Tetrahedron Letters 50 (2009) 6329–6331

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Diastereoselective, large scale synthesis of β-amino acids via asymmetric enamide hydrogenation as α2δ ligands for the treatment of generalized anxiety disorder and insomnia

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ARTICLE INFO

Article history:
Received 7 July 2009
Revised 27 August 2009
Accepted 28 August 2009
Available online 2 September 2009

Keywords:
β-Amino acid
α2δ Ligand
Asymmetric enamide reduction
Rh catalyst
Generalized anxiety disorder
Insomnia

ABSTRACT

The syntheses of β-amino acids **1** and **2** are presented by means of an alternative route to the asymmetric Michael-addition route reported in the preceding article. These two compounds, which bind to the α2δ subunit of calcium channels and have important medical applications, have been prepared on multi-kilogram scale in our pilot plant through a new approach that introduces the chirality at the β-carbon via asymmetric hydrogenation of an enamide precursor. Two Rh-based catalysts, (*R*)-mTCFP-Rh(COD)BF_4 and (*R*)-binapine-Rh(COD)BF_4, were found to be superior in this transformation and gave very high diastereoselectivities. The process development for catalyst selection is described.

In the preceding Letter,[1] we reported the synthesis of β-amino acids **1** and **2** through two key steps: first, an asymmetric Michael addition that set the stereochemistry at carbon 5; second, an asymmetric *aza*-Michael addition that generated the second stereocenter at the 3 position. This efficient route allowed for the preparation of multi-kilogram quantities of API to support clinical studies. We now wish to report a second approach for the synthesis of these two compounds on scale, where the key step is the asymmetric hydrogenation of an enamide intermediate. This methodology is shown in Scheme 1 for the preparation of **1** as a representative example.

The synthesis started with the activation of (*R*)-3-methylhexanoic acid (**3**)[2] with 1,1′-carbonyldiimidazole (**4**) to give imidazolide **5** which, without isolation, was treated with potassium ethyl malonate (KEM, **6**) in the presence of $MgCl_2$[3] to afford β-keto ester **7** in excellent yield. This transformation required longer reaction times on scale and it was speculated that the reason could be that the CO_2 from the imidazolide solution might form adduct **11** of KEM (Scheme 2). This was confirmed by the experiments that showed that when the vessel was purged with nitrogen gas, the reaction proceeded at a faster rate than when CO_2 was added to the vessel (Fig. 1).

The formation of enamine **8** was accomplished by treating **7** with ammonia in ethanol at 55 °C in a pressure vessel.[4] Previously, NH_4OAc had been employed as the nitrogen source, but ammonia is a more desirable reagent since it produces no solid waste, eliminates the need for a filtration step to remove the inorganics, and facilitates the equipment clean-up. Enamine **8** then underwent the reaction with acetic anhydride in octane at 100 °C to give enamide **9** as a 95/5 ratio of *Z*/*E* diastereomers.[5] The solvent was changed from toluene to octane after it was found that residual toluene poisoned the Rh catalyst in the subsequent hydrogenation.[6]

With intermediate **9** on hand, we proceeded to investigate the key asymmetric hydrogenation step. Several Rh-based catalysts have been reported to reduce enamides with high enantioselectivity.[7] A ligand screen[8] revealed that (*R*)-mTCFP (**12**)[9,10] and (*R*)-binapine (**13**)[5,11] gave the best results for reducing enamide **9** to acetamide **10**, with Rh(COD)BF_4 as the catalyst (Fig. 2).

It was observed that (*R*)-mTCFP gave much faster reactions than (*R*)-binapine and 100% conversion was consistently achieved. On the other hand, during preliminary experiments the latter gave

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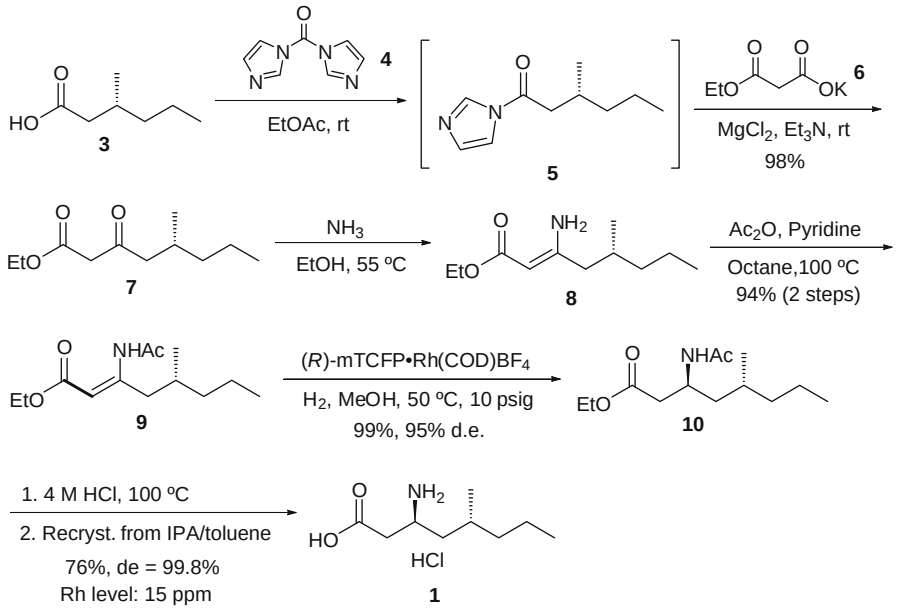
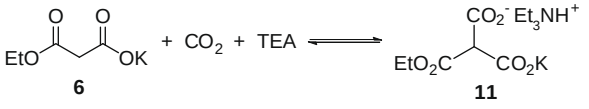
doi:10.1016/j.tetlet.2009.08.111



Scheme 1. Synthesis of **1** through the asymmetric enamide hydrogenation approach.



Scheme 2. Reaction between KEM (**6**) and CO_2 in the presence of TEA to produce ammonium salt **11**.

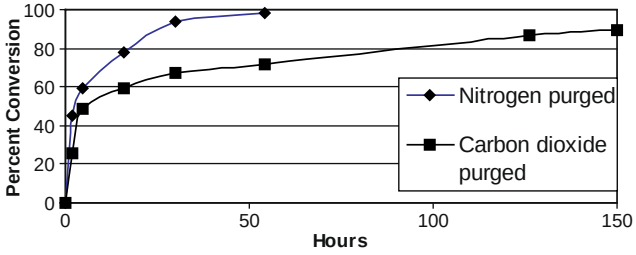


Figure 1. β-Keto ester **7** formation: conversion rate versus reaction time in the presence or absence of CO_2.

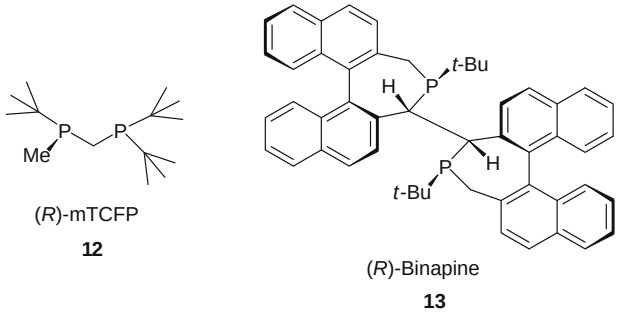


Figure 2. (*R*)-mTCFP and (*R*)-binapine ligands employed in the asymmetric hydrogenation step.

slightly better diastereoselectivity (95–96% vs 92–94%). Because the undesired (3*R*,5*R*)-isomer was easily removed from the product in subsequent steps and due to the availability and lower cost of (*R*)-mTCFP, this was the ligand of choice for our process.[12] In addition, the (*R*)-mTCFP/Rh(COD)BF_4 combination had been previously shown to provide high ee for mixtures of (*E*)- and (*Z*)-enamides.[10b]

Further screening of the reaction conditions showed that the concentration had little or no effect on this transformation and that in methanol spiked with 5% water, the hydrogenation was faster and gave better diastereoselectivity (95% de). The reaction is also dependent on the pressure and temperature, and the best results were obtained between 5 and 15 psi and 50 °C. Higher pressures and lower temperatures had a detrimental effect on the selectivity of the process.[13] Finally, the substrate/catalyst (s/c) ratio was also investigated. No erosion of the selectivity was observed when the s/c ratio was increased up to 1000/1. A target was set of achieving $\geqslant$92% de for this process in the pilot plant and this goal was successfully accomplished at 10 psig in methanol at 50 °C and a substrate/catalyst ratio of 1000/1.[14]

With the asymmetric hydrogenation step completed, the final acidic hydrolysis of acetamido ester **10** was carried out in 4 M HCl at 100 °C to give **1**. This molarity gave faster hydrolysis than more concentrated solutions and, after a toluene wash of the aqueous phase to remove some organic impurities, the product could be crystallized from the reaction mixture as the HCl salt by adding 37% HCl.

Unfortunately, from this crystallization protocol HCl salt **1** showed a Rh content in the 115–847 ppm, which was considerably higher than our specification of $\leqslant$20 ppm. Several approaches were considered to reduce the level of this metal in the API: (a) treatment of the aqueous HCl solution after acetamide and ester hydrolysis (Table 1); (b) isolation of the HCl salt as described above and treatment of a 2-propanol (IPA) solution of **1** (Table 2); and (c) recrystallization from an IPA solution through the addition of an anti-solvent (Table 3).

Several options were promising in the laboratory experiments to accomplish this goal. Thus, the treatment of an aqueous HCl solution of **1** with Darco G60 at 35 °C for 30 min was able to reduce the Rh level from 847 to 16 ppm (Table 1, entry 6). A second alternative was passing an IPA solution of **1** through a carbon cartridge, which resulted in material with only 23 ppm of Rh metal (Table 2, entry 4). Finally, it was found that a simple recrystallization from IPA/toluene was able to give less than 10 ppm from material that initially con-

Table 1
Treatment of HCl solution of **1** to reduce Rh level

Entry	Initial Rh level (ppm)	Isolation method	Final Rh level (ppm)
1	847	1:1 Aqueous HCl/37% HCl	357
2	847	1:2 Aqueous HCl/37% HCl	353
3	604	1:2 Aqueous HCl/37% HCl	329
4	117	Aqueous HCl, Magnesol filtration	45
5	115	Aqueous HCl, Fuller's Earth filtration	40
6	847	Aqueous HCl with Darco G60, 35 °C, 30 min	16
7	847	Aqueous HCl with Darco G60, 30 °C, 1 h	108

Table 2
Treatment of IPA solution of **1** to reduce Rh level

Entry	Initial Rh level (ppm)	Isolation method	Final Rh level (ppm)
1	130	Filter through silica 10 times, rt	94
2	130	Filter through Darco G60/celite, 10 times, rt	117
3	130	Filter through Darco G60/silica, 10 times, rt	115
4	60	Carbon cartridge (52S), one filtration	23

Table 3
Recrystallization of **1** from IPA/toluene to reduce Rh level

Entry	Initial Rh level (ppm)	Isolation method	Final Rh level (ppm)
1	353	IPA/toluene mixture, no additional treatment	7

tained 353 ppm of Rh (Table 3, entry 1). Due to the operational simplicity of this last option, it was decided to implement it in our pilot plant, and API with only 15 ppm of Rh was obtained. At the same time, the optical purity was upgraded to 99.8% de.

In conclusion, a scalable route for the preparation of α2δ ligands **1** and **2** has been described that represents an alternative to the Michael-addition route disclosed in the preceding Letter. The key step in the synthesis is the asymmetric reduction of an enamide intermediate to introduce the chirality at the β-carbon. An efficient protocol has been developed that employs the ligand (*R*)-mTCFP, developed in Pfizer laboratories, and $Rh(COD)BF_4$ as catalyst to give, after amide hydrolysis, **1** and **2** in very high de and low Rh content. The feasibility of this technology has been demonstrated in our pilot plant to produce kilogram quantities of API to advance this program.

Acknowledgments

The authors thank Peter Wuts, Tom Mulhern, Jim Zeller, Dan Belmont, Denis Sobieray, Margaret Evans, and Sandra Jennings for helpful discussions during the implementation of this project, and Mark Maloney and Phil Nixon for reviewing this manuscript.

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9. (*R*)-mTCFP ligand (**12**) refers to 'methyltrichickenfootphos', as it is known in Pfizer laboratories. This name is derived from visual inspection of the ligand and the association of *tert*-butyl groups with chicken feet.
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12. Although the selectivity was lower for the (*R*)-mTCFP ligand, the conditions were not fully optimized and the turnover was higher than that observed for (*R*)-binapine. It is also possible that the (*R*)-mTCFP ligand was not of 100% optical purity, as this assay and preparation were still under development. The authors believe that the lower turnover for the (*R*)-binapine catalyst is due to the poisoning of rhodium by the aryl groups of the ligand, as similar poisoning was also observed for low levels of toluene.
13. The correlation of lower pressure with higher selectivity has been observed by others (see: Heller, D.; Holz, J.; Komarov, I.; Drexler, H.-J.; You, J.; Drauz, K.; Borner, A. *Tetrahedron: Asymmetry* **2002**, *13*, 2735), but the authors believe that the observation about the water content is unique to this application.
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