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The Development of a Practical Multikilogram Synthesis of the Chiral β-Amino Acid Imagabalin Hydrochloride (PD-0332334) via Asymmetric Hydrogenation

Melissa Birch, Stephen Challenger,* Jean-Philippe Crochard, David Fradet, Hayley Jackman, Amy Luan, Evelyn Madigan, Neil McDowall, Kevin Meldrum, Charles M. Gordon, Magnus Widegren, and Stephen Yeo

Department of Chemical Research and Development, Pfizer World Wide Research and Development, Sandwich Laboratories, Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom

ABSTRACT: The development and implementation of a robust process for the manufacture of metric ton quantities of the α2δ ligand imagabalin hydrochloride **4** is described. Key aspects of the synthesis include a chromatography-free, two-step telescoped process to prepare a mixture of *Z*:*E*-enamides **7** followed by a robust asymmetric hydrogenation with the rhodium-trichickenfootphos catalyst **8** to install the (3*S*)-stereocentre. Hydrolysis of the acetamide and ester protecting groups in the final step followed by isolation and recrystallisation of the hydrochloride salt gave high purity **4** in 40−50% overall yields.

INTRODUCTION

The use of compounds that bind to the α2δ subunit of voltage-gated calcium channels are of considerable interest in the treatment of pain, fibromyalgia, and a variety of psychiatric and sleep disorders. As part of a program to identify second-generation analogues of the marketed α2δ ligands, gabapentin (Neurontin) **1**[1] and pregabalin (Lyrica) **2**,[2] the β-amino acids **3**[3] and imagabalin hydrochloride (PD-0332334) **4** were nominated as development candidates (Figure 1). Imagabalin hydrochloride was advanced into clinical development for the treatment of generalized anxiety disorder (GAD). GAD is the most commonly encountered anxiety disorder and has significant negative social consequences and economic costs.[4]

A synthetic route to imagabalin hydrochloride **4** was required that was suitable for rapid scale-up to support preclinical and clinical evaluation. The requirement to prepare significant quantities of **4** (driven by a relatively high projected dose) and cost of goods concerns were important factors in route selection. The key synthetic challenge was the control of relative and absolute stereochemistry of the two stereocentres in **4** and an approach involving an asymmetric synthesis rather than a resolution-based approach was considered to more likely meet cost of goods targets. Also, the paucity of crystalline intermediates in potential routes to the synthesis of this class of compound limited purification options and was a significant issue in the control of achiral and chiral purity. The lack of a chromophore also presented significant analytical challenges. Three different routes were developed and used to support the early development programme.

The original medicinal chemistry route to imagabalin hydrochloride **4** involved a ten-step linear synthesis from (*S*)-(−)-β-citronellol with an overall yield of 21%.[5] In this route, the (5*R*)-stereocentre was obtained from the chiral pool and the (3*S*)-amino stereocentre was installed by a diastereoselective enolate alkylation followed by a Curtius rearrangement. Although the first-generation route allowed for the preparation of kilogram quantities of **4**, the use of toxic chromium(VI) oxide and potentially hazardous reagents hydrogen peroxide and diphenylphosphoryl azide (DPPA), prohibited implementation and further scale-up. A second-generation route to **4** was developed at the Pfizer Michigan laboratories to address these issues.[5a,6] The two chiral centers in this approach were introduced through diastereoselective asymmetric Michael and *aza*-Michael addition reactions. While this route had been demonstrated on multikilogram scale, there were still concerns as to whether it would be capable of delivering sufficient material to support the development programme and long-term meet the required cost of goods targets. In particular, the use of two cryogenic steps, moderate selectivity (92% de) in the key *aza*-Michael addition and the need to upgrade diastereoisomeric purity was deemed prohibitively expensive.

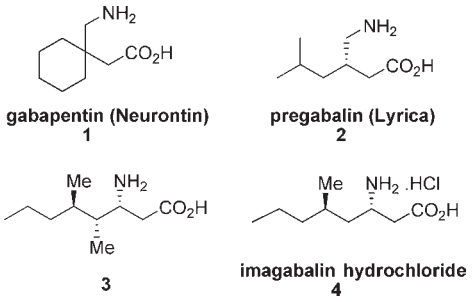

Figure 1. α2δ-Ligands neurontin **1**, pregabalin **2**, **3** and imagabalin hydrochloride **4**.

The asymmetric reduction of β-(acylamino)acrylates (enamides) is an established method for the synthesis of chiral β-amino acid derivatives[7] and a number of chiral Rh,[8] Ru,[9] and Cu[10] catalysts have been reported that are capable of reducing mixtures of *E*- and

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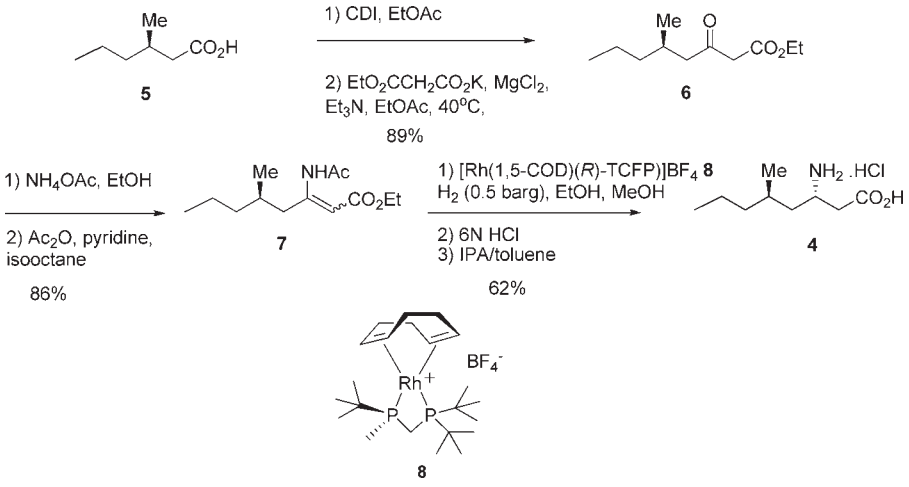
Scheme 1. Enamide asymmetric hydrogenation route to 4



Z-enamides with high enantioselectivity and low catalyst loading, thus obviating the need to prepare isomerically pure substrates. A more expedient and cost-effective route to **4** was rapidly developed within the Process Research group that introduced the chirality at the β-carbon via asymmetric hydrogenation of an enamide precursor (Scheme 1).[11] Herein, we report our efforts to develop this enantioselective route and describe its successful implementation on scale to manufacture 1.6 t of imagabalin hydrochloride **4**.

(*R*)-3-Methylhexanoic acid **5** was a key intermediate in the original medicinal chemistry and third-generation enamide hydrogenation routes to **4**. Through the duration of this project, metric ton quantities of **5** were purchased from commercial suppliers. There are a number of published procedures for the preparation of optically active **5** or its ester derivatives.[12] The route used to manufacture this material on scale involved accessing (*S*)-(+)-2-pentanol using a biocatalytic reduction of 2-pentanone followed by chain homologation via malonate alkylation, hydrolysis and decarboxylation.[12c] The material was purchased to a chiral purity specification of not less than 97% ee, which was shown to give active pharmaceutical ingredient (API) with acceptable chiral purity following downstream processing.

RESULTS AND DISCUSSION

Synthesis of Asymmetric Hydrogenation Substrate 7. The published[11a] two-step procedure was followed to synthesise the enamide asymmetric hydrogenation substrate **7** from (*R*)-3-methylhexanoic acid **5**. The first step involved the preparation of β-ketoester **6** via the acylation of potassium monoethyl malonate with the imidazolide derived from **5** in the presence of magnesium chloride and triethylamine. Ethyl acetate was selected as the solvent of choice based on the original work of Wemple.[13] The use of excess reagents (potassium monoethyl malonate 1.4 equiv, $MgCl_2$ 1.4 equiv, Et_3N 1.6 equiv relative to the most expensive component **5**) and an increase in reaction temperature to 40 °C were necessary to provide high-purity product **6** in laboratory yields consistently greater than 90%. The urgent need for material to support the clinical development programme lead to the decision to rapidly scale up this modified process in the pilot plant using up to 55 kg (422 mol) input of the acid **5**. It was reported[11a] that this transformation requires longer reaction times on scale-up, and it was postulated that the liberated carbon dioxide, from the imidazolide formation, could react with potassium monoethyl malonate to form a carbonate adduct. To overcome this problem the imidazolide solution was stirred under vacuum (−0.60 barg) for one hour to remove carbon dioxide prior to transfer to a slurry of the monoethyl malonate salt in ethyl acetate (see Experimental Section for details). In addition, representative sampling from the heterogeneous mixture to confirm reaction completion was challenging and was assessed only after quench of the reaction with aqueous hydrochloric acid. A flexible workup procedure was developed, with pH monitoring (pH of aqueous phase >6) and variation of the number of aqueous $NaHCO_3$ washes depending on the amount of residual unreacted **5**.[14] The purification of β-ketoester **6** by distillation under vacuum has been reported on a kilogram scale.[15] However, this was considered impractical with the equipment available, and moreover, the ethyl acetate solution of the product **6** was considered to be of suitable quality to be telescoped directly into the amidation step without further purification.

This process was found to give variable yields on scale-up (assayed yields 72−99%, 15 batches). However, it was considered acceptable in the short term and was used to manufacture over one metric ton of intermediate **6** in the pilot plant. The heterogeneous nature of this reaction posed a significant robustness risk to further scale-up, and also the process suffered from the disadvantage of low throughput (24 mL/g of ethyl acetate with respect to **5**) and long cycle time.

Our concerns over the robustness of this process on commercial scales were initially unfounded. The high demand for the candidate **4** and time constraints dictated that the process was rapidly transferred to a commercial manufacturing facility. The process was successfully run on up to 270 kg (2,073 mol) input of **5** in a 12500-L glass-lined reactor (impeller motor power 23 kW, P/V = 2.9 W/L), without incident, to manufacture a total of 1.8 t of **6** in 88% average yield (85.5−91.3%) over five batches. However, a second manufacturing campaign required a change to the equipment train for this step, and a 16000-L vessel (impeller motor power 16 kW, P/V = 1.6W/L) was used with poorer mixing characteristics; the batch size was increased by 30%. A significant issue occurred during the reaction in the larger vessel when the agitator failed due to a high load and insufficient mixing capacity. This result confirmed our concerns over the ability to scale up this process due to the physical characteristics of the reaction mixture. Whilst alternative

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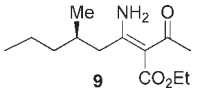


Figure 2. C-Acylated impurity 9.

solvents or mixed-solvent combinations were considered for this reaction, a homogeneous process was preferred. Work towards the development of an efficient homogeneous process to prepare β-ketoester **6** from **5**, involving Meldrum's acid chemistry will be reported in a subsequent communication.

Amination of β-ketoester **6** was achieved by diluting the ethyl acetate product solution from the previous step with ethanol (5 L/kg) and reacting with ammonium acetate (2.0 equiv) at 60 °C for 4 h. The reaction was concentrated, followed by solvent switch to 2,2,4-trimethylpentane (isooctane) and the excess ammonium acetate removed by filtration. Addition of acetic anhydride (2.0 equiv) and pyridine (2.7 equiv) and heating to 95 °C for 12 h led to formation of the desired enamide **7** in typical assay yields of 80−85%. The product **7** was isolated as a mixture of *Z*- and *E*-enamides (*Z*:*E* ratio approximately 5−6:1 by ^{1}H NMR) in isooctane solution after quenching the reaction with water and incorporating an acidic wash to remove pyridine. Pyridine was shown to be an inhibitor in the subsequent asymmetric hydrogenation step, and its level in the isolated product solution was controlled to less than 100 ppm. Dilute sulfuric acid was used as the acidic wash instead of hydrochloric acid due to the known sensitivity of rhodium-bisphosphine catalysts to chloride.[16] A significant impurity (less than 5 area %) in the process was found to be the *C*-acylated compound **9** (Figure 2). The limited purification options for intermediate **7** dictated that the isooctane product solution was solvent switched to ethanol by distillation and the concentrated product solution telescoped directly into the asymmetric hydrogenation step without further purification. This process was successfully scaled up in the pilot plant and in commercial manufacturing facilities on a scale of up to 450 kg (2246 mol) input of **6**. A total of 1.6 t of **7** was manufactured in the commercial facility in 81% average yield (79.1−84.7%) over four batches.

Asymmetric Hydrogenation of Enamide 7. An initial asymmetric hydrogenation screen on the *E*:*Z* mixture of enamides **7** with a limited series of chiral cationic rhodium complexes identified three catalysts, [((*R*)-TCFP)Rh(COD)]BF4 **8**[17] (92−94% de), [((*R*)-binapine)Rh(COD)]BF_4[18] (96−98% de) and [((*S*,*S*,*R*,*R*)-tangphos)Rh(COD)]BF_4[19] (94−97% de) that gave the (3*S*,5*R*)-acetamide product with encouraging levels of diastereoselectivity and conversion.[11] The rhodium catalyst containing the (*R*)-binapine ligand was the most diastereoselective but was not as active in the hydrogenation and required a higher catalyst loading [substrate to catalyst ratio (S/C) 200:1] to achieve complete conversion compared with the catalyst containing the trichickenfootphos (TCFP) ligand (S/C 950:1) under comparable hydrogenation conditions (MeOH, H_2 0.5 barg, 12 h). As part of a development programme in the Pfizer Process Research group on previous substrates, in-house experience was available with a structurally similar enamide that was successfully hydrogenated using a combination of the (*R*)-binapine and (*R*)-TCFP catalysts at 100 kg scale.[11b] However, improvements to the synthesis and optical purity of the commercially supplied (*R*)-TCFP catalyst resulted in an increase in diastereoselectivity with enamide **7** from 92% de to consistently greater than 95% de. It was also noted that an enhancement of diastereoisomeric purity occurred during the isolation and crystallisation of **4** from 94% de to give material of acceptable optical purity (specification >98% de). Given the previous in-house experience with the Pfizer proprietary rhodium-(*R*)-TCFP catalyst, **8**, and its higher activity and commercial availability[20] on multikilogram scale, this catalyst was selected for further scale-up. Optimisation of the hydrogenation conditions led to the use of the rhodium-(*R*)-TCFP catalyst **8** (S/C 950:1) at low hydrogen pressure (0.5 barg) and a temperature of 50−55 °C. The alcoholic solvents, methanol or ethanol, were the solvents of choice, and the hydrogenation proceeded to greater than 95% conversion in typically 12−24 h. The diastereoselectivity was consistent over the temperature range 15−55 °C, and a temperature of 45−55 °C was selected to ensure an acceptable hydrogenation rate at the economically viable S/C ratio of 950:1. Increasing the hydrogen pressure to 3 barg lead to lower diastereoselectivity (91% de), and attempts to reduce the catalyst loading with the crude mixture of enamides gave incomplete conversion. The asymmetric hydrogenation of the separated *E*- and *Z*-enamide substrates was not investigated.

Our concerns over the robustness and sensitivity of this process to catalyst poisoning (oxygen and pyridine are known catalyst poisons) for scale-up, bearing in mind that the crude mixture of *Z*- and *E*-enamides was prepared over two telescoped steps without purification by isolation of a crystalline intermediate, were unfounded. To our delight, the asymmetric hydrogenation protocol used to ensure vigorous exclusion of oxygen (see Experimental Section) worked extremely well and gave consistent results in terms of diastereoselectivity (95% de) and conversion. A total of 30 batches of enamide **7** was successfully hydrogenated in the pilot plant and commercial manufacturing facilities on a maximum scale of up to 420 kg (1740 mol) input of **7** to convert a total of approximately 3.5 t of enamide substrate. A total of approximately 8 kg of catalyst **8** was used in these campaigns. The product solution after concentration was telescoped directly into the following deprotection step without further purification.

Preparation of Imagabalin Hydrochloride 4. The completion of the synthesis of imagabalin hydrochloride **4** was accomplished with the concomitant hydrolysis of the acetamide and ester protecting groups using 6 M hydrochloric acid. Vigorous reaction conditions (reflux 36−48 h) were required to effect this transformation, and two intermediate distillations to lower volume were required to remove ethanol and to drive the hydrolysis of the intermediate amino ester to completion. Once the reaction was complete, two hot (55−60 °C) toluene extractions of the aqueous acidic phase were employed to remove organic soluble impurities. A simple direct crystallisation from a two-phase mixture of aqueous acid and toluene gave **4** in typically 63−72% yields after cooling to −10 °C and ageing for a minimum of 1.5 h. The potential formation of methyl and ethyl chloride was carefully monitored in this process and a specification for alkyl chlorides in the product API set at less than 2 ppm. The purity of isolated product was further upgraded to meet the required specification by recrystallisation from 2-propanol/toluene to provide high-purity imagabalin hydrochloride **4** (18 batches, average yield 78%). A combination of the toluene extractions during the workup of the acidic hydrolysis reaction and subsequent crystallisation and recrystallisation of **4** were sufficient to meet a residual rhodium specification of not more than 10 ppm (ICP-MS) without recourse to the use of metal scavengers.

Significant drawbacks to this route were the long processing times involved in introducing and deprotection of the *N*-acetyl directing group and the significant impact this had on our ability to meet cost of goods targets. Whilst alternative deprotection

conditions were considered, an alternative route based on the asymmetric hydrogenation of an unprotected enamine intermediate was considered highly desirable. Work towards achieving this goal was instigated in parallel with scale-up of the enamide hydrogenation route and will be reported in a subsequent communication.

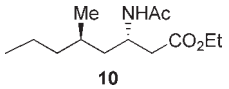
In conclusion, we have modified and developed the published enamide asymmetric hydrogenation route to the α2δ ligand imagabalin hydrochloride **4** and successfully demonstrated this process on-scale to prepare over 1.6 t of **4** in an overall yield in the range of 40−47% over four steps from (*R*)-3-methylhexanoic acid **5**.

EXPERIMENTAL SECTION

All raw materials, reagents, and solvents were purchased from commercial suppliers and used without further purification. All reactions were performed under an atmosphere of nitrogen. ^{1}H NMR spectra were acquired in dimethylsulfoxide-d_6 (DMSO-d_6) using a Varian Inova 500 (499.93 MHz) instrument.

The conversion of (*R*)-3-methylhexanoic acid **5** to ethyl (*R*)-5-methyl-3-oxooctanoate **6** was followed by GC using an Agilent Technologies 6890 or 6850 capillary GC configured with a fast oven ramp option. A nitroterephthalic acid (TPA) modified polyethylene glycol GC column BP21 (FFAP), 25 m × 0.22 mm × 0.25 μm, was used at a constant flow of 2.2 mL/min. The inlet temperature was set at 240 °C, and the oven was warmed from 55 to 240 °C at a rate of 500 °C/min and maintained at 240 °C for 10 min. Helium was used as a carrier gas with hydrogen used for FID detection at 250 °C. Retention times: ethyl (*R*)-5-methyl-3-oxooctanoate **6** 8.2 min; (*R*)-3-methylhexanoic acid **5** 9.1.

The conversion of ethyl (*R*)-5-methyl-3-oxooctanoate **6** to enamide **7** was followed by GC using an Agilent Technologies 6890 capillary GC configured with a fast oven ramp option. A RTX-1 capillary column, 30 m × 0.25 mm × 0.25 μm, was used at a constant flow of 1.4 mL/min. The inlet temperature was set at 250 °C, and the oven was warmed from 125 to 175 °C at a rate of 5 °C/min then from 175 to 340 °C at a rate of 30 °C/min and maintained at 34 °C for 5 min (total run time 20.5 min). Helium was used as a carrier gas with hydrogen used for FID detection at 350 °C. Retention times: (*R*)-5-methyl-3-oxooctanoate **6** 5.4 min; ethyl (*Z*,*R*)-3-acetamido-5-methyl-oct-2-enoate **7** 10.1 min. The above capillary GC method was also used to follow the conversion of the enamide **7** to the hydrogen product **10** and its subsequent hydrolysis to **4**. Retention times: hydrogenation product **10** 10.2 min; (3*S*,5*R*)-3-amino-5-methyloctanoic acid hydrochloride **4** 8.5.



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Ethyl (*R*)-5-Methyl-3-oxooctanoate 6. To a stirred EtOAc (432.2 kg, 479 L) slurry of 1,1′-carbonyldiimidazole (72.6 kg, 447.7 mol) in Reactor A at 23 °C was added a solution of (*R*)-3-methylhexanoic acid **5** (55.2 kg, 423.9 mol) in EtOAc (39.6 kg, 44 L) over a period of 1 h (*CAUTION! CO_2 evolution!*) followed by an EtOAc (19.8 kg, 22 L) line wash. The reaction mixture was agitated at 21−25 °C for a minimum of 1 h and then for an additional 1 h under vacuum (−0.6 barg) to remove CO_2. To an agitated EtOAc (634.4 kg, 704 L) slurry of potassium monoethyl malonate (100.7 kg, 591.4 mol) and magnesium chloride (56.3 kg, 591.4 mol) in Reactor B was added Et_3N (68.4 kg, L) over a period of 2.6 h at a rate that maintained the internal temperature between 20 and 27 °C. The reagent line was washed with EtOAc (8.9 kg, 9.9 L) and the resulting mixture stirred for a minimum of 1 h. The contents of Reactor A were then transferred to Reactor B at a rate that maintained the internal temperature between 30 and 40 °C (typical addition time 15 min), followed by an EtOAc (59.5 kg, 66 L) vessel and transfer line wash. The reaction mixture was stirred at 40 °C for 24 h with a N_2 purge, cooled to 10−12 °C, and quenched by the cautious addition of 4 M aqueous solution of hydrochloric acid (659 L) over a period of 2 h at a rate that maintained the internal temperature between 20 and 40 °C and an acceptable rate of CO_2 evolution. A sample of the aqueous phase was removed and the pH confirmed to be less than 3. The resulting biphasic mixture was allowed to settle for 15 min, and the layers were separated. The organic phase was diluted with water (220 kg, 220 L); the mixture was agitated for 15 min and allowed to settle for 20 min, and the layers were separated. The organic phase was diluted with an aqueous solution of sodium hydrogen carbonate [7.5 w/v %, prepared by adding 28.1 kg of sodium hydrogen carbonate to 374 L of water], the mixture stirred for a minimum of 2 h (*Caution! CO_2 evolution!*), and the layers were separated. The organic phase was diluted with a second portion of aqueous sodium hydrogen carbonate solution [7.5 w/v % prepared by adding 28.1 kg of sodium hydrogen carbonate to 374 L of water], and the mixture stirred for a minimum of 2 h (pH of the lower aqueous layer was measured at 7.8). The organic phase was separated, washed with water (220 L), separated, and then concentrated under reduced pressure (−0.9 barg, 25−30 °C) to a volume of approximately 165 L. Ethyl acetate (148.7 kg, 165 L) was added and the mixture concentrated under reduced pressure (−0.9 barg, 25−30 °C) to a volume of 162 L. The ethyl acetate solution containing **6** (75.1 kg of **6** in 186 kg solution, 40.4% w/w assay, 88.8% yield) was used directly in the next step. Spectroscopic analysis of a sample evaporated to dryness was in agreement with the reported data.[6]

Ethyl (*Z*, *R*)-3-Acetamido-5-methyl-oct-2-enoate 7. A solution of ethyl (*R*)-5-methyl-3-oxooctanoate **6** (369.4 kg of solution containing 161.1 kg of **6**, 804 mol) in ethyl acetate was charged to a suitable vessel and the reagent line washed with anhydrous ethanol (20 kg, 25 L). The agitated reaction mixture was diluted with anhydrous ethanol (616 kg, 781 L), and ammonium acetate (130.1 kg, 1688 mol) was charged in one portion at 20 °C. The resulting suspension was warmed to 58−62 °C over a period of 90 min and the reaction mixture aged for a minimum of 4 h. After cooling to 55 °C a sample was removed and the residual level of ethyl (*R*)-5-methyl-3-oxooctanoate **6** confirmed to be less than 5% by capillary GC. The reaction mixture was cooled to 20−25 °C and concentrated under vacuum (−0.90 barg) to approximately 258 L. 2,2,4-Trimethylpentane (isooctane) (602 kg, 870 L) was added, and the mixture was concentrated under vacuum (−0.90 barg) to approximately 322 L (final batch temperature 40.8 °C). This process was repeated by adding isooctane (368 kg, 532 L), and the mixture was concentrated under vacuum (−0.90 barg) to approximately 322 L (final batch temperature 43.5 °C). The mixture was cooled to 25 °C, and a final portion of isooctane (446 kg, 644 L) was added. Once the addition was complete, the slurry was aged for 30 min at 20−25 °C, the solid (ammonium acetate) was isolated by filtration, the cake washed with isooctane (168 kg, 242 L), and the filtrate and washings were transferred

into a second vessel. Acetic anhydride (164.2 kg, 150.6 L, 1608 mol) was added over a period of 3.5 h, and the reagent line was washed with isooctane (25 kg, 35 L). Pyridine (171.7 kg, 175.6 L, 2171 mol) was then added over a period of 2.6 h, followed by an isooctane (25 kg, 35 L) reagent line wash. The reaction mixture was warmed to 95 °C and held at this temperature for a minimum of 12 h. After cooling to 55 °C a sample was removed and the residual level of the intermediate **6** confirmed to be less than 5% by capillary GC. The reaction mixture was cooled to 20 °C and quenched by the cautious addition of water (322 kg, 322 L) at a rate that maintained the internal temperature below 30 °C. The reaction mixture was stirred for at least 45 min and allowed to settle for 15 min, and the phases separated. The organic phase was washed successively with water (2 × 322 kg, 322 L), sulfuric acid (prepared by adding 59.2 kg, 32.1 L of concentrated sulfuric acid to 322 L of water), and finally water (2 × 322 kg, 322 L). The organic phase was then concentrated under reduced pressure (−0.9 barg, 20 °C) to a volume of approximately 322 L (final batch temperature 27.2 °C). This process was repeated by adding isooctane (223 kg, 322 L), and the mixture was concentrated under vacuum (−0.9 barg) to approximately 322 L (final batch temperature 28.6 °C). The mixture was diluted with ethanol (508 kg, 644 L) and concentrated under reduced pressure (−0.9 barg, 20 °C) to a volume of approximately 322 L. The ethanol/isooctane solution containing **7** (213.4 kg solution of assay 56.9%, 121.4 kg of **7**, 85.7% yield) was used directly in the next step. Spectroscopic analysis of a sample evaporated to dryness matched the published data.[11b]

(3*S*, 5*R*)-3-Amino-5-methyloctanoic Acid Hydrochloride 4. A deoxygenated solution of (*Z*,*R*)-3-acetamido-5-methyloct-2-enoate **7** (*Z*:*E*-mixture of enamides) (161.4 kg of solution containing 84.7 kg of **7**, 351 mol) in a mixture of ethanol and isooctane was charged to a suitable hydrogenation vessel [the vessel was previously purged four times with nitrogen (6 barg) to achieve an oxygen content of <1%] and the reagent transfer line washed with deoxygenated methanol (7 kg, 8.5 L). In a separate nitrogen-inerted 50-L mobile head-tank a catalyst solution was prepared by charging (+)-(*R*)-*tert*-butylmethylphosphino-di-*tert*-butylphosphinomethane)-(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate **8** (0.216 kg, 0.386 mol) and the system inerted by pressurising with nitrogen (0.8 barg) and venting three times. Deoxygenated methanol (15.8 kg, 20 L) was charged to the mobile head tank, the mixture stirred for a minimum of 5 min and the resulting catalyst solution transferred to the hydrogenation vessel. The vessel was pressurized with nitrogen (6 barg), vented, and then pressurized with hydrogen (0.5 barg) and stirred at 45−55 °C (set-point 50 °C) for a minimum of 12 h. After cooling to 20 °C, venting, and purging the vessel with nitrogen, a sample was removed and the residual level of **7** confirmed to be less than 5% by capillary GC analysis. The hydrogenation procedure was repeated on the same scale (161.4 kg of solution containing 84.7 kg of **7**, 351 mol), and the product solutions from the two hydrogenations were transferred to a second vessel followed by two separate methanol (7.9 kg, 10 L) line washes. The combined reaction solutions and line washings were diluted with water (339 kg, 339 L) and concentrated under vacuum (−0.90 barg, 30 °C) to approximately 510 L. The mixture was cooled to 25 °C, and a 36% solution of hydrochloric acid (600 kg, 508 L) was added at a rate that maintained the internal temperature between 25 and 30 °C. The reagent transfer line was washed with water (10 kg, 10 L), and the mixture was stirred and heated to reflux (reflux temperature 93 °C) for a minimum of 16 h. The mixture was concentrated by distillation at atmospheric pressure to approximately 810 L and cooled to 50 °C; a second portion of 36% aqueous hydrochloric acid solution (240 kg, 203 L) was added and the transfer line flushed with water (10 kg, 10 L). The mixture was heated to reflux for an additional 17 h. This process was repeated by concentrating to a volume of approximately 810 L and charging a third portion of 36% aqueous hydrochloric acid (240 kg, 203 L) followed by a line wash with water (10 kg, 10 L). The mixture was heated to reflux for a minimum of 10 h and cooled to 50 °C; a sample was removed and the residual level of the intermediate amino ester confirmed to be less than 5% by capillary GC analysis. Toluene (587 kg, 678 L) was added and the resulting biphasic mixture stirred at 55−60 °C for a minimum of 20 min. The phases were separated, and the aqueous phase was diluted with toluene (411 kg, 474 L), and the resulting biphasic mixture was stirred at 55−60 °C for a minimum of 20 min. The phases were separated, and the aqueous phase was diluted with toluene (499 kg, 576 L). The stirred biphasic mixture was cooled from a range of 55−60 °C to −10 °C over a period of 4 h and the resulting slurry aged for a minimum of 1.5 h at −10 °C. The solid was isolated by filtration, washed with precooled (<0 °C) toluene (176 kg, 203 L), and dried under vacuum (−0.9 barg, 50 °C) to give crude (3*S*,5*R*)-3-amino-5-methyl-octanoic acid hydrochloride salt **4** as a colorless solid (106.9 kg; 72.7%).

The crude product **4** (48.3 kg, 230.3 mol) was suspended in 2-propanol (417 kg, 531 L, 11 L/kg) and the mixture stirred at 25−30 °C for a minimum of 2 h. The resulting solution was filtered through a 1.2 μm filter to remove specs, the filter was washed with 2-propanol (39 L, 30 kg, 0.8 L/kg), and the combined filtrate and washings were concentrated under reduced pressure (−0.9 barg, 50−60 °C) to a volume of approximately 145 L (3 L/kg). Toluene (251 kg, 289 L, 6 L/kg) was added and the mixture cooled to 0 °C over a period of 1 h. The slurry was aged for a minimum of 6 h, filtered, washed with precooled toluene (<0 °C) (54 kg, 63 L, 1.3 mL/g), and dried under vacuum (−0.9 barg) at 50 °C to give the pure product (3*S*,5*R*)-3-amino-5-methyloctanoic acid hydrochloride **4** as a white solid (41.4 kg; 85.7%).

^{1}H NMR (500 MHz, DMSO-d_6): 0.84 (d, J = 6.1 Hz, 3H), 0.85 (t, J = 7.0 Hz, 3H), 1.08 (m, 1H), 1.17−1.35 (m, 4H), 1.58−1.64 (m, 2H), 2.54 (dd, J = 6.7, 16.9 Hz, 1H), 2.66 (dd, J = 6.7, 16.9 Hz, 1H), 3.40 (m, 1H), 8.08 (s br, 3H), 12.66 (s br, 1H); mp (Form A) 141 °C. HRMS (ES) Calcd for $C_9H_{20}NO_2$ (MH^+) 174.1494. Found 174.1507. Chiral purity evaluation by HPLC: Thermo Electron Corp. BDS Hypersil C18 column, 10.0 × 0.46 cm i.d. with 5 μm packing. UV detection was set at 340 nm with a flow rate of 1.0 mL/min. The mobile phases used were 1.0% v/v aqueous triethylamine adjusted to pH 3.0 with phosphoric acid (mobile phase A) and acetonitrile (mobile phase B). The starting level of acetonitrile at 38% was maintained for 25 min, increased to 80% in 30 min, then decreased to 38% in 0.1 min and finally maintained at 38% for 4.9 min (total run time 35 min). Retention times for **4** 10.0 min; (3*S*, 5*S*)-diastereoisomer 9.0 min; (3*R*,5*R*)-diastereoisomer 16.5 min; (3*R*,5*S*)-diastereoisomer 18.3 min.

AUTHOR INFORMATION

Corresponding Author

*stephen.challenger@pfizer.com.

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(20) (+)-(*R*)-*tert*-Butylmethylphosphino-di-*tert*-butylphosphinomethane)-(1,5-cyclooctadiene)rhodium (I) tetrafluoroborate [((*R*)-TCFP)-Rh(COD)]BF_4 **8** is commercially available in kilogram quantities from Solvias AG, Johnson Matthey, and Celtic Catalysts.