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A Simplified Process for the Manufacture of Imagabalin Hydrochloride (PD-0332334), an $\alpha 2\delta$-Ligand for the Treatment of Generalised Anxiety Disorder

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ABSTRACT: The development of a highly efficient two-step process for the manufacture of the $\alpha 2\delta$-ligand imagabalin hydrochloride **1** is described in 50% overall yield from (*R*)-3-methylhexanoic acid **2**. Key aspects of this route include the development of a one-pot process for the synthesis of β-enamine ester **7** and its subsequent diastereoselective hydrogenation with a Ru-(*S*)-BINAP catalyst. The use of a combination of TFA, ammonium trifluoroacetate, and relatively low pressures in the asymmetric hydrogenation are novel conditions reported for this type of transformation. The simplified process described realised a 4-fold reduction in cost of goods compared with the previously described enabling route.

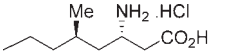
INTRODUCTION

The $\alpha 2\delta$-ligand imagabalin hydrochloride **1** (Figure 1) was chosen as a development candidate for the potential treatment of generalised anxiety disorder (GAD).[1] Significant challenges with this project were the requirement to prepare metric ton quantities of **1** to support the development programme and cost of goods concerns with the need to achieve a competitive selling price. An enabling synthesis, involving the asymmetric hydrogenation of an enamide intermediate **4** (Scheme 1) to install the key (3*S*)-amino stereocentre, was rapidly and successfully scaled up to provide over one metric ton of **1** to supply the development programme (Scheme 1).[2]

A major drawback of this route, and a significant contribution to the high cost of goods, were the forcing conditions and prolonged reaction time (6 M HCl, reflux 36−48 h) to effect deprotection of the acetamide protecting group. Although milder conditions for the deprotection of secondary acetamides have been reported,[3] an alternative route based on the asymmetric hydrogenation of an unprotected enamine intermediate was considered highly desirable.

In this contribution we describe the modification of the enabling process depicted in Scheme 1 to incorporate the asymmetric hydrogenation of an unprotected enamine intermediate **7** which resulted in an efficient synthesis of **1** (Scheme 2).

The asymmetric hydrogenation of β-enamine esters or amides and the direct reductive amination of β-ketoesters with chiral Ru, Rh, or Ir catalysts is an emerging technology, and a number of applications have been reported for the synthesis of chiral β-amino acid derivatives substituted at the β-position with aryl or alkyl groups.[4] Highly efficient and enantioselective hydrogenations have been reported with commercially viable catalyst loadings. However, the diastereoselective hydrogenation of β-enamine ester substrates of type **7**, with an existing chiral centre in close proximity to the prochiral centre, had not been reported prior to this work.



imagabalin hydrochloride
1

Figure 1. $\alpha 2\delta$-Ligand imagabalin hydrochloride **1**.

A second concern with the first-generation enamide hydrogenation route was the high dilution and low throughput, long cycle time, and robustness issues observed at scale with the heterogeneous process to prepare β-ketoester **3** (Scheme 1).[2] It was therefore necessary for us to develop a more efficient process for the manufacture of β-ketoester **3** and the β-enamine ester **7** asymmetric hydrogenation substrates from the readily available starting material (*R*)-3-methylhexanoic acid[2] in addition to studying the subsequent hydrogenation.

RESULTS AND DISCUSSION

Synthesis of Asymmetric Hydrogenation Substrate 7. Inspired by the elegant work of the Merck Process Research group on the one-pot preparation of dehydrositagliptin from a phenylacetic acid derivative using Meldrum's acid chemistry, this approach formed the starting point for our work.[4g,5] The Merck process involved activation of an acid with pivaloyl chloride followed by reaction with Meldrum's acid. The resulting Meldrum's acid adduct, after decarboxylation and reaction of the derived ketene intermediate with an amine gave a β-keto amide intermediate that was subsequently converted into an enamine amide hydrogenation substrate with ammonium acetate. Initial results on the preparation of Meldrum's acid adduct **9** from acid **2**

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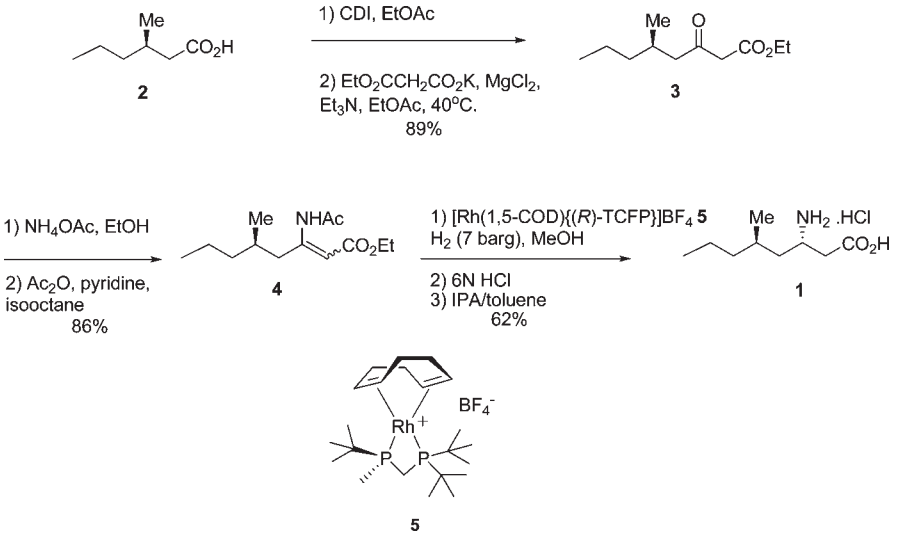
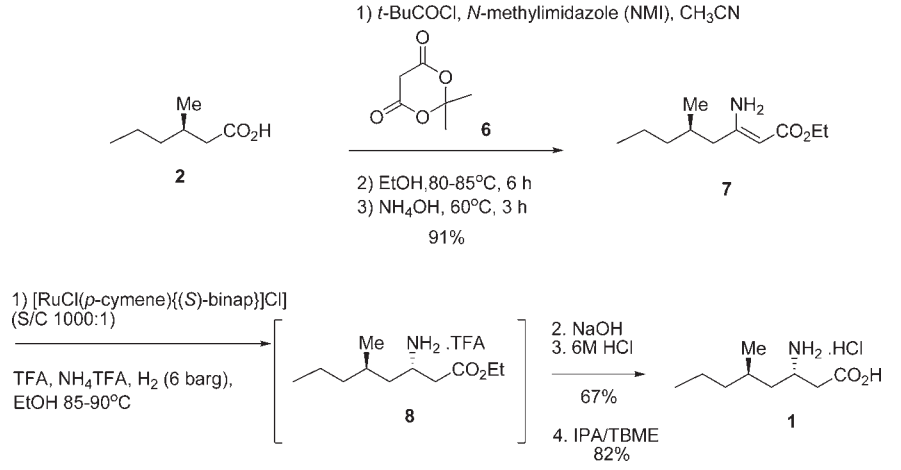
Scheme 1. Enamide asymmetric hydrogenation route to 1



Scheme 2. Unprotected enamine asymmetric hydrogenation route to 1



using the Merck sitagliptin conditions were encouraging. Activation of **2** with pivaloyl chloride and reaction with Meldrum's acid **6** in the presence of *N*,*N*-diisopropylethylamine and dimethylaminopyridine (DMAP) in acetonitrile afforded the Meldrum's acid adduct **9** in 85% conversion (Table 1, entry 1). However, a long reaction time (72 h) was required to achieve this conversion, and decomposition of **9** was a significant issue at higher temperatures.

A screen of base type and reagent stoichiometry quickly identified the beneficial effects of *N*-methylimidazole (NMI) on the rate of reaction (entry 2). Increasing the stoichiometry of NMI (3.2 equiv) and pivaloyl chloride (1.2 equiv) gave excellent conversion of **2** to **9** within 4 h and a clean reaction profile (entries 3 and 4). The use of excess base to stabilise Meldrum's acid adducts as an anionic salt form has been previously reported.[4g,6] Reaction calorimetry with *in situ* monitoring by IR (Figure 2) and ^{1}H NMR[7] studies to probe the formation of **9** suggested a dual reaction mechanism. The first pathway is a dose-controlled reaction that leads to the formation of approximately 85% of the Meldrum's acid adduct **9** via mixed anhydride **10** (Scheme 3, pathway A). During the addition of pivaloyl chloride to **2**, a second reactive intermediate is formed (10−15%, see Figure 1). ^{1}H NMR analysis confirmed this species to be pivalic anhydride which presumably arises from the reaction of the pivalic acid byproduct with pivaloyl chloride.

This second pathway (Scheme 3, pathway B) leading to the formation of **9** involves the activation of residual **2** with pivalic anhydride to generate mixed anhydride **10** followed by reaction with Meldrum's acid. The accumulation of pivalic anhydride (pathway B) contributes to the typical 4−6 h reaction time for this process.[8] Once the formation of **9** was complete, ethanol (2 equiv) was added and the mixture heated to 80−85 °C for 6 h to effect clean conversion of **9** into the β-keto ester **3**.[9]

The ethanolysis of **9** to β-keto ester **3** was briefly investigated under the standard conditions on a laboratory scale in a pressure plug flow reactor (PFR). At a temperature of 120 °C clean conversion of **9** into **3** was achieved in a residence time of less than 5 min, highlighting the potential of this technology to further reduce processing time and cost through continuous processing. Since β-keto ester **3** is an oil and obtained in high purity using this

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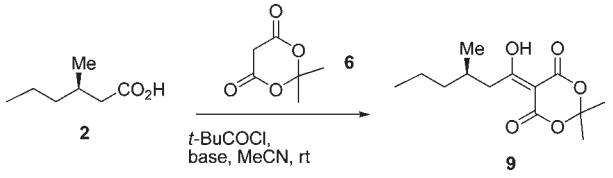
Table 1. Optimisation of the conditions for the conversion of 2 to Meldrum's acid adduct 9



entry	conditions	reaction time (h)	conversion (%)[a]
1	*t*-BuCOCl (1.1 equiv), **6** (1.1 equiv), *i*-Pr_2NEt (2.15 equiv), 4-DMAP (0.08 equiv)	72	85
2	*t*-BuCOCl (1.1 equiv), **6** (1.2 equiv), NMI (2.2 equiv)	1.5	85
3	*t*-BuCOCl (1.1 equiv), **6** (1.1 equiv), NMI (3.2 equiv)	2.5	91
4	*t*-BuCOCl (1.2 equiv), **6** (1.1 equiv), NMI (3.3 equiv)	4.0	98

[a] Conversion estimated by ^{1}H NMR.

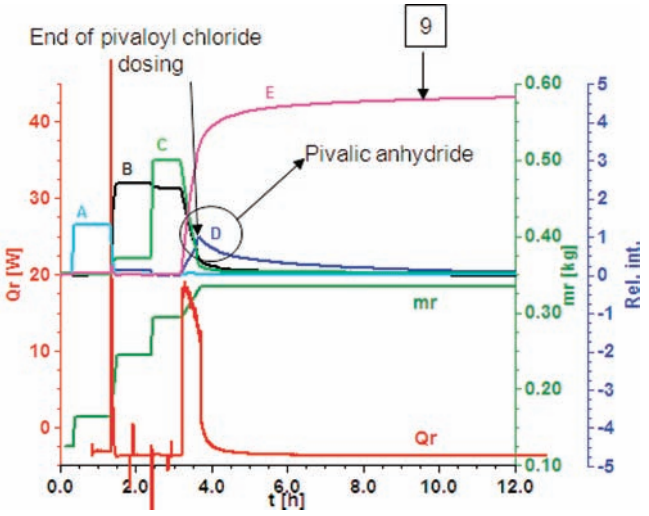


Figure 2. Reaction calorimetry data for the formation of Meldrum's acid adduct **9**. Mettler Toledo ConcIRT reaction heat (Q_r), reaction mass (m_r), pivaloyl chloride added in three doses (A, B, C).

process, our preferred option was not to isolate this intermediate but to simply telescope it into the amination step as part of a one-pot process. In the enabling synthesis of **1**, β-keto ester **3** was aminated with ammonium acetate (2.0 equiv) in EtOH (60 °C, 4 h).[2] Reinvestigation of the optimal conditions for the amination of crude β-keto ester **3** derived from the Meldrum's acid chemistry led to the selection of aqueous ammonia as the preferred aminating reagent based on the purity of **7** produced. Treatment of **3** with 30% aqueous ammonia (3.3 equiv) in aqueous acetonitrile at 60 °C (2−4 h) gave greater than 95% conversion to the desired product **7** and a clean reaction profile (96−98 area % by GC). Acetonitrile was shown to be an inhibitor in the subsequent asymmetric hydrogenation step, and its level in the isolated enamine product solution was controlled to less than 200 ppm by incorporating an additional ethanol distillation in the workup (see Experimental Section for details of the isolation of **7**). The quality of the material prepared using this process gave consistent performance in the subsequent hydrogenation, and no further purification was required. This process was successfully scaled up in the pilot plant on a scale of up to 110 kg (845 mol) input of **2**. A total of 859 kg of **7** (as a solution in EtOH) was manufactured in 91% average overall yield from **2** (range 89−96%) over six batches. The development of a more efficient one-pot process had a significant impact on reducing cost of goods by addressing the high dilution, long cycle time, and robustness issues with the original heterogeneous enabling route process.[2] This process showed excellent potential for reaction completion monitoring by mid-IR. Details of this Process Analytical Technology (PAT) application will be published elsewhere.[10]

Asymmetric Hydrogenation of β-Enamine Ester 7. At the inception of this work there were limited examples of the asymmetric hydrogenation of β-enamine esters documented in the literature.[4a,d] Initially, the Rh-Josiphos system used by Merck and Solvias[4b,g] in the synthesis of sitagliptin was investigated, and encouraging levels of diastereoselectivity (92% de) were achieved in the hydrogenation of substrate **7** [2,2,2-trifluoroethanol (TFE), H_2 100 psig, 50 °C, substrate to catalyst ratio (S/C) 250:1].[11] However, this was not considered to be a commercially viable option without further optimisation due to the low activity of the catalyst. Instead, we focused on the Ru complexes containing biaryl bisphosphine ligands reported by Takasago[4a,f] and Lanxess[4d] due to the significant cost advantage of Ru metal compared with Rh at the time. A significant limitation of this technology was the relatively high pressures (typically 10−30 bar) reported for the asymmetric hydrogenation of β-enamine esters or the reductive amination of β-keto esters.[4d,f] The development of a potential synthesis of **1** was restricted to a pressure of less than 8 bar by the capabilities of our in-house commercial hydrogenation facilities. A limited study on the direct asymmetric reductive amination of β-keto ester **3** with ammonium acetate at these lower pressures was unsuccessful, and our efforts were therefore focused on the asymmetric hydrogenation of β-enamine ester **7**.

A range of commercially available Ru-precatalysts[12] were screened for the asymmetric hydrogenation of **7**; the best hits from the screen are summarised in Table 2. In the reported examples of this type of hydrogenation, the addition of acid was necessary to achieve a high reaction rate. Trifluoroacetic acid (TFA) quickly emerged as a preferred acid catalyst for our substrate since it gave a cleaner reaction profile than AcOH.[13] Hydroxylic solvents such as MeOH, EtOH, and 2,2,2-trifluoroethanol (TFE) are typically used for the asymmetric hydrogenation of β-enamine esters. For our purposes, TFE was discounted as a suitable solvent on the grounds of cost; the higher-boiling solvent EtOH was preferred over MeOH to ensure the efficient

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Scheme 3. Mechanistic pathways for the formation of 9 (the role of NMI omitted for clarity)

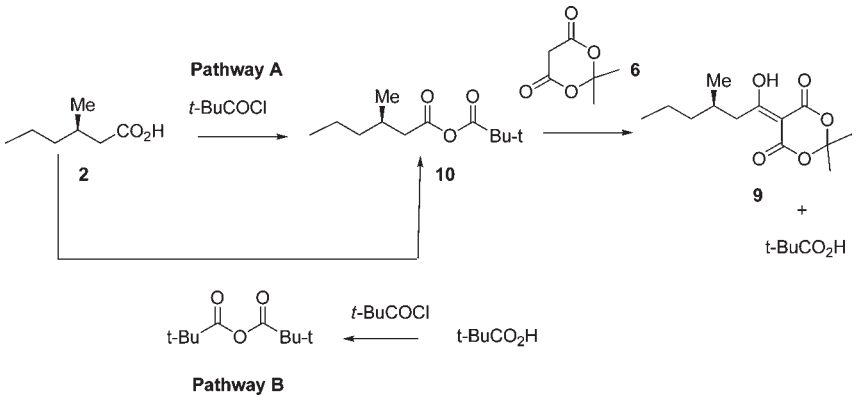
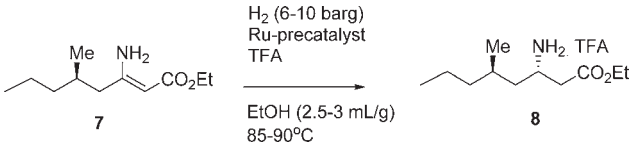


Table 2. Asymmetric hydrogenation of 7



entry	catalyst /(S/C ratio)/H_2 pressure (barg)	additive (equiv)	conv (%)/ reaction time (h)	de (%)[a]	purity[b] (%)
1	$Ru(OAc)_2$ [(*S*)-binap] (350:1)/10	TFA (0.95)	100 (7)	97.7	88
2	[RuCl(*p*-cymene){(*S*)-binap}]Cl (350:1)/ 10	TFA (0.95)	100 (7)	98.2	87
3	$Ru(OAc)_2$[(*S*)-dtbm-segphos] (500:1)/10	TFA (0.95)	100 (17)	98.6	96
4	$Ru(OAc)_2$[(*S*)-dm-segphos] (350:1)/10	TFA (0.95)	100 (9)	98.3	68
5	[RuCl(*p*-cymene){(*S*)-binap}]Cl (350:1)/10	TFA (1.2)	100 (5−6)	97.9	72
6	$Ru(OAc)_2$[(*S*)-binap] (350:1)/10	TFA (0.95) NH_4TFA (0.35)	100 (6)	97.7	97
7	[RuCl(*p*-cymene){(S)-binap}]Cl (1000:1)/ 6	TFA (0.95) NH_4TFA (0.35)	100 (26)	98.3	98

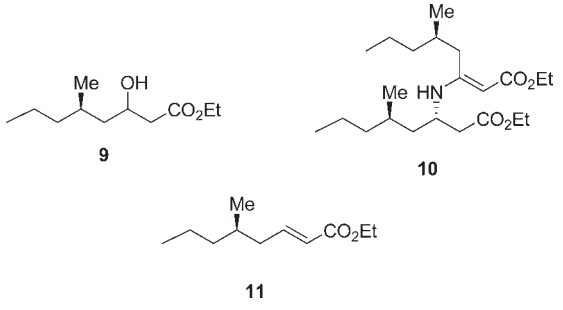
[a] De assayed by GC. [b] Purity estimated by ^{1}H NMR.

removal of the volatile catalyst inhibitors acetonitrile and 2,2,4-trimethylpentane (isooctane) by distillation in the isolation of **7**. Ethanol was therefore selected for further development.

For all of the Ru-precatalysts described in Table 2, the (*S*)-enantiomer of the catalyst was required to give the desired (3*S*,5*R*)-diastereoisomer **8**. Diastereoselectivity in the hydrogenation was uniformly high with the three catalysts containing different chiral bisphosphine ligands (entries 1, 3, and 4) and two catalyst precursors (entries 1 and 2) investigated. There was no apparent advantage in using catalysts containing the second-generation SEGPHOS ligands; therefore, the [Ru(*p*-cymene)-{(*S*)-binap}]Cl precatalyst was selected for further optimisation and scale-up. Analysis of the crude products from these hydrogenation reactions by LC−MS identified β-hydroxy ester **9** (3-hydroxyl stereocentre unassigned), dimer **10**, and elimination product **11** as the major impurities (Scheme 4). These impurities are typical in the reported examples of this type of process.[4g,h]

The stoichiometry of TFA was critical to achieve high conversion and a clean reaction profile (entries 2 and 5) with 0.9−1.0 mol equiv being the optimal range. At 0.8 mol equiv of TFA incomplete conversion to **8** was observed (with approximately 20% of unreacted **7** present after the typical hydrogenation period of 20 h), while higher stoichiometries increased the levels of **9** formed by hydrogenation of **3** (entry 5). The addition of acid is known to catalyse the asymmetric reduction of β-keto

Scheme 4. Impurities formed in the asymmetric hydrogenation of 7



esters with Ru-BINAP catalysts.[14] β-Keto ester **3** is presumably formed from the hydrolysis of β-enamine ester **7**. It is known that heating an ethanolic solution of TFA generates ethyl trifluoroacetate and water.[15] The formation of impurity **9** had a significant impact on yield although it was subsequently shown that up to 10% could be effectively purged in the isolation and recrystallisation of **1**. A significant breakthrough was achieved with the addition of a catalytic amount of ammonium trifluoroacetate to the hydrogenation, which resulted in a cleaner reaction profile (entries 6 and 7). The role of the ammonium trifluoroacetate

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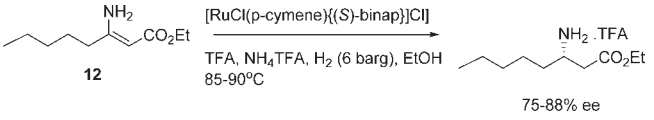
Scheme 5. Asymmetric hydrogenation of des-methyl derivative 12



is not clearly understood in this process. It was postulated that the ammonium salt shifts the equilibrium between β-keto ester **3** toward **7**. During this work the Merck and Takasago groups highlighted the beneficial effect of adding ammonium salts to a Ru-catalysed asymmetric hydrogenation of a β-enamine amide.[4h,16] In the published work the addition of ammonium salicylate was also found to prevent the formation of a dimer impurity related to **10**.[4h]

Temperature was also a critical parameter in the hydrogenation, and at least 85 °C was required to ensure a reasonable rate of reaction. At 75 °C the reaction proceeded much more slowly, and a higher level of β-keto ester **3** was formed through competing hydrolysis of **7**. We observed that an acceptable reaction rate could be achieved (85−90 °C, 20−24 h) at relatively low hydrogen pressure (6 barg) using a commercially viable catalyst loading of 1000:1. Pressure had very little effect on the diastereoselectivity of the reaction across a range of pressures up to 34 barg (500 psi). Hydrogenation of **7** using the (*R*)-enantiomer of the Ru-BINAP catalyst afforded the (3*R*,5*R*)-diastereoisomer of **8** with equally high diastereoselectivity at the 3-amino stereocentre; indicating that the overriding chiral control element in this process comes from the catalyst. Asymmetric hydrogenation of the *des*-methyl derivative **12** (Scheme 5) under standard reaction conditions proceeded with significantly lower enantioselectivity (75−88% ee), suggesting that branching on the β-carbon to the prochiral centre is important in achieving high diastereoselectivity in the hydrogenation of substrates such as **7** (this effect has also been noted by researchers at Takasago[4f]).

The final optimised conditions (entry 7) gave product **8** with *in situ* yields of 90−95%. The product solution from the hydrogenation was telescoped directly into the following deprotection step without further purification. To our delight, this asymmetric hydrogenation protocol proved to be robust and was successfully run in the pilot plant on a scale of 45 kg input of **7** to convert over 500 kg of the β-enamine ester substrate **7** to **8** in 12 batches.

Preparation of Imagabalin Hydrochloride 1. The completion of the synthesis of imagabalin hydrochloride **1** was accomplished by the hydrolysis of the ester protecting group with NaOH (22−28 °C, 1 h). The crystalline hydrochloride salt of **1** was isolated in 67% yield (average yield from **7** over four batches) from a mixture of aqueous hydrochloric acid/*tert*-butyl methyl ether (TBME) after dilution with water and concentration to remove the EtOH. The purity of the isolated product was further upgraded to meet the required specification by recrystallisation from 2-propanol/TBME (82% yield). The isolation and recrystallisation of **1** were not optimised processes and significant losses of product were observed to the mother liquors. It is likely, had the project continued in development, that further optimisation would have resulted in a higher overall yield for this process. A combination of the isolation of crude **1** and its recrystallisation were sufficient to meet a residual ruthenium specification of not more than 10 ppm (ICP-MS) without recourse to the use of metal scavengers.

In conclusion, we describe the development of a highly efficient, two-step process for the manufacture of the $\alpha 2\delta$-ligand imagabalin hydrochloride **1** in 50% overall yield from (*R*)-3-methylhexanoic acid **2**. Key aspects of this route include the development of a one-pot process for the synthesis of β-enamine ester **7** and its subsequent asymmetric hydrogenation with a Ru-(*S*)-BINAP catalyst. The modified process realised a 16-fold reduction in cycle time and a 4-fold reduction in cost of goods compared with those of the enabling route.

In parallel with this work an alternative approach to imagabalin hydrochloride **1** was investigated involving a transaminase biocatalyst to transform β-ketoester **3** to **1**.[17] This process had the potential to reduce the cost of goods further.

EXPERIMENTAL SECTION

All raw materials, reagents and solvents were purchased from commercial suppliers and used without further purification. All reactions, with the exception of hydrogenations, 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 **2** to Meldrum's acid adduct **9** was followed by ^{1}H NMR or GC using an Agilent Technologies 6890 or 6850 capillary GC configured with a fast oven ramp option. A 5% (phenyl)-methylpolysiloxane capillary column (e.g., ZB-5 MS, Phenomenex, London, U.K., part no. 7FD-G010-08), 20 m × 0.18 mm × 0.18 μm, was used at a constant flow of 1.0 mL/min. The inlet temperature was set at 250 °C, and the oven was held at 40 °C for 0.5 min and warmed to 130 °C at a rate of 15 °C/min and then from 130 to 250 °C at a rate of 50 °C/min. Helium was used as a carrier gas with hydrogen used for FID detection at 250 °C. Retention time: **2** typically 4−5 min.

The conversion of ethyl (*Z*,*R*)-3-amino-5-methyloct-2-enoate **7** to the hydrogenation product **8** and subsequent conversion to **1** was followed by GC using an Agilent Technologies 6890 capillary GC configured with a fast oven ramp option: an RTX-1 or equivalent capillary column (e.g., Restek cat. no. 10123-124). It is recommended that the column is fitted with a retention gap), 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 150 °C, and the oven was held at 130 °C for 2.0 min and warmed to 165 °C at a rate of 5 °C/min and then from 165 to 340 °C at a rate of 40 °C/min. Helium was used as a carrier gas with hydrogen used for FID detection at 350 °C. Retention time: **7** 8.9 min; **8** 6.9 min.

The diastereoisomeric purity of imagabalin hydrochloride **1** was determined using the previously published HPLC method.[2]

Ethyl (*Z*,*R*)-3-Amino-5-methyloct-2-enoate 7. To an agitated acetonitrile (369 kg, 468 L) solution of (*R*)-3-methylhexanoic acid **2** (110 kg, 845 mol, limiting reagent), *N*-methylimidazole (229 kg, 222 L, 2789 mol), and 2,2-dimethyl-(1,3)-dioxane-4,6-dione (134 kg, 930 mol) was added pivaloyl chloride (122 kg, 125 L, 1014 mol) at a rate that maintained the internal temperature of the vessel between 15 and 25 °C. The reagent line was washed with acetonitrile (20 kg, 25 L) and the resulting mixture stirred for a minimum of 6 h at 22−27 °C. A sample was removed and the residual level of (*R*)-3-methylhexanoic acid confirmed to be less than 5.0% by gas chromatography analysis. Ethanol (78 kg, 99 L, 1690 mol) was then charged to the vessel, and the mixture was refluxed for a minimum of 6.0 h by heating its content to 80−85 °C (*Caution*! CO_2 evolution). A sample was removed after cooling down the vessel content to 20−25 °C, and

the residual level of 5-acyl Meldrum's acid intermediate was confirmed to be less than 5.0% by HPLC analysis. Purified water (45 L) was added to the reaction mixture followed by 30% (w/w) aqueous ammonium hydroxide (158 kg, 178 L, 2789 mol) (internal temperature was kept below 30 °C by adding the aqueous ammonium hydroxide solution over 3.0 h) . The reagent line was washed with purified water (10 L) and the reaction mixture agitated at 58−62 °C for a minimum of 3.0 h. A sample was removed and the residual level of ethyl (*R*)-5-methyl-3-oxooctanoate intermediate confirmed to be less than 5.0% by gas chromatography analysis. The reaction mixture was then concentrated under reduce pressure (−0.9 barg) at 25−30 °C to a volume of approximately 730 L before being diluted with purified water (253 L) and 2,2,4-trimethylpentane (502 kg, 726 L). The resulting biphasic mixture was stirred for a minimum of 30 min at 22−27 °C before settling for a minimum of 30 min at 22−27 °C. The organic layer was separated, washed twice with purified water (330 L for each wash), and then concentrated under reduced pressure (−0.9 barg) at 25−30 °C to a volume of approximately 220 L. Ethanol (424 kg, 550 L, denatured with cyclohexane), was added ,and the resulting solution was concentrated under reduced pressure (−0.9 barg) at 25−30 °C to a volume of approximately 280 L. Ethanol (200 kg, 252 L, denatured with cyclohexane) was added, and the resulting solution was concentrated under reduced pressure (−0.9 barg) at 25−30 °C to a volume of approximately 280 L. (This final supplementary distillation was carried out to ensure that the residual level of acetonitrile in the **7** ethanol solution was below 200 ppm.) The ethanol solution containing **7** (320 kg solution of assay 46.74% (w/w), 150 kg of **7**, 752 mol, 89.0% yield) was used directly in the next step. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 (m, 6H), 1.14 (t, 3H), 1.26 (m, 4H), 1.80 (m, 3H), 2.06 (m, 1H), 3.96 (q, 2H), 4.27 (s, 1H), 6.84 (br s, 1H), 7.76 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.05, 14.47, 18.94, 19.42, 31.24, 38.40, 43.08, 57.32, 81.50, 164.08, 169.15.

HREIMS Calculated for $C_{11}H_{22}NO_2$ 200.164505 $[M + H]^+$; measured 200.164475 $[M + H]^+$.

(3*S*,5*R*)-3-Amino-5-methyl-octanoic Acid Hydrochloride 1. An ethanol solution containing **7** (98 kg, 114 L, 47.5% (w/w), 46.5 kg of **7**, 234 mol) was charged to Reactor A previously inerted by applying four N_2 pressurization/vent cycles to achieve an O_2 content <1.0%. The reagent line was washed with ethanol (10.0 kg, 12 L, denatured with cyclohexane), and the vessel was agitated at 22−27 °C. Ammonium trifluoroacetate (9.2 kg, 70 mol) was charged to Reactor A followed by trifluoroacetic acid (25.3 kg, 17.1 L, 222 mol) (internal temperature was kept below 25 °C by adding trifluoroacetic acid over 45 min). The reagent line was washed with ethanol (10.0 kg, 12 L, denatured with cyclohexane), and the vessel content was agitated at 22−27 °C to provide a homogeneous solution. [RuCl(*p*-cymene){(*S*)-binap}]Cl (0.217 kg, 0.234 mol) was charged to a 50-L mobile head-tank (previously inerted by applying three consecutive N_2 pressurization/vent cycles) followed by ethanol (20 kg, 25 L, denatured with cyclohexane). Agitation was maintained in the 50-L mobile head-tank until full dissolution of the catalyst was achieved (visual check). Reactor A content was transferred to a preinerted hydrogenation vessel followed by the catalyst ethanol solution. The reaction mixture was agitated, pressurised with hydrogen (+3.0 barg), and heated to 85−90 °C. Once the desired temperature was reached, the hydrogenator was pressurised with hydrogen (+6.0 barg) and stirred until cessation of the hydrogen uptake (theoretical uptake: 4400 L). A sample was removed after depressurizing and cooling down the hydrogenator content to 20−25 °C, and the residual level of **7** was confirmed to be less than 5% by HPLC analysis. This hydrogenation procedure was repeated twice on the same scale (i.e., starting from 98 kg of **7** ethanol solution containing 47.5% (w/w) of **7**), and the three hydrogenated intermediate solutions were combined in Reactor B, diluted with ethanol (30 kg, 38 L, used as vessel and transfer line wash), and agitated at 12−18 °C. Aqueous sodium hydroxide (131 kg, 89 L, 47% (w/w), 1542 mol) was charged in Reactor B at a rate that maintained the temperature below 35 °C. The reagent line was washed with purified water (23 L) and the reaction mixture agitated at 22−28 °C for a minimum of 1.0 h at which point HPLC analysis confirmed >98% conversion to **8**. The reaction mixture was concentrated by distillation at atmospheric pressure to a volume of approximately 350 L, diluted with purified water (420 L), and concentrated by distillation at atmospheric pressure to a volume of approximately 350 L. Purified water (420 L) was added, and the reaction mixture was concentrated by distillation at atmospheric pressure to a volume of approximately 350 L. A sample was removed, and the residual level of ethanol confirmed to be <0.5% by gas chromatography analysis. The reaction mixture was diluted with *tert*-butyl methyl ether (103 kg, 139 L) and carefully acidified by addition of concentrated hydrochloric acid (414 kg, 345 L, 37% (w/w), 4201 mol) over a period of 2.7 h at a rate that maintained the temperature below 28 °C. The reagent line was washed with purified water (10 L) and the batch stirred at 20−28 °C until crystallization of **1** was observed. The slurry was cooled down to −3/+3 °C at a rate of 0.3 °C/min, stirred for a minimum of 1.0 h, and then transferred to 0.75 m^2 Hastelloy filter drier. The cake was washed three times with *tert*-butyl methyl ether (278 L for the first wash, 417 L for the last two washes) and dried on the filter at 55 °C (jacket temperature of the filter drier) under reduced pressure (−0.9 barg) for 12 h to give **1** as a white solid (99.7 kg, 475 mol, 67.9% yield).

Into Reactor A charged with 2-propanol (469 kg, 597 L) was added **1** (42.6 kg, 203 mol) under stirring at 20−25 °C. Once complete dissolution was visually observed, the hazy solution was passed and recirculated through a Gauthier filter for a minimum of 1.0 h. The speck-free solution was concentrated under reduced pressure (−0.9 barg) at 25−30 °C to a volume of approximately 190 L and then agitated at 50−60 °C prior to being transferred to reactor B (preheated at 50−60 °C) via a transfer line fitted with a 1.2 μm polypropylene filter cartridge. Reactor A and the transfer line were washed with 2-propanol (13.4 kg, 17 L), and Reactor B content was agitated at 50−55 °C. *tert*-Butyl methyl ether (316 kg, 427 L) was charged to Reactor A, warmed to 38−42 °C, and transferred to Reactor B at a rate that maintained Reactor B content between 47 and 55 °C. Crystallization of **1** was visually observed at this point, and the slurry was cooled down to 15−25 °C at a rate of 0.2 °C/min. The slurry was agitated at 15−25 °C for a minimum of 10.0 h and then transferred to a 0.50 m^2 mobile Nutsche filter. The cake was washed twice with *tert*-butyl methyl ether (95 kg, 128 L for each wash), transferred to a tray drier and dried at 50 °C under reduced pressure (−0.9 barg) for 8 h. **1** was obtained as a white solid (35.0 kg, 167 mol, 82.2% yield).

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(8) In a separate experiment the reaction was repeated with pivalic anhydride as the activating reagent and shown to give Meldrum's acid adduct **9** under similar reaction conditions. However, the reaction was slower compared with that using pivaloyl chloride, giving 75−80% conversion to product after 6 h compared with typically greater than 95%.

(9) In the Merck sitagliptin process a catalytic quantity of trifluoroacetic acid was added to catalyse the decarboxylation of a Meldrum's acid adduct. The mechanism of this decarboxylation was proposed to occur via a α-oxoketene species.Xu, F.; Armstrong, J. D., III; Zhou, G. X.; Simmons, B.; Hughes, D.; Ge, Z.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **2004**, *126*, 13002–13009.

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(11) Unpublished results by Nanninga, T. N.; Wu, H.-P.

(12) Diacetato[(*S*)-(−)-2,2′-bis(diphenylphosphino)-1,1′-binapthyl] ruthenium(II) ($Ru(OAc)_2$[(*S*)-binap]), chloro[(*S*)-(−)2,2′-bis(diphenylphosphino)-1,1′-binaphthyl](*p*-cymene)ruthenium(II) chloride ([RuCl(*p*-cymene){(*S*)-binap}]Cl), Diacetato{(*S*)-(+)-5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole}ruthenium(II) ($Ru(OAc)_2$[(*S*)-dtbm-segphos]) and diacetato{(*S*)-(−)-5,5′-bis[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole} ruthenium(II) ($Ru(OAc)_2$-[(*S*)-dm-segphos]) are commercially available from Takasago International Corporation and Strem Chemicals, Inc.

(13) In addition to TFA and acetic acid, methanesulfonic acid, trichloroacetic acid, and chloroacetic acid were included in the screen.

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