ORGANIC LETTERS

2005
Vol. 7, No. 10
1947−1950

Synthesis of PPAR Agonist via Asymmetric Hydrogenation of a Cinnamic Acid Derivative and Stereospecific Displacement of (*S*)-2-Chloropropionic Acid

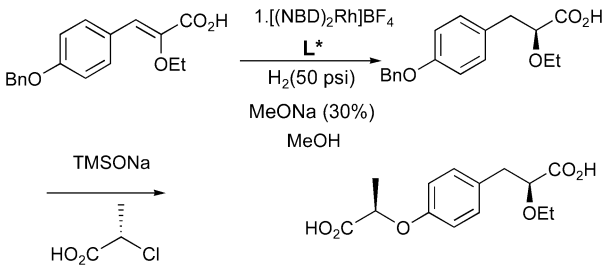
Ioannis N. Houpis,*,† Lawrence E. Patterson,‡ Charles A. Alt,‡ John R. Rizzo,‡ Tony Y. Zhang,‡ and Michael Haurez†

Chemical Product Research and Development, Lilly Development Center, Rue Granbonpre 11, B-1348, Mont. St. Guibert, Belgium, and Lilly Technology Center, B-110, Indianapolis, Indiana 46285

houpis_ioannis@lilly.com

Received February 21, 2005

ABSTRACT



The synthesis of the peroxime proliferator activated receptor (PPAR) α,γ-agonist (1) was accomplished with high enantio- and diastereoselectivity by employing an asymmetric hydrogenation strategy, of an α-alkoxy cinnamic acid derivative, to set the C-2 chiral center. A diastereospecific S_N2 displacement under mild basic conditions established the C-10 stereochemistry without any detectable racemization of the two epimerizable chiral centers.

Peroxime proliferator activated receptor (PPAR) agonists have attracted significant attention in the pharmaceutical industry due to their potential usefulness in the treatment of type 2 diabetes and dislepedimia,[1] and several compounds of this class are now in various stages of development.[2] We have recently described the synthesis of the PPAR agonist **1** via a sequence that utilized the starting material **2** (Scheme 1), which was readily available via several pathways from our laboratory and recent literature precedence.[3] Particular features of this synthesis were the ethylation of **2** to give the ethyl ether **3** via a variation of the Williamson ether synthesis. Despite the fact that the chemistry performed well on the kilogram scale, we were concerned about the

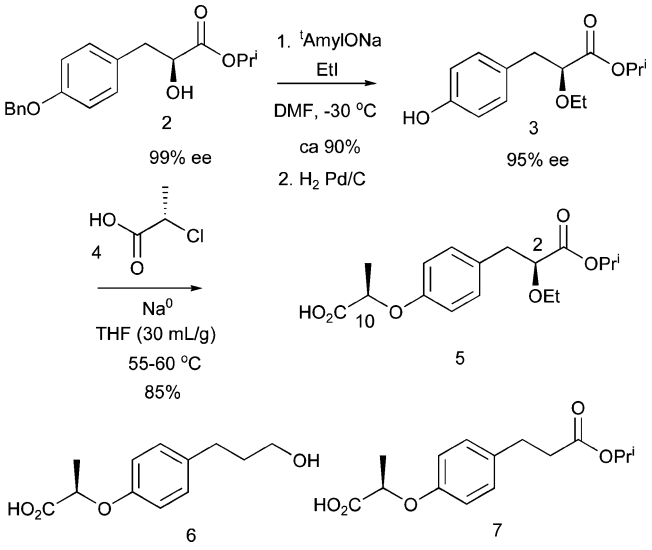
† Lilly Development Center.
‡ Lilly Technology Center.

(1) (a) Lehman, J. M.; Moore, L. B.; Smith-Oliver, T. A.; Wilkinson, W. O.; Willson, T. M.; Kliewer, S. A. *J. Biol. Chem.* **1995**, *270*, 12953. (b) Staels, B.; Dallongeville, J.; Auwerx, J.; Schoonjans, K.; Leitersdorf, E.; Fruchart, J.-C. *Circulation* **1998**, *41*, 5020. (c) Oliver, M. F.; Heady, J. A.; Morris, J. N.; Cooper, J. *Lancet* **1984**, *2*, 600.

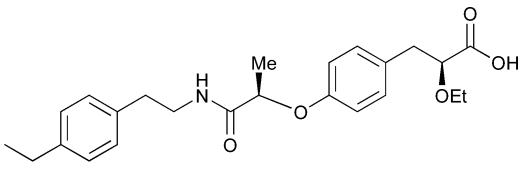
(2) (a) Haigh, D.; Birrell, H. C.; Cantello, B. C. C.; Eggleston, D. S.; Haltiwanger, R. C.; Hindley, R. M.; Ramaswamy, A.; Stevens, N. C. *Tetrahedron: Asymmetry* **1999**, *10*, 1353. (b) Liu, K. G.; Smith, J. S.; Ayscue, A. H.; Henke, B. R.; Lambert, M. H.; Leesnitzer, L. M.; Plunket, K. D.; Willson, T. M.; Sternbach, D. D. *Bioorg. Med. Chem. J.* **2001**, *11*, 2385. (c) Sauerberg, P.; Pettersson, I.; Jeppeses, L.; Bury, P. S.; Mogensen, J. P.; Wassermann, K.; Brand, C. L.; Sturis, J.; Woeldike, H. F.; Fleckner, J.; Andersen, A.-S. T.; Mortesen, S. B.; Svensson, L. A.; Rasmussen, H. B.; Lehmann, S. V.; Polivka, Z.; Sindelar, K.; Panajotova, V.; Ynddal, L.; Wulff, E. M. *J. Med. Chem.* **2002**, *45*, 789. (d) Deusen, H.-J.; Zundel, M.; Valdois, M.; Lehmann, S. V.; Weil, V.; Hjort, C. M.; Ostergaard, P. R.; Marcussen, E.; Ebdrup, S. *Org. Process Res. Dev.* **2003**, *7*, 82.

10.1021/ol050367e CCC: $30.25
Published on Web 04/15/2005

Scheme 1. Initial Approach to **5**



robustness of this reaction, as some laboratory work indicated significant variability in the retention of optical purity of the existing C-2 center. Furthermore, the key coupling of **3** and **4**, to produce intermediate **5**, also posed particular challenges. Namely, the reaction utilized pyrrophoric Na^0 and, more importantly, had to be performed at substantial dilution (30 mL/g) in order to avoid the formation of two impurities resulting from single electron transfer reaction, **6** and **7**. Moreover, we were particularly concerned about the effect of the Na^0 quality, particularly its potassium content, on the formation of **6** and **7**. Therefore, for economic reasons and due to the usefulness of the α-alkoxy, and particularly ethoxy and methoxy, ester functionality in PPAR agonists and coagonists as well as other biologically significant molecules,[4] we sought a general solution to the introduction of that functionality without the intermediacy of the alcohol **2** and the need for a difficult alkylation reaction.

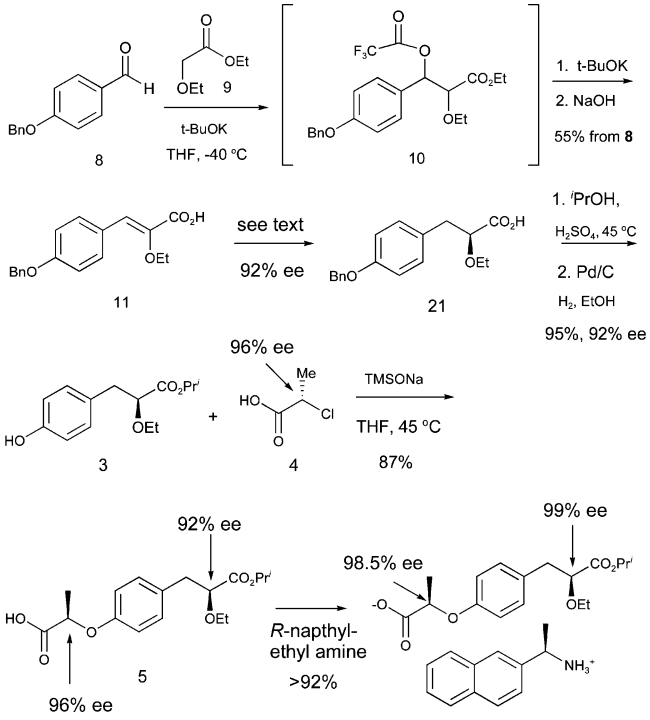


1

In this Letter, we would like to describe our synthesis of intermediate **5** via an asymmetric hydrogenation of **11** and subsequent coupling conditions with **4** to this key intermediate while preserving the epimerizable chiral centers and avoiding the formation of the single electron transfer byproducts.

The key intermediate **11** was synthesized via the route shown in Scheme 2. A mixture of the readily available

Scheme 2. Optimized Synthesis of **5**



benzaldehyde derivative **8** and ethoxy ethyl acetate **9** was added to a cold (−40 °C) solution of potassium *t*-butoxide in THF to produce the adduct, which was treated in situ with trifluoroacetic anhydride to give **10**. Compound **10** was not isolated; instead, the reaction was warmed to ambient temperature and treated with an additional amount (4 equiv) of potassium *t*-butoxide to effect the elimination to the corresponding α,β-unsaturated ester. This crude material was hydrolyzed in MeOH−5 N NaOH to afford the desired acid, **11**, in ca. 50−55% overall yield. It is worth noting that only the (*Z*)-isomer was detected in the crude reaction mixture. With the starting material in hand, we pursued the asymmetric hydrogenation reaction.

Despite the explosion in the development of chiral ligands for the asymmetric hydrogenation of a variety of olefin derivatives, relatively few examples exist for the successful reduction of α-alkoxy cinnamoyl derivatives.

More commonly, these enoate asymmetric reductions[5] contain at the α-position an acetamido, acetyl, or other functionality (e.g., MEM protecting group) that coordinates the transition metal and thus provides an ordered transition

(3) (a) Aikins, J.; Haurez, M.; Rizzo, J.; Van Hoeck, J. P.; Brione, W.; Kestemont, J.-P.; Stevens, C.; Lemaire, X.; Forst, M.; Houpis, I. N. *J. Org. Chem.*, in press. (b) Liang, T.; Deng, L. *J. Am. Chem. Soc.* **2002**, *124*, 2870.

(4) Linderberg, M. T.; Moge, M.; Sivadasan, S. *Org. Process Res. Dev.* **2004**, *8*, 838. Lindenber, M. T.; Moge, M.; Sivadasan, S. *Org. Process Res. Dev.* **2004**, *8*, 838.

(5) For recent reviews describing a plethora of ligand and metal systems, see: (a) Noyori, R.; Kitamura, M.; Ohkuma, T. *PNAS* **2004**, *101*, 5356. (b) Studer, M.; Blaser, H.-U.; Exner, C. *Adv. Synth. Catal.* **2003**, *345*, 45. (c) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindleer, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103. (d) Crepy, K. V. L.; Imamoto, T. *Adv. Synth. Catal.* **2003**, *345*, 79. (e) Sturm, T.; Weissensteiner, W.; Spindler, F. *Adv. Synth. Catal.* **2003**, *345*, 160. (f) Genet, J.-P. *Acc. Chem. Res.* **2003**, *36*, 908.

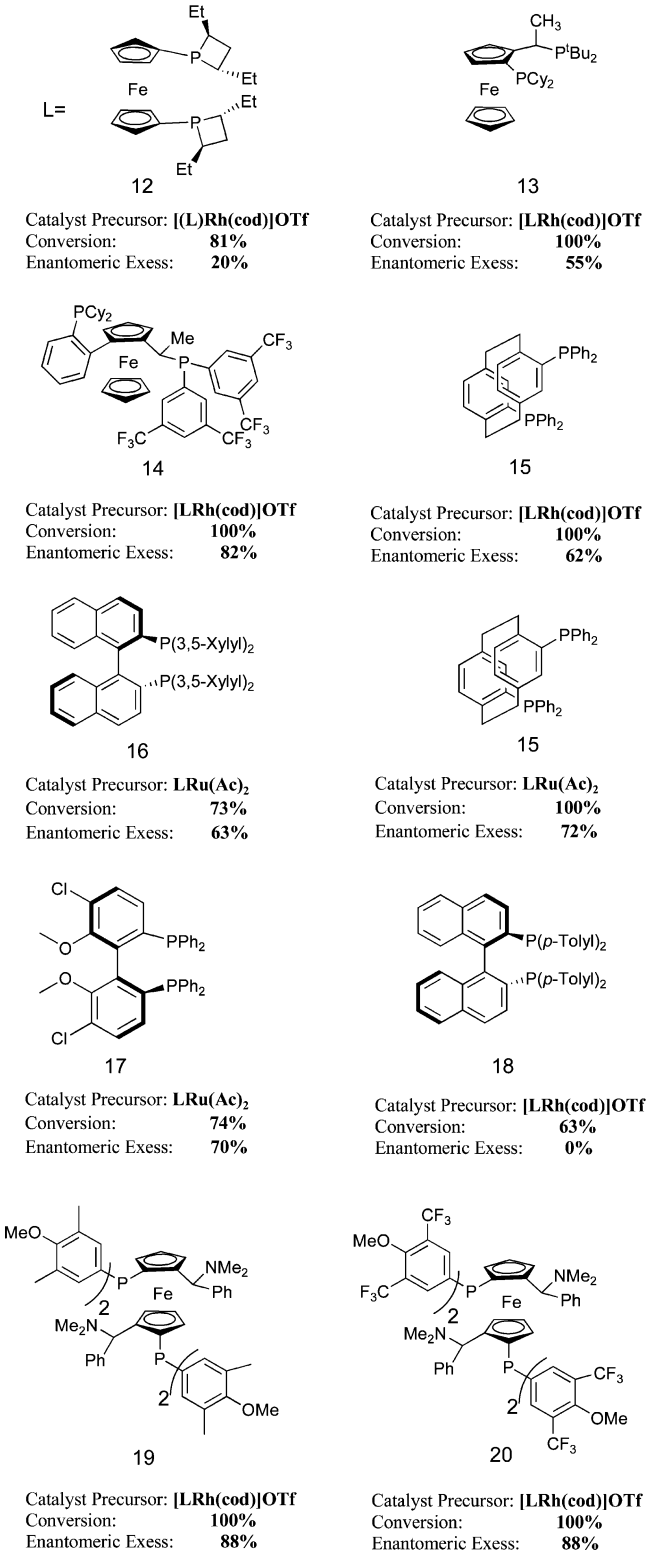


Figure 1. Results of the hydrogenation screen.

state that enhances enantioselectivity. To our knowledge, α-alkoxy cinnamic acid derivatives have not been widely described.

Our initial attempts to effect the desired transformation utilized cationic Rh(I) and Ru(I) catalyst precursors and the BiNAP, BiPHEP, and DuPhos family of ligands that have been successfully used in the reduction of MEM-protected hydroxymethyl enoates in the multiton scale.[6] Unfortunately, in our case, these ligands afforded the product in low conversion and low enantiomeric excess under a variety of conditions. Furthermore, the ferrotane analogue **12** gave 81% conversion and <20% ee.

As a consequence, a hydrogenation screen of over 250 catalysts and conditions was performed with our catalyst libraries under our standard conditions.[7] Figure 1 shows some representative results of our screen.

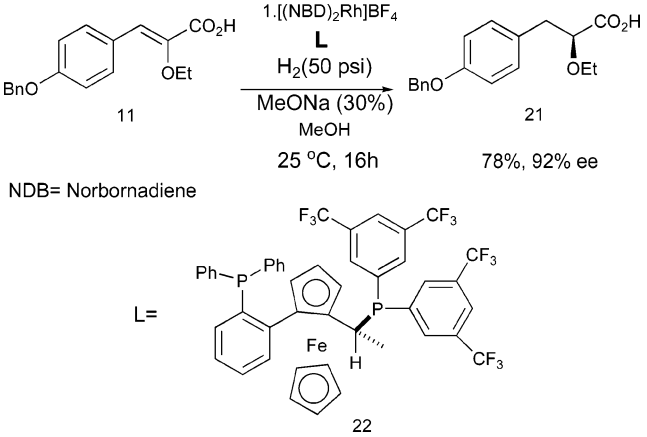
Similarly to the Duphos family of ligands, Jopishos and BiNAP[8] derivatives (**13** and **15**−**18** in Figure 1) gave either low conversion or low enantiomeric excess under our conditions. Gratifyingly, the Rh-based systems using the aforementioned ligand motifs afforded conversions and asymmetric induction between 70 and 80% ee. It was the MandyPhos family of ligand that gave us the first truly useful enantiomeric excess (ligands **19** and **20**, 88% ee, Figure 1). Table 1 shows a summary of our initial screen with MandiPhos ligand **19**.

Table 1. **11** ⟹ **21** with MandyPhos[$(COD)_2$Rh]OTf **19** at 25 °C

solvent	pressure	conversion	% ee	TON	TOF
MeOH	700 psi	100%	88%	2800	140
MeOH	200 psi	59%	86%		
EtOH	700 psi	100%	83%		
*i*PrOH	700 psi	100%	79%		
dioxane	700 psi	100%	71%		
CH_3CN	700 psi	100%	83%		
c-hexane	700 psi	100%	79%		

However, it was finally the Valphos ligand **22** (Scheme 3) that gave the best results upon optimization of the solvent (MeOH), pressure (50 psi, Table 1 shows little effect of pressure on ee), and additives (Et_3N and MeONa). To date,

Scheme 3. Hydrogenation of **11** with Rh−Valphos



the finalized process involves the addition of a solution of $[(NDB)_2Rh]BF_4$ and the ligand (1:1.1 ratio) to a mixture of the acid and MeONa (10 mol %) in degassed MeOH. Under these conditions, high pressures are not required as in the case of the MandyPhos ligand. Therefore, the homogemeous mixture was treated with H_2 at 50 psi at ambient temperature for 16 hours to afford the crude acid, which was transformed to the product **21** in 78% yield.

Capillary electrophoresis and chiral HPLC methodologies established the enantiomeric excess at ca. 92%. Although our final process to the synthesis of **1** can easily accommodate such optical purity, an upgrade to ca. 98% ee can be obtained by formation of the D-alaninol salt in ethanol (94% yield). The latter allowed us to establish the absolute stereochemistry of **21** by X-ray defraction analysis. It is worth noting that in the absence of MeONa, only 33% of **21** was produced, indicating that formation of the carboxylate is essential for the success of this process. Release of the salt and esterification with *i*PrOH and catalytic H_2SO_4, followed by *heterogeneous* catalytic hydrogenation with 10% Pd/C in EtOH, afforded **3** in nearly quantitative yield. *No epimerization was observed at the ciral center during the esterification*.

With the latter in hand, we set out to identify conditions that would effect the desired coupling reaction with complete inversion at the (*S*)-2-chloropropionic (**4**) acid center while avoiding epimerization of the starting materials or product and the possibility for single election transfer.

A number of bases and solvents were evaluated in the coupling of **3** and **4** in an automated fashion in a ChemSpeed multireactor system. The bases used included K_2CO_3, Cs_2CO_3, AcONa, NaOH (under phase-transfer catalysis conditions), LDA KHMDS, NaHMDS, *t*BuOK, and *t*AmylONa, while solvents and solvent mixtures varied from THF, toluene, and 2-methyl-THF to DMSO, methyl isobutyl ketone, and CH_3CN.[9]

Despite these efforts, the results were disappointing, ranging from no reaction with the lower pK_a bases to extensive hydrolysis (NaOH) to significant epimerization at both C-2 and C-10 with the stronger bases.

Finally, we discovered that TMSONa in THF afforded superior results to all the methods investigated, including the original Na^0 procedure (Scheme 2). Indeed deprotonation of the phenol with 2 equiv of TMSONa at ambient temperature in THF produced the phenoxide as a homogeneous solution. Warming of the solution to 45 °C with slow (*S*)-2-chloropropionic acid addition resulted in a thin slurry of the sodium chloropropionate. The reaction proceeded to completion overnight to give a good yield of the desired compound with *complete retention the optical purity at both chiral centers*.[10] Solvent and counterion screens indicated that the original conditions were optimal. For example, TMSOK had the same reactivity in THF; however, it is more expensive and less soluble in THF than the Na analogue. Similarly, nonpolar and polar aprotic solvents gave lower yields of the coupling product or an increased number of impurities. From an operational standpoint, the reaction is much more robust, as the use of the homogeneous base avoided some of the issues observed in our previous procedure such as coating of the Na metal by the precipitation of Na−chloropropionate. It is worth noting that none of the SET reaction products **6** or **7** were detected and the reaction no longer exhibited any sensitivity in the concentration. ReactIR experiments have established that the reaction does not proceed via an α-lactone intermediate,[11] while correlation experiments have established the inversion of configuration at the propionate center.

Diastereomeric upgrade and chemical purification of **5** can be easily accomplished via the (*R*)-(+)-naphthylethylamine salt in isopropyl acetate. That intermediate can be used to conclude the synthesis of the final active pharmaceutical ingredient, **1**, as we have described previously.[3]

In conclusion, we have been able to complete the synthesis of **1** through the direct access of the cinnamic acid derivative **21** via an asymmetric hydrogenation reaction. We have also demonstrated the stereospecific S_N2 displacement of (*S*)-2-chloropropionic acid by phenoxide using TMSONa as the base.

Supporting Information Available: Experimental procedures to the final product **1**, NMR spectra and chiral HPLC spectra, X-ray data for the D-alaninol salt of **21**, and proof of the absolute configuration of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050367E

(6) Bulliard, M.; Laboue, B.; Lastanet, J.; Roussiasse, S. *Org. Process Res. Dev.* **2001**, *5*, 438.

(7) Screens were typically performed on 0.05 mmol of substrate in MeOH at 200 psi with 2 mol % catalyst precursor and 2 mol % ligand, at ambient temperature on an Endevor multireactor system

(8) BiNAP itself afforded 60 and 40% conversion with Rh(I) and Ru(I), respectively. The product was racemic.

(9) For examples of displacement of activated lactic acid or nonracemic 2-halo propionic acid derivatives, see: (a) Effenberger, F.; Burkard, U.; Willfahrt, J. *Angew. Chem.* **1983**, *95*, 50. (b) Burkard, U.; Effenberger, F. *Chem. Ber.* **1986**, *119*, 1594. (c) Sato, T.; Otera, J. *J. Org. Chem.* **1995**, *60*, 2627 and references therein. (d) Otera, J.; Nakazawa, K.; Sekoguchi, K.; Orita, A. *Tetrahedron* **1997**, *53*, 13633. (e) Larcheveque, M.; Petit, Y. *Synthesis* **1991**, 162. (f) Nestler, H. J.; Hoerlein, G.; Handte, R.; Bieringer, H.; Schwerdtle, F.; Langelueddeke, P.; Frisch, P. U.S. Patent US005712226A, 1998, and references therein.

(10) Commercially available (*S*)-2-chloropropionic acid was determined to be of 96% ee. Within the limit of detection of our HPLC method (ca. 0.1%), there was no erosion of the enantiomeric excess, indicating complete inversion of stereochemistry at C-10. The C-2 center was similarly unaffected.

(11) For formation and identification of α-lactones, see: Chapman, O. L.; Wojtkowski, P. W.; Adam, W.; Rodriquez, O.; Rucktaeschel, R. *J. Am. Chem. Soc.* **1972**, *94*, 1365. α-Lactones have also been postulated in solvolysis reactions of α-bromo propionates: Grunwald, E.; Winstein, S. *J. Am. Chem. Soc.* **1948**, *70*, 841.