy-2-methyl-3-{6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)-ethoxy]pyridin-3-yl}propanoic acid, a dual PPARα/γ agonist

Paul S. Humphries *, Quyen-Quyen T. Do, David M. Wilhite

Pfizer Global R&D, Department of Medicinal Chemistry, 10614 Science Center Drive, San Diego, CA 92121, USA

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ABSTRACT

Large quantities of an enantiomerically pure novel dual PPARα/γ agonist were required. Three routes were successfully developed to achieve this goal, with the chosen route utilized to deliver 40 g of material.

Peroxisome proliferator-activated receptors (PPARs) are pharmaceutical targets of great importance. Their wide-ranging effects on key transcriptional pathways for lipid handling, insulin sensitivity, inflammation, and other functions have led to marketed drugs and vast clinical and preclinical research efforts.[1–4]

As part of an ongoing PPAR drug discovery program in our laboratories, we originally synthesized racemic **1** and showed it to be of further interest to the team.[5] Chiral supercritical fluid chromatography (SFC) separation was performed on the racemic material, and the two enantiomers were isolated in >95% ee.[6] It was quickly established that the majority of the in vitro activity resided in the first eluting enantiomer **2** (Fig. 1).

During the progression of **2** through the project's screening cascade, material was accessed via large-scale chiral SFC separation of **1**. The optimized synthetic route to **1** is shown in Scheme 1.[7] Alcohol **3** was brominated, using a modified procedure from the Imperiali group,[8] to afford **4**. Bromide **4** was then reacted with the sodium enolate of **5** to form ester **6** in excellent yield. Buchwald reaction between **6** and alcohol **7** gave ester **8** in good yield.[9,10] Intermediate **8** was then hydrolyzed to afford the desired racemic acid **1** in excellent recovery.

Enantiomerically pure **2** was then required to enter an in vivo toleration (IVT) study, and we would thus necessitate a further 30–50 g of material. In order to access **2** on this scale, we decided to avoid chiral SFC separation of racemic **1**. The three successful strategies that were used are outlined in Figure 2.

For the biotransformation route, racemic ester **6** was submitted for initial enzyme screening studies, and it was found that both *Bacillus lentus protease* and *Aspergillus oryzae protease* gave >95% ee after 45–50% conversion. Interestingly, the two proteases selectively produced opposite enantiomers to one another. Slight modifications were made during the scale-up of this step, including a switch to protease from bovine pancreas. Ester **9** was subjected

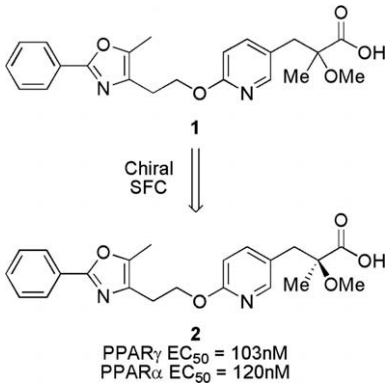

Figure 1. Racemic lead **1** and enantiomerically pure **2**.

* Corresponding author. Tel.: +1 860 686 0256; fax: +1 860 715 8624.
E-mail address: phumphri@gmail.com (P.S. Humphries).

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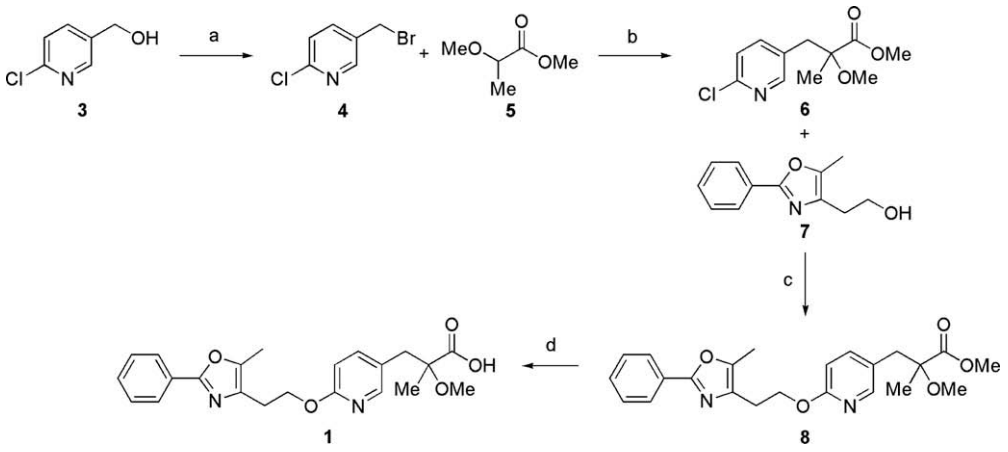


Scheme 1. Reagents and conditions: (a) PS–PPh_3, NBS, CH_2Cl_2, rt, 30 min, 87%; (b) NaHMDS, THF, −50 °C, 90 min, 96%; (c) $Pd(OAc)_2$ (cat.), racemic-2-(di-*t*-butylphosphino)-1,1′-binaphthyl (cat.), Cs_2CO_3, PhMe, 115 °C, 16 h, 85%; (d) $LiOH{\cdot}H_2O$, THF, MeOH, H_2O, rt, 1 h, 100%.

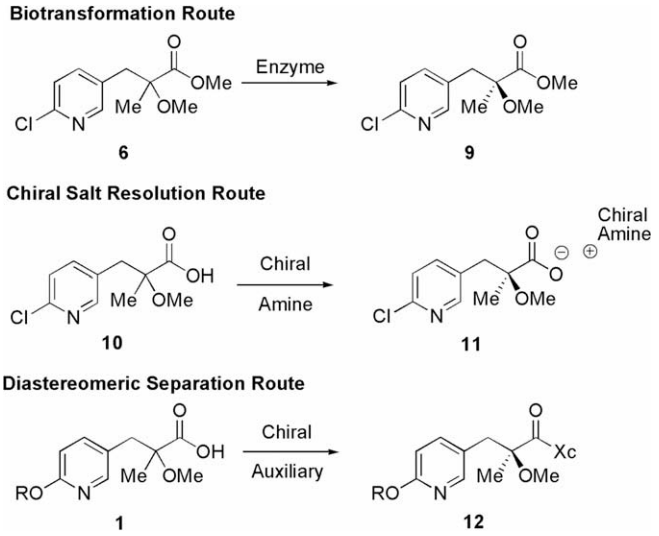
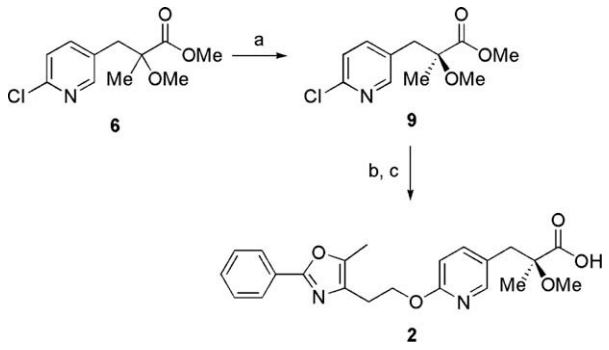


Figure 2. Successful strategies to obtain **2** on large-scale.

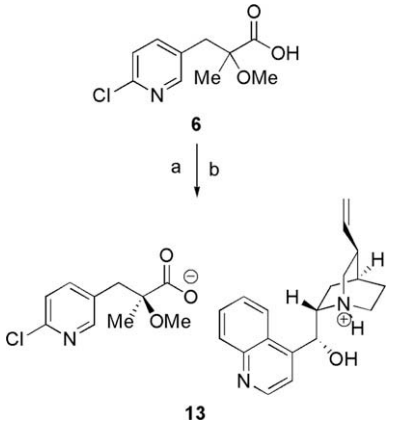
to the Buchwald reaction followed by hydrolysis, as in the racemic route, and the product was shown to be **2** (>98% ee) by chiral analytical SFC (Scheme 2).

For the chiral salt resolution route, racemic ester **6** was hydrolyzed to afford acid **10**, which was our key intermediate for the initial chiral amine screening studies. Initially, only six chiral amines were utilized and these were chosen from the PPAR patent literature. The initial conditions used 1 equiv of the chiral amine stirring in ethyl acetate at ambient temperature, and the best result was afforded by (−)-Cinchonidine (60% ee). This salt **13** (Scheme 3) was further recrystallized, which afforded material of 81% ee. The above reactions were then repeated in acetonitrile, but all gave products ⩽20% ee. Focusing on the (−)-Cinchonidine result, we repeated the ethyl acetate and acetonitrile experiments, but this time using only 0.5 equiv of the chiral amine. The salt formed from the ethyl acetate trial gave material of 96% ee, which could be further recrystallized to >99% ee. Salt **13** was neutralized, and then esterified to afford ester **9**. This material was once again taken through the last two steps to afford the final acid **2** (>98% ee) by chiral analytical SFC.

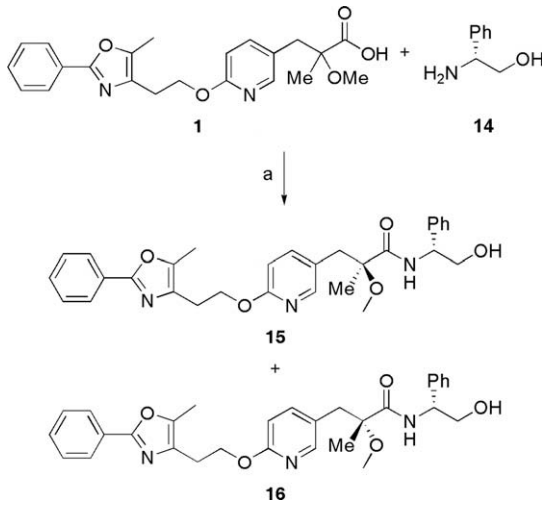
For the diastereomeric separation route, our choice of chiral auxiliary was (*R*)-phenylglycinol **14**, following work by the AstraZeneca PPAR group.[11] Racemic acid **1** was successfully reacted with chiral amino alcohol **14** to afford the pair of diastereomeric amides **15** and **16** (Scheme 4). The two diastereomers were easily separable by flash column chromatography, with the first eluting product **15** being a white solid and the second eluting product **16** a colorless oil. Diastereomer **15** was then hydrolyzed, using sulfuric acid in dioxane/water, to afford an optically pure acid that was proven (by chiral analytical SFC) to be **2**.



Scheme 2. Reagents and conditions: (a) Protease from bovine pancreas, potassium phosphate buffer (0.1 M, pH 7.2), MeCN, 30 °C, >98% ee, 44%; (b) $Pd(OAc)_2$ (cat.), racemic-2-(di-t-butylphosphino)-1,1′-binaphthyl (cat.), Cs_2CO_3, PhMe, 115 °C, 16 h, 81%; (c) $LiOH{\cdot}H_2O$, THF, MeOH, H_2O, rt, 1 h, 96%.



Scheme 3. Reagents and conditions: (a) (−)-Cinchonidine (0.5 equiv), EtOAc, rt, 16 h, 96% ee, 44%; (b) Recrystallization from EtOAc, >99% ee, 91%.



Scheme 4. Reagents and conditions: (a) EDC, DMAP, CH_2Cl_2, rt, 16 h, diastereomer **15** = 44%, diastereomer **16** = 40%.

To obtain enantiomerically pure **2** in crystalline form, an initial set of 30 recrystallization conditions was performed. All crystals obtained from this work were the same polymorph, which had an onset of melting at 104 °C. The large-scale synthesis of **2** was successfully completed by utilizing the diastereomeric separation route. The final material was crystallized from acetone/hexanes to afford crystalline material of suitable purity for the IVT study.

In summary, we have successfully developed three routes to provide optically pure **2**, a molecule with a chiral quaternary stereogenic center. The diastereomeric amide route was chosen and successfully delivered 30–50 g of crystalline material for a rat IVT study.

Acknowledgements

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