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Chemical Development of an $\alpha 2\delta$ Ligand, (3*S*,5*R*)-3-(Aminomethyl)-5-methyloctanoic Acid

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ABSTRACT: Three synthetic approaches, suitable for the large scale manufacture of the $\alpha 2\delta$-ligand, (3*S*,5*R*)-3-(aminomethyl)-5-methyloctanoic acid **3**, have been evaluated. The selected seven step manufacturing process has then been optimized and used to deliver over 20 kg of API; salient features of the synthesis include the use of 4,4,4-trimethoxybutyronitrile as an efficient four carbon amino acid equivalent. Highly selective kinetic resolution of the C3 stereocentre was accomplished *via* diastereoselective hydrolysis of a cyanoester intermediate using Amano Lipase PS-SD. Extensive process optimisation of the route starting from (*R*)-2-methylpentanol, led to significant improvements through telescoping, with less than 62 kg of solvent being needed to produce 1 kg of API.

INTRODUCTION

Over recent years there has been a great deal of interest in $\alpha 2\delta$-ligands, following the discovery that gabapentin **1** and pregabalin **2** (Figure 1), identified in 1976 and 1991, respectively,[1] bind with very high affinity to the $\alpha 2\delta$-protein, an auxiliary subunit of voltage-gated calcium channels (VGCC).[2] Binding at these sites modulates calcium influx at the VGCC, which in turn leads to decreased neurotransmitter release in the central nervous system and results in the observed pharmacological effects (analgesic and anticonvulsant). Both gabapentin and pregabalin have been developed as treatments for a number of conditions such as generalized anxiety disorder, insomnia, fibromyalgia, epilepsy, neuropathic pain, anxiety, depression, and attention deficit hyperactivity disorder.[3]

We were interested in developing efficient syntheses to support the development of the $\alpha 2\delta$-ligand, (3*S*,5*R*)-3-(aminomethyl)-5-methyloctanoic acid **3** (Figure 1), a lipophilic γ-aminobutyric acid (GABA) analogue nominated for development for the treatment of interstitial cystitis.[4] At the outset it was clear that the Medicinal Chemistry route, whilst suitable for the preparation of material to support early toxicological and clinical studies, would not be a suitable long-term manufacturing process without extensive modification. An approach was required that would enable the team to provide significant quantities of material for the ongoing clinical program, whilst at the same time develop a viable manufacturing process. In the following paper we describe three approaches which resulted in significant advances towards this goal.

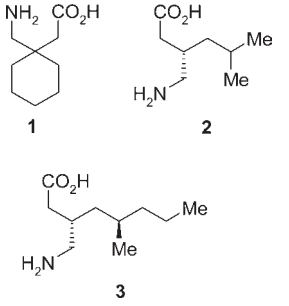

Figure 1. Structure of known $\alpha 2\delta$ ligands.

The modified Medicinal Chemistry route used for the preparation of early quantities of **3** is shown in Scheme 1 and made use of related synthetic methodology to that previously employed in early routes to pregabalin.[5] (*S*)-β-Citronellol was a convenient starting material as it possesses the correct absolute configuration corresponding to the C5 position of the target API. Moreover the starting material provides six further carbon atoms found in the backbone of the API. The absent C7 terminal methyl group was introduced in a two step homologation process, through mesylation of the primary alcohol to give **4** and then displacement of the mesylate with methyl magnesium

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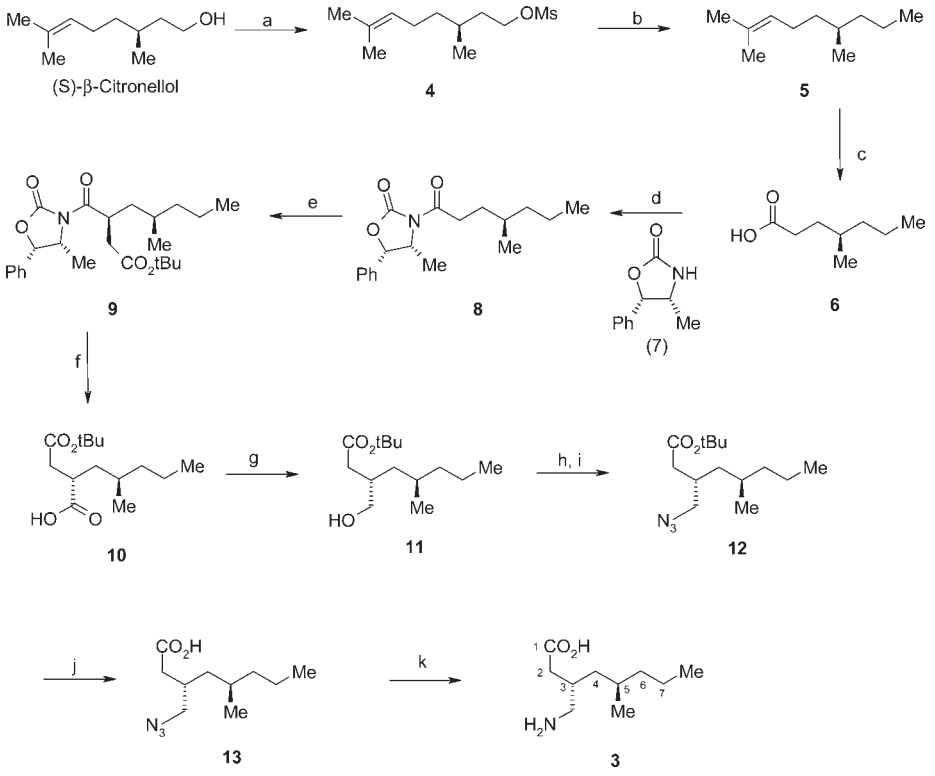
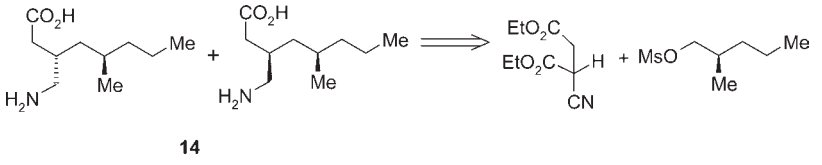
Scheme 1. Medicinal Chemistry route for the preparation of (3*S*,5*R*)-3-(aminomethyl)-5-methyloctanoic acid[a]



[a] *Reagents and conditions*: (a) MsCl, NEt_3, DCM (95%); (b) MeMgCl, $CuCl_2$, LiCl, THF, DCM (97%); (c) $KMnO_4$, hexanes; (d) i) NEt_3, THF, Me_3CCOCl, ii) LiCl + (7); (e) LDA, THF, $BrCH_2CO_2{}^tBu$, −50 °C (67%); (f) LiOH, H_2O_2, THF, H_2O, (92%); (g) BH_3SMe_2, TBME; (h) MsCl, NEt_3, TBME (quant); (i) NaN_3, DMSO, 50 °C, (92%); (j) H_2SO_4, HCO_2H, (79%); (k) i) $Pd(OH)_2/C$, H_2 ii) IPA reslurry, (68%).

Scheme 2. First generation process route *via* chiral salt resolution of amino acid mixture 14



chloride in the presence of LiCl and $CuCl_2$ providing the alkene **5**. Oxidative cleavage of the alkene with potassium permanganate gave the acid **6**, a suitable substrate for introduction of the second stereocentre at C3 using asymmetric Evans alkylation methodology.[6] Thus treatment of **6** with pivaloyl chloride in the presence of Et_3N gave the mixed anhydride, which was treated directly with oxazolidinone **7**, derived from (+)-norephedrine, to give the acyl oxazolidinone **8**. Deprotonation of **8** with LDA, followed by addition of *tert*-butyl bromoacetate at −50 °C afforded **9** in good yield and excellent diastereoselectivity (97:3). Cleavage of the chiral auxiliary with LiOH and H_2O_2 generated acid **10** as a viscous oil in high yield (92%).The *tert*-butyl ester was required to minimize lactone formation during the workup of the subsequent borane reduction, which proceeded smoothly giving alcohol **11**. Mesylation and displacement with sodium azide gave the azido ester **12**. Finally, ester deprotection and reduction of the azide **13** gave the API **3** in eleven steps from (*S*)-*β*-Citronellol in 11.7% overall yield.

This modified Medicinal Chemistry route provided approximately 20 kg of material for early toxicological and clinical studies, but suffered from several issues. The eleven step synthesis is relatively lengthy with poor atom economy (considering 6 carbons of the final API are present in the starting material) and high predicted cost of goods (COG). Furthermore, several intermediates were isolated as oils and certain reagents were undesirable from an industrial perspective (sodium azide in DMSO, peroxide, BH_3SMe_2 and alkylation at −50 °C). As a result of these limitations, we explored a number of different synthetic approaches to the molecule to develop a route more amenable to scaling to a manufacturing process.

Chiral Salt Approach. The first process chemistry approach considered synthesis of **3** using a classical chiral salt resolution of the diastereomeric amino acid mixture **14**. It was envisaged that **14** could be readily accessed *via* alkylation of diethylcyanosuccinate with (*R*)-2-methylpentylmethanesulfonate, (Scheme 2).

Initially the required (*R*)-2-methylpentanol was not readily available on a large scale; therefore, this material was obtained through enzymatic resolution of racemic 2-methylpentanol using an enantioselective acylation in the presence of Amano Lipase PS-C1 (Scheme 3). Screening work identified vinyl decanoate as

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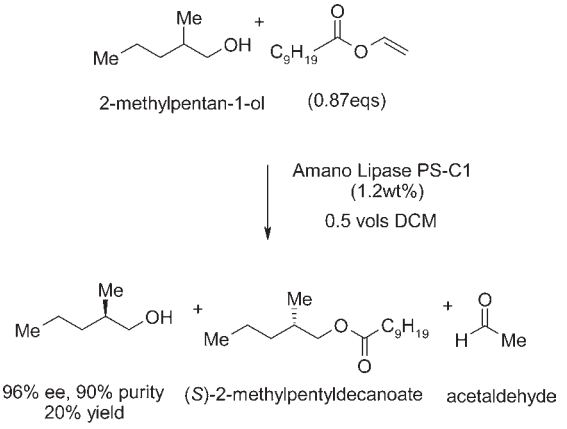
the optimal acyl donor and gave a suitable boiling point difference between the alcohol and the corresponding decanoate ester, enabling facile separation of the desired (*R*)-2-methylpentanol by fractional distillation. However, as the process was scaled (>1000 L), erosion of the chiral purity became a significant problem, presumably through transesterification of the (*R*)-alcohol, and (*S*)-ester during distillation regenerating some of the enantiomeric alcohol. To circumvent this, it was essential to filter the enzyme from the reaction mixture once the required ee of the alcohol was achieved and to avoid prolonged reaction times. As the project progressed, a commercial process was developed by Codexis utilizing enantiospecific enzymatic reduction of 2-methylvaleraldehyde.[7]

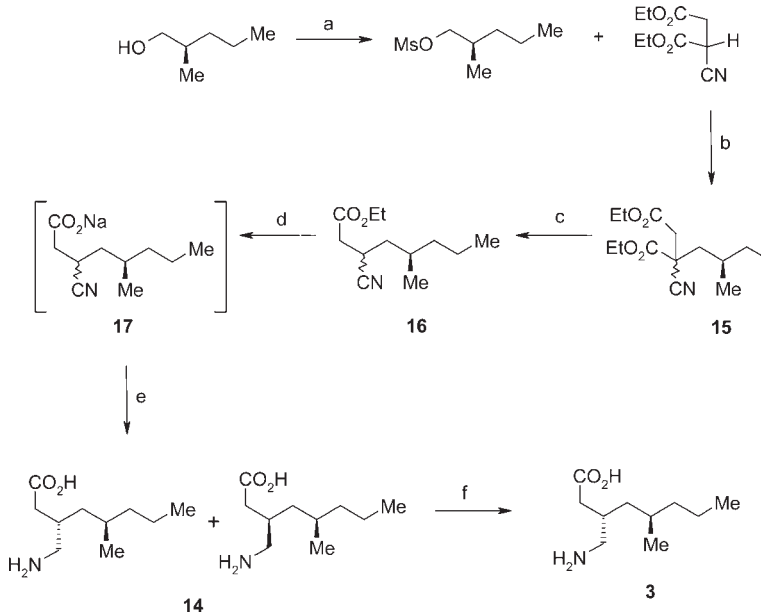
Once sufficient quantities of the chiral alcohol were available, synthesis of **3** was carried out according to Scheme 4. Mesylation provided (*R*)-2-methylpentylmethanesulfonate, which was alkylated by diethylcyanosuccinate using potassium carbonate and TBAB in toluene/water at 100 °C, to give **15** as a dark brown oil (65−70% yield). As the process was scaled-up into the kilolab (~20 kg), the mixture formed a gel like phase which coated the reaction vessel. The gel could be dispersed or reduced by the addition of water to the reaction, but this resulted in significant decomposition of the product **15**. The gel was thought to be generated by the potassium methanesulfonate salt formed during the reaction. Changing the base to sodium carbonate gave a slight decrease in gel formation, by improving the solubility of the salt byproduct, but increased the reaction time from 5 to 17 h. Switching to cesium carbonate eliminated the gel, but because of concerns over the cost of cesium carbonate and the disposal of cesium methanesulfonate, alternative alkylation conditions were sought. Screening a range of reaction conditions identified that NaOEt/EtOH at 70 °C both aided the overall reaction solubility and gave improved reaction time. On reaction completion acidification of the mixture to pH 2 aided the organic/aqueous phase separation on workup, giving after evaporation, **15** in 79% yield and 78% purity.

Decarboxylation of the diester **15** was performed under Krapcho decarboxylation conditions,[8] (NaCl, DMSO, H_2O, 150 °C, 18hrs). There were initial concerns that with extended heating >150 °C, the system could dehydrate, resulting in the exothermic decomposition of DMSO.[9] The reaction could be carried out at lower temperatures (135−140 °C) but required extended reaction times (5 days) to reach completion, resulting in isolation of material of poor quality as a dark oil, (85% yield, 72% purity). To improve the reaction rate, a range of other decarboxylation conditions were explored and a number of trends were observed (Table 1). The rate of decarboxylation increased significantly by increasing the solubility of the chloride ion, LiCl > NaCl, (Table 1, entries 2 and 5). Addition of a phase transfer catalyst initially improved the reaction rate with NaCl, (Table 1, entry 3), but was found not to have a significant benefit on the overall rate and purity profile with LiCl, (Table 1, entry 4).

Scheme 3. Enzymatic resolution of 2-methylpentanol



Scheme 4. Mandelic acid resolution route to (3*S*,5*R*)-3-(aminomethyl)-5-methyloctanoic acid[a]



[a] *Reagents and conditions*: (a) MsCl, NEt_3(quant.); (b) NaOEt, EtOH; (c) LiCl, DMSO, water, 135−138 °C; (d) NaOH, THF, water, (quant.); (e) (i) Sponge Ni, water, H_2, (50 psi, 30 °C), (ii) AcOH, EtOH, water; (f) (*S*)-Mandelic acid (0.55 equiv), EtOH, water.

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Table 1. Screening results for the Krapcho decarboxylation conditions

entry	conditions	temp (°C)	reaction time (h)	yield (purity)
1	NaCl, DMSO, H_2O	150	18	86% (85%)
2	NaCl, DMSO, H_2O	135	5 days	85% (72%)
3	NaCl, TBAB, DMSO, H_2O	135	36	93% (80%)
4	LiCl, TBAB, DMSO, H_2O	135	24	86% (hydrolysis product)
5	LiCl, DMSO, H_2O [a]	100	28.5	85% (97%)
6	LiCl, NMP	100	48	89.4%[e]
7	LiCl, DMF	100	48	45.9%[e]
8	LiCl, DMSO	100	48	34%[e]
9	NaCl, DMSO	100	48	3%[e]
10	LiCl, H_2O	100	48	starting material [e]
11	LiCl, NMP [b]	100	42	85% (81.6%)
12	LiCl, NMP [c]	100	26	86% (84.6%)
13	LiCl, NMP [d]	100	4	52%[e]
14	$CaCl_2$, DMSO	100	48	55%[e]
15	LiOEt/EtOH, H_2O	100	20	complex mixture

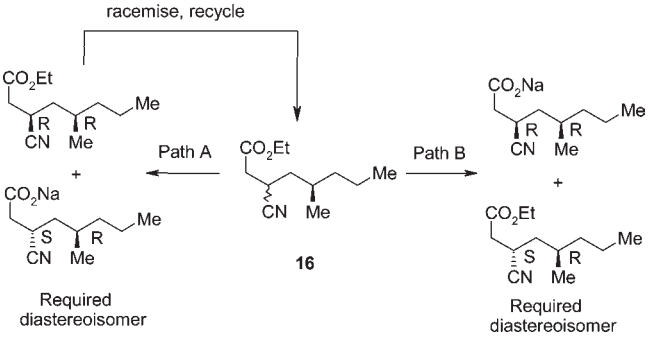
[a] LiCl (1.3 equiv), DMSO (5 vols), H_2O (5 vols). [b] LiCl (3 equiv), NMP (10 mL/g). [c] LiCl (6 equiv), NMP (5 mL/g). [d] Dimethylcyanosuccinate LiCl (6 equiv), NMP (5 mL/g. [e] GC data.

The reaction worked well only in high boiling, polar solvents, with the observed rate of decarboxylation as follows, NMP > DMF > DMSO > H_2O. The rate was also influenced by the choice of succinate ester with dimethylcyanosuccinate ester reacting substantially faster than diethylcyanosuccinate ester, (although dimethylcyanosuccinate was not commercially available at scale at the time of this work, so process development continued using diethyl cyanosuccinate ester). Optimum conditions for scale−up of the reaction employed diethylcyanosuccinate, LiCl, DMSO and water at 100 °C, (entry 5).[10]

To complete the synthesis, the cyanoester **16** was saponified to give **17** and the resulting aqueous solution was hydrogenated using Sponge Nickel catalyst, (20% w/w) at 50 psi and 30 °C. Once the reduction was complete, the catalyst was filtered from the aqueous solution and the pH of the mixture adjusted with AcOH to precipitate a 1:1 diastereomeric mixture of amino acids **14**. Initially **14** precipitated as material of very small particle size (<10 μm), and filtered poorly as particles either passed underneath the filter cloth or blocked the filter. This was remedied by including a temperature cycle with ethanol/water prior to isolation, which gave material of a larger particle size and avoided product loss to the filtrate. Screening the crude diasteromeric mixture **14** for salt formation with a range of chiral acids and solvents, identified that (*S*)-mandelic acid preferentially formed a salt with the undesired (3*R*,5*R*) diastereomer. Moreover by judicious choice of ethanol−water as solvent, and using (*S*)-mandelic acid (0.55 equiv), the desired (3*S*,5*R*) diasteroisomer crystallized directly from the reaction mixture as the zwitterion to give the product API **3** in 24% yield and 99.4% purity, containing about 0.2% (3*R*,5*R*) diastereomer. The resolution is unusual in that the free zwitterionic (3*S*,5*R*) amino acid **3** is isolated directly, not the (3*R*,5*R*) mandelic acid salt, which remains in solution, (Scheme 4).

Whilst this approach provided rapid access to the API in six steps in 11.4% overall yield, the use of the late stage resolution without the opportunity to efficiently recycle the unwanted diastereomer, coupled with relatively high predicted COG, meant there was still considerable scope for improvement. An additional drawback to this route, was that residual mandelic acid present in the API at low levels, (~0.05%) promoted lactam formation in both the API and drug product on storage. Lactam formation was accelerated in the drug product, requiring drug product manufactured via this route to be stored at <5 °C to avoid lactam formation.

Scheme 5. Enzymatic resolution of ethyl (5*R*)-3-cyano-5-methyloctanoate 16



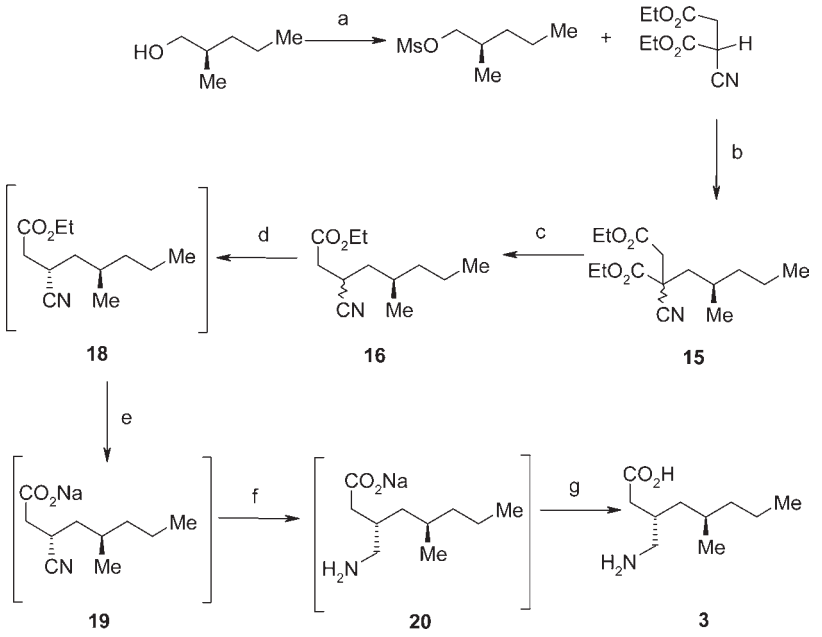
Lipase Resolution Approach. To address the issues of the mandelic acid resolution route, the focus of the next-generation process was to resolve the C3 stereocentre earlier in the synthetic route. The approach was to explore kinetic resolution of cyanoester **16**, (an intermediate in the mandelic acid route) *via* diastereoselective enzymatic hydrolysis (Scheme 5). Ideally we desired an enzyme which would preferentially hydrolyze the (3*S*,5*R*) diastereoisomer as this would enable the undesired (3*R*,5*R*)-ester to be easily extracted, racemised at C3, and recycled back through the resolution process (Path A).

An initial screen of 96 commercially available enzymes (lipases, esterases, and proteases,) identified seven hits.[11] Several enzymes (fungal lipases) did show the desired preference for hydrolysis of the (3*S*,5*R*)-ester (Path A); however, only modest diastereoselectivity was observed, (Table 2, entries 4−7); significant improvements in diastereoselectivity would be needed to achieve a viable process. Much higher diastereoselectivity was seen for the hydrolysis of the (3*R*,5*R*)-ester, (Path B) with

Table 2. Enzymatic screening for the resolution of ethyl (5*R*)-3-cyano-5-methyloctanoate

entry	enzyme (supplier)	*E* value	conv.	selectivity
1	*Burkholderia cepacia* Lipase (Amano Lipase AH)	200	15	(3*R*,5*R*)
2	*Pseudomonas fluorescens* Lipase (Amano Lipase AK)	200	25	(3*R*,5*R*)
3	*Burkholderia cepacia* Lipase (Amano Lipase PS)	200	45	(3*R*,5*R*)
4	*Thermomuces lanuginosus* Lipase (Sigma L10 Lipolase)	15	50	(3*S*,5*R*)
5	*Thermomuces lanuginosus* Lipase (Sigma Novo871)	10	68	(3*S*,5*R*)
6	*Rhizomucor miehei* Lipase (Sigma L6 Palatase)	5.3	90	(3*S*,5*R*)
7	*Rhizopus delemar* Lipase (Amano Lipase D)	6	44	(3*S*,5*R*)

Scheme 6. Lipase resolution route to 3[a]



[a] *Reagents and conditions*: (a) MsCl, NEt_3(quant.); (b) NaOEt, EtOH; (c) LiCl, DMSO, 110 °C; (d) Amano lipase PS SD, $NaHCO_3$, water, then TBME, NaCl (sat. aq); (38−45%) (e) NaOH, THF, water, (quant.); (f) i) Sponge Ni, water, H_2, (50 psi), 30 °C, ii) AcOH, EtOH, water, (60%); (g) EtOH, water.

Pseudomonas lipase enzymes (Table 2, entries 1−3). A decision was taken to progress with the Path B route using commercially available Amano lipase PS-SD, (a strain of *Burkholderis cepacia*,) since the (3*S*,5*R*)-ester with the required stereochemistry and the (3*R*,5*R*) acid were readily separable and hydrolysis of the (3*S*,5*R*)-ester could be performed as a separate step.

Numerous factors were explored to ensure the enzymatic process was reproducible and robust to scale up. Initially the pH of the reaction was maintained at pH 7 throughout the process, due to concerns that the enzyme activity would drop if the pH were to fall significantly; however, it was found that the enzyme is relatively stable across the pH 4.5−11 range. Practically, charging 0.75 equiv of sodium bicarbonate at the start of the reaction to an aqueous/toluene solution of **16** prior to enzyme addition, was sufficient to maintain the reaction within a suitable pH range and avoided the need to have a laborious pH titration ongoing throughout the process. The activity of the enzyme was maximal at 45 °C, declining rapidly at higher temperature or after ageing. Furthermore the enzyme efficiency was found to be sensitive to concentration, but tolerant of some organic solvent. The optimum conditions for the reaction were to run the reaction at a concentration of 5 mL/g at 45 °C with 20% w/w organic solvent concentration and an enzyme loading of 20% w/w. The reaction was continued until less than 2% of the (3*R*,5*R*) diastereomer remained in the organic phase, as it was demonstrated that this level of diastereomer would purge to give <0.2% in the final API. On completion, an emulsion had formed and 3 kg salt per kg of input starting material was added, aiding efficient breakdown of the emulsion and extraction of the (3*S*,5*R*)-ester **18** into TBME. The TBME solution of **18** was carried through downstream chemistry analogous to that described above, giving **3** as the next isolated product in seven steps overall and 19.6% yield, (99.8% de, 99.6% chemical purity) from diethylcyanosuccinate, (Scheme 6).

Whilst this second-generation route gave an efficient resolution at C3 earlier in the synthesis, the remaining drawback originated in the alkylation/decarboxylation steps. A myriad of low-level impurities (<0.1−0.2%) were generated in these two steps and carried through to the final API. If this sequence could be optimized or avoided, there was still scope for yet further improvement in the overall route to **3**.

Orthoester Approach. In order to circumvent the problematic alkylation/decarboxylation sequence, we envisaged that

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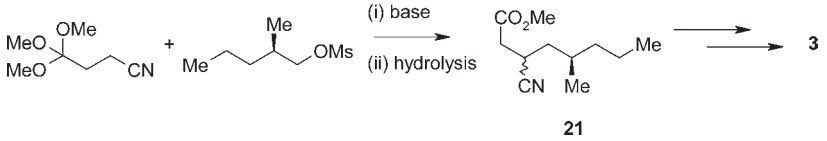
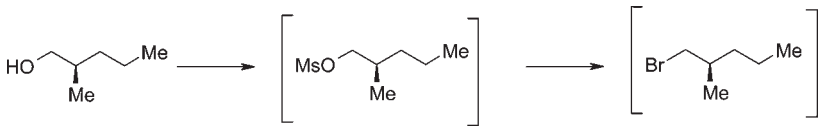
Scheme 7. 4,4,4-Trimethoxybutyronitrile (Orthoester) Approach to 3

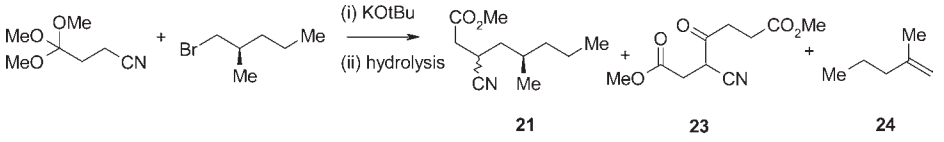


Scheme 8. Formation of (*R*)-1-bromo-2-methylpentane[a]



[a] *Reagents and conditions*: (a) MsCl, NEt_3, toluene, (quant.); (b) NaBr, TBAB, water, 65 °C.

Scheme 9. Decomposition of the starting materials in KOtBu



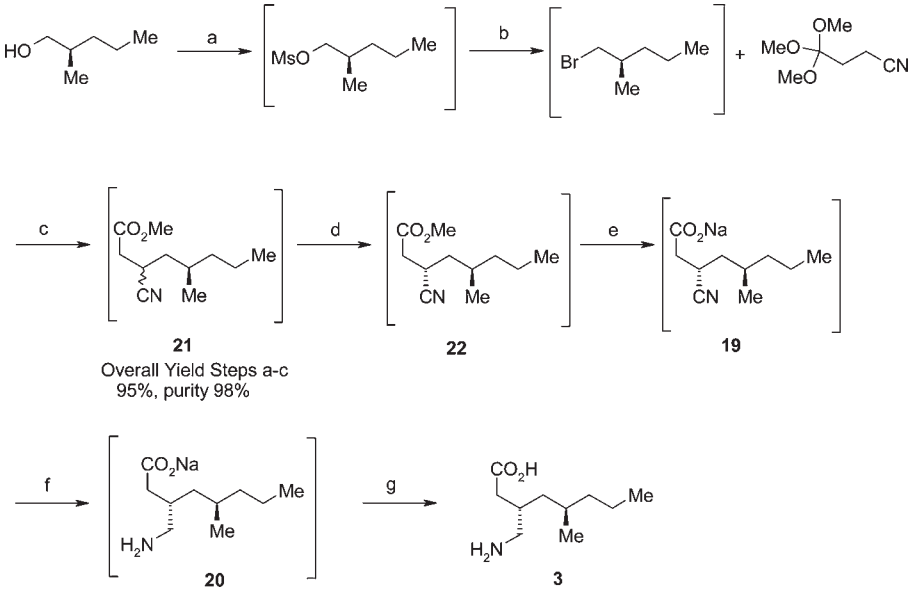
starting from commercially available 4,4,4-trimethoxybutyronitrile would enable regioselective alkylation to generate the C3 stereocentre, (Scheme 7). Hydrolysis of the product would give directly methyl (5*R*)-3-cyano-5-methyloctanoate **21**, an intermediate in the previous lipase route prior to enzymatic resolution, thus avoiding the need for the harsh decarboxylation conditions of the earlier routes.

Initial attempts at alkylation of 4,4,4-trimethoxybutyronitrile with (*R*)-2-methylpentylmethanesulfonate using LDA, gave a poor reaction profile, with significant self-condensation of trimethoxybutyronitrile being observed. A screen of alternative alkylating reagents indicated that (*R*)-1-bromo and (*R*)-1-iodo-2-methylpentane gave improved reaction rates and purity profiles, but the corresponding alkyl chloride and tosylate were sluggish or unreactive. (*R*)-1-Bromo-2-methylpentane was initially formed directly by treatment of the alcohol with phosphorous oxybromide; however, issues with the lead time and availability of $POBr_3$ became evident when trying to source large quantities (500 kg). Consequently, a telescoped two-step procedure to the bromide from the alcohol, *via* the mesylate, was developed, (Scheme 8). Performing the reactions in toluene enabled the bromide to be formed and used directly in the next step as a toluene solution.

With the bromide in hand, a range of bases, counterions, additives and solvents for the alkylation of the orthoester were explored. Significant issues when using strong bases, (LDA, nBuLi, LiHMDS) were: (i) elimination of the bromide to generate the alkene **24** and (ii) dialkylation of the cyanorthoester. Potassium butoxide looked to be a promising lead; however, the order of addition of reagents was pivotal to the success of the reaction; both the bromide and trimethoxybutyronitrile were unstable in KOtBu on their own, forming the alkene **24** or self-condensation to the ketonitrile **23**, respectively, (Scheme 9). The key to a successful reaction was to prepare a cooled (−10 °C) solution of the bromide and trimethoxybutyronitrile in toluene and then add this to 3 equiv of the base in toluene. Less base significantly slowed the desired reaction, resulting in decomposition of the starting materials, whereas higher levels resulted in the formation of a viscous paste which was difficult to stir at scale (due to precipitation of the potassium salt of the nitrile starting material from solution). On reaction completion, the reaction was quenched with water and the pH adjusted to pH 1−2, resulting in hydrolysis of the alkylated trimethoxybutyronitrile, to give **21** directly as a toluene solution in three steps from (*R*)-2-methylpentanol in 95% yield and 98% chemical purity, (Scheme 10). It was subsequently found that, by reducing the toluene concentration to 20% w/w, **21** could be telescoped directly into the lipase resolution step, under the conditions used previously. Amano Lipase PS-SD enzyme exhibited a performance for hydrolysis of methyl (5*R*)-3-cyano-5-methyloctanoate similar to that observed previously for ethyl (5*R*)-3-cyano-5-methyloctanoate in the original Lipase route.

To complete the orthoester route, the resolved methyl (3*S*,5*R*)-3-cyano-5-methyloctanoate **22** was telescoped through the hydrolysis and reduction steps under the conditions used in the earlier lipase route. API from these steps was initially isolated post reduction by a pH adjustment of the hydrogenation solution to pH 6.5 with acetic acid precipitating crude **3**, which was recrystallised directly from EtOH/water. The API was then given a final polishing recrystallisation from EtOH:water, however a persistent haze was observed, this did not dissolve with additional solvent or heating. The solid was isolated and ICP-MS analysis showed it to contain aluminium (most likely aluminium hydroxide, leached from the catalyst). A number of different grades of sponge nickel were explored in an attempt to minimize aluminium leaching without success, but it was found that by neutralizing with citric acid at the end of the hydrogenation reaction resulted in the aluminium species remaining in solution. API isolated from crude material via this process contained <10 ppm aluminium, (vs >100 ppm *via* AcOH process). The final recrystallization, (EtOH:water) gave **3** with increased bulk density which was easy to filter and dry, (Figure 2a), compared to

Scheme 10. Optimised 4,4,4-trimethoxybutyronitrile (orthoester) approach to 3[a]



[a] *Reagents and conditions*: (a) MsCl, NEt_3, toluene; (b) NaBr, TBAB, water, 65 °C; (c) (i) KOtBu, toluene/THF, (ii) HCl (aq); (d) i) Amano lipase PS SD, water, ii) TBME, NaCl (sat. aq); (e) NaOH, THF, water, (quant.); (f) (i) Sponge Ni, water, H_2O, (50 psi), 30 °C, (ii) citric acid, EtOH, water; (g) EtOH, water.

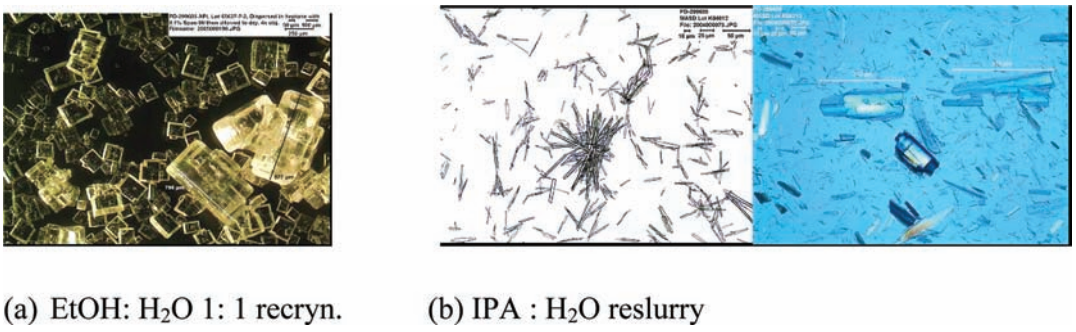


Figure 2. Recrystallization of **3**.

Table 3. Comparison of the routes to 3

	citronellol route A	mandelic acid route B	Krapcho decarboxylation route C	cyano-orthoester route D	% improvement from A to D
total solid waste	–	–	1.2 kg/kg API	0.18 kg/kg API	–
total water	734.3 L/kg API	200.4 L/kg API	232 L/kg API	175 L/kg API	76
total solvent	735.5 L/kg API	354.7 L/kg API	149.6 L/kg API	61.6 L/kg API	92
total reagents	137.3 kg/kg API	74.9 kg/kg API	84 kg/kg API	30.3 kg/kg API	78
route yield	11.7%	11.4%	19.6%	24.6%	105%

the needlelike crystals obtained from the original Medicinal Chemistry isolation (IPA/water) (Figure 2b).

To further optimize the orthoester route, considerable attention was paid to minimization of solvents, batch processing, and drying operations. All of the intermediates in the route prior to isolation of the crude API were oils, and thus there was no opportunity to purge impurities through crystallization. However, the route was amenable to telescoping, and it was found that the first four steps of the synthesis could be performed in toluene, including the enzymatic resolution. After extraction of the resolved ester **22** into TBME, the downstream steps were also telescoped through to the crude API, giving a significant saving in solvent usage, batch processing, and drying times over previous routes. (3*S*,5*R*)-3-(Aminomethyl)-5-methyloctanoic acid **3** was produced in an overall yield of 24% with 99.6% purity and 99.4% de, from (*R*)-2-methylpentanol *via* this route. Overall only four solvents are used with water contributing 65% of the solvent usage in the process. The efficiency of the orthoester route can be

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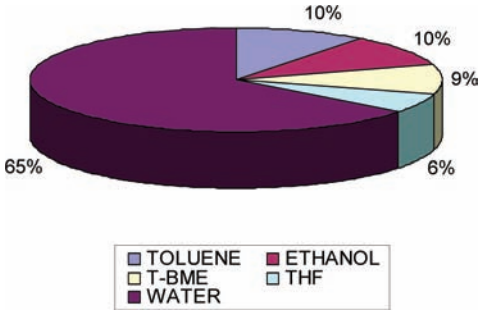

Figure 3. Solvent usage in the orthoester route.

shown by a comparison of the solvent and reagent usage of the four routes used (Table 3), giving a 92% improvement in overall solvent usage from the Medicinal Chemistry citronellol route; performing the resolution early in the synthetic sequence enables a 78% reduction in the total reagent usage.

Summary. A scalable seven-step, telescoped manufacturing process for (3*S*,5*R*)-3-(aminomethyl)-5-methyloctanoic acid **3** has been developed and used to deliver over 20 kg of API in 24.6% and 99.4% de from 4,4,4-trimethoxybutyronitrile. The use of this 4-carbon synthon enables a capricious alkylation/Krapcho decarboxylation of earlier routes to be avoided. Resolution of the C3 stereocentre by diastereoselective hydrolysis using the commercially available lipase, Amano lipase PS-SD, with high substrate loading, ultimately results in the formation of API in high yield and diastereomeric purity. Through extensive use of telescoped processing, minimization of solvent usage and drying times, a highly efficient and environmentally benign synthesis was achieved (see Figure 3).

EXPERIMENTAL SECTION

General Procedures. Unless noted otherwise, reagents and solvents were used as received from commercial suppliers. Technical grade solvents were used for all experiments. All reactions were carried out under a positive pressure of nitrogen. Yields are weight-based and not corrected for assays unless otherwise noted. The chemical purity and conversions were determined by HPLC (% by area). Enantiomeric excesses (ee) were determined by HPLC on chiral stationary phase using the indicated conditions. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ultrashield 400 Plus spectrometer at 400 and 100.6 MHz, respectively. Data are presented as follows: chemical shift (δ) in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (J) in Hz, and integration. Absorptions in IR spectra are recorded in wavenumbers (cm^{-1}). Low-resolution mass spectra were obtained by positive or negative ion spray ionization (ESI). Intermediates were analysed by GC with flame ionization detection, on an Agilent 6890 GC, according to the following conditions: column DB-1, 30 m × 0.53 mm i.d., 0.5 μm film, injection volume 5 μL, program: hold at 60 °C for 6 min, then ramp to 260 at 10 °C per min, hold at 260 °C for 4 min. Injection type: cool on column, carrier gas: 5.0 mL/min (constant), detector temp: 300 °C, FID gas flow rates: 30 mL/min H_2; 300 mL/min air; approximately 10 mL/min makeup, flow mode: Constant = makeup and column. Chiral purity of **18** and **22** was determined by GC with flame ionization detection, according to the following conditions: column, Chiraldex A-TA; 20 m × 0.25 mm i.d. × 0.125 μm film thickness; column temp program: 130 °C for 25 min; injection type: split 25:1; injector temp: 220 °C; carrier gas: helium; 1 mL/min (constant flow); injection volume: 1 μL; detector temp: 250 °C; FID gas flow rates: hydrogen: 30 mL/min; air: 400 mL/min; nitrogen makeup: 25 mL/min, flow mode: constant flow.

Citronellol Route. *Methanesulphonic Acid (S)-3,7-Dimethyloct-6-enylester* ***4***. A reactor was charged with methylene chloride (2840 kg), (*S*)-(−)-β-citronellol (170 kg, 1.08 mol), and methanesulfonyl chloride (139.4 kg, 1.22 mol) the mixture was stirred and cooled to −10 °C. Triethylamine (136 kg, 1.34 mol) was added maintaining the temperature at −10 to 0 °C. The mixture was stirred at 0−5 °C for a least one hour. The reaction was quenched with aqueous sodium hydroxide (50% solution 128 kg) and water (880 L) and stirred for 5−10 min at 20−25 °C. The phases were separated, and the organic phase was washed with aqueous hydrochloric acid (132 kg) in water (500 L) and stirred for 5 to 10 min at 20−25 °C. The phases were separated, and the organic phase was washed with water (1000 L) and stirred for 5−10 min at 20−25 °C. The phases were separated, and the organic phase was distilled under vacuum to an oil, maintaining the temperature at less than 35 °C. Tetrahydrofuran (640 L) was charged to this oil and the mixture redistilled under vacuum to afford the title compound **4** as an oil, (240 kg, 94.8%) which was used directly in the next step.

(R)-2,6-Dimethyl-non-2-ene ***5***. To a 3900-L reactor under nitrogen were added tetrahydrofuran (2466 L), **4** (263.5 kg, 1123.4 mol), lithium chloride (14.8 kg, 350 mol), and copper(II) chloride (23.6 kg, 175.6 mol) and cooled to 5 °C. Methylmagnesium chloride (3 M in THF, 540 kg, 1819.3 mol) was added, maintaining the temperature −5−5 °C, and the reaction mixture stirred for a least 3 h or until reaction completion by HPLC. Methanol (300 L) was added, maintaining the temperature <25 °C. The mixture was distilled to low volume (1000 L) at a temperature of 68−70 °C. The reaction was quenched with water (625 L), conc. hydrochloric acid (259 kg), and hexane (1880 L) and stirred for 5−10 min at 20−25 °C. The phases were separated, and the organic phase was washed with water (625 L). The organic phase was separated and distilled under vacuum to an oil maintaining the temperature at <20 °C, to afford the *title compound* **5**, (159.6 kg, 97.4%). The product was used directly in the next step. ^{13}C NMR ($CDCl_3$) 131.13, 125.28, 39.50, 37.35, 32.35, 25.92, 25.77, 20.31, 19.74, 17.81, 14.60

(R) 4-Methylheptanoic Acid ***6***. To a 3900-L reactor was charged, water (150 L) and sulphuric acid CP (128 kg), and the mixture was stirred and cooled to 20 °C; adogen 464 (4.5 kg), acetic acid (48 kg, 800 mol), **5** (50 kg, 229.6 mol), and DCM (890 kg) were added, and the mixture was cooled to 18 °C. A solution of potassium permanganate (120 kg, 760 mol) in water (1750 L) was added to the mixture, maintaining the reaction temperature at 20−25 °C. The reaction was stirred at this temperature for a further 16 h, or until completion by HPLC analysis. The mixture was then added to a solution of sodium bisulfite (115 kg, 1105 mol) in water (150 L) maintaining the temperature through the addition at less than 30 °C. The mixture was stirred for 30 min, the layers were allowed to separate. The pH of the reaction was adjusted to less than pH 1.6 using sulfuric acid and stirred at 30 °C for at least 30 min. The phases were separated, and the organic phase was washed with aqueous hydrochloric acid (40 kg in water 300 L) and stirred at 25 °C for at least 10 min. The phases were separated, and the organic phase was washed with aqueous sodium hydroxide (60 kg in 200 L water) and stirred at 25 °C for at least 10 min. The product containing aqueous phase was separated, charged with hexane, and

cooled to 10−5 °C. The pH was adjusted to less than 2.0 using hydrochloric acid, maintaining the temperature at 35 °C. The phases were separated, and the organic phase was distilled under vacuum to an oil, maintaining the temperature at <40 °C, to afford the *title compound* **6** as an oil (16.1 kg, 34.4%) which was used directly in the next step. MS, *m*/*z* (relative intensity): 143 [M − H, 100%]

(4R,5S)-4-Methyl-5-phenyl-2-oxazolidinone ***7***. To a reactor were charged toluene (51 L), (1*S*,2*R*)-(+)-norephedrine (25 kg, 165.3 mol), potassium carbonate (2.8 kg, 20.3 mol), and diethyl carbonate (25 kg, 211.6 mol). The mixture was stirred and heated at reflux (∼110 °C) for at least 18 h or until reaction completion by HPLC. The reaction was then distilled until a vapor temperature of 105−110 °C was reached. The reaction was cooled to 67 °C, and water (22 L) was added. The mixture was stirred for at least 15 min at 67 °C. The phases were separated, and the wash was repeated; the organic layer was then distilled to low volume (approx 71 L). The reaction was cooled to 5 °C, and the slurry was charged to a centrifuge and deliquored. The wet product from the centrifuge was tray dried under vacuum at 37 °C to give the product **7** (29.3 kg, 84.3%).

(4R,5S)-4-Methyl-3-((R)-4-methylheptanoyl)-5-phenyloxazolidin-2-one ***8***. To a reactor were charged tetrahydrofuran (560 L), **6** (84 kg, 414 mol), and triethylamine (125.6 kg, 1241 mol); the mixture was stirred and cooled to 0−5 °C. Trimethylacetyl chloride (54.9 kg, 455 mol) was added, maintaining the temperature at 5 °C. The reaction was cooled to 3 °C and stirred for at least 2 h. A solution of **7** (73.3 kg, 414 mol) in tetrahydrofuran (280 L) was added to the mixture, followed by lithium chloride (19.3 kg, 455 mol), maintaining the temperature at <10 °C. The mixture was then warmed to 20 °C and stirred for at least 16 h. The reaction was quenched with water (123 L) and stirred for at least 15 min at <25 °C. Phases were separated and the organic phase was distilled under vacuum to low volume maintaining the temperature at <55 °C. *tert*-Butylmethylether (395 L), water (138 L) and conc. hydrochloric acid (18.4 kg) were added and stirred for at least 15 min at <25 °C. The phases were separatedh and the organic phase was washed with water (153 L). Phases were separated ,and the organic phase was distilled under vacuum to afford the title compound **8** as an oil, (114.4 kg, 91.2%) $[\alpha]_D$ = 5.5 (*c* = 1 in $CHCl_3$). MS, *m*/*z* (relative intensity): 304 [M + H, 100%].

(3S,5R)-5-Methyl-3-((4R,5S)-4-methyl-2-oxo-5-phenyloxazolidine-3-carbonyl)octanoic Acid tert-Butyl Ester ***9***. To a reactor were charged tetrahydrofuran (280 L) and **8** (141.2 kg, 343.5 mol); the mixture was stirred and cooled to −55 °C. Meanwhile in a separate vessel was charged tetrahydrofuran (100 L) and diisopropylamine (54.7 kg, 540 L); the mixture was cooled to 0−5 °C and *n*-butyl lithium 15 wt % in hexane (226.3 kg, 536.7 mol) was added −5 °C. The solution of LDA was then added to the THF solution of **8**, maintaining the temperature of the reaction mixture at −55 °C throughout the addition. The mixture was stirred for a further 10 min. *tert*-Butyl bromoacetate (100.5 kg, 515.2 mol) was then added to the reaction, and the reaction was stirred at −50 °C for 3−7 h or until reaction completion by HPLC analysis. A solution of ammonium chloride (90 kg) in water (250 L) was added to the reaction, maintaining the temperature between −30−0 °C during the addition. The reaction was then warmed to 22 °C, and hexane (100 L) was added and stirred for at least 10 min. The phases were separated, and the organic phase was distilled under vacuum until the batch temperature reached 55 °C. Hexane (500 L) was added to the mixture, and the mixture was warmed to 60 °C; water (100 L) was added to the mixture, and the phases were allowed to separate. The aqueous phase was removed, and the water wash was repeated at 60 °C. The organic phase was the distilled under atmospheric to low volume until the batch temperature reached 77 °C. The reaction was cooled to 45 °C and stirred for at least 1 h. Seed crystals of **9** (0.05 kg) were added, and the reaction was stirred at 45 °C for at least 2 h, then cooled to 25 °C, and stirred for at least 1 h. Hexane was added to keep the slurry mobile, and the mixture was cooled to −5 °C and stirred for at least 2 h. The slurry was then charged to a centrifuge and deliquored; the product was dried under vacuum at 45 °C, to afford the *title compound* as a white solid, (90.41 kg, 63.4%). $[\alpha]_D$ = 30.2(*c* = 1 in $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 176.47, 171.24, 152.72, 133.63, 128.87, 125.86, 80.85, 78.88, 55.34, 39.98, 38.77, 38.15, 37.58, 30.60, 28.23, 20.38, 20.13, 14.50, 14.28.

(S)-2-((R)-2-Methylpentyl)succinic Acid 4-tert-Butylester ***10***. To a stirred reactor were charged water (442 L) and lithium hydroxide monohydrate (32.7 kg, 779.9 mol), and the mixture was cooled to 5 °C under nitrogen. Thirty-five percent hydrogen peroxide (86.6 kg, 891.3 mol) was added to the mixture, maintaining the temperature of the reaction at 5 °C throughout the addition. The reaction mixture was stirred for at least 15 min at this temperature. A solution of **9** (218.7 kg, 524 mol) in tetrahydrofuran (1163 L) was added to the reaction, maintaining the temperature of the reaction mixture at 5 °C. The reaction was stirred at this temperature for a further 3 h or until reaction completion by HPLC. A solution of sodium bisulfite (173.9 kg, 1671.3 mol) in water (710 L) was added to the reaction mixture, maintaining a reaction temperature of 0−20 °C through the addition; the mixture was then warmed to 22 °C and stirred at this temperature for at least 30 min. The layers were allowed to separate, and the lower aqueous layer was removed. The organic layer was then washed with a solution of sodium chloride (272.4 kg, 6810 mol) in water (885 L), the layers were separated, and the organic layer was distilled under reduced pressure to give an oil. Heptane (60 kg) was added to the oil and distilled under reduced pressure to an oil. Heptane (535 kg) was then added to the oil and the mixture cooled to 0−5 °C and granulated for at least 1 h. The slurry was filtered and washed with heptane (110 kg), and the product was dried under vacuum at 40−45 °C to afford the recovered chiral auxiliary **7** as a white solid (87.4 kg, 94%). Meanwhile to the combined heptane filtrates, (containing product) was added hot water (435 L), the mixture was stirred at 60 °C for at least 10 min, and then the layers were allowed to separate for at least 15 min, and the hot water wash was repeated twice (2 × 435 L). The combined heptane layers were then distilled under vacuum to an oil, TBME (340 L) was added to the oil at 20 °C to afford the title compound **10** as a solution in TBME (124.8 kg, 92.2%) MS, *m*/*z* (relative intensity): 257 [M + H, 100%].

(3S,5R)-3-Azidomethyl-5-methyloctanoic Acid tert-Butylester ***12***. To a stirred reactor was charged a solution of **10** in TBME (842.7 kg, 1090 mol, 1000 L), the reaction was cooled to 17 °C, and borane dimethylsulfide (101 kg, 1253 mol) was added to the solution whilst maintaining the temperature of the reaction at 25 °C. The reaction mixture was stirred at this temperature for at least 3 h, or until reaction completion by HPLC. Water (165 L) was charged to the reaction mixture, ensuring the temperature was maintained below 10 °C. The reaction mixture was washed with aqueous sodium bicarbonate (20 kg in 240 L water) and the mixture allowed to warm to 25 °C; the layers were allowed to separate for at least 30 min. The organic layer was separated, the

sodium bicarbonate wash was repeated, and again the layers were allowed to separate for at least 15 min. The organic layer was separated and washed with water (110 L) and aqueous sodium chloride (35 kg in 110 L water), the layers were allowed to separate, and the lower aqueous layer was removed. The organic layer was then distilled under vacuum to give **11** as an oil. To the oil was added TBME (1500 L) and methanesulphonyl chloride (156 kg, 1363 mol), the reaction mixture was cooled to 5 °C, and triethylamine (138 kg, 1363 mol) was added to the mixture, maintaining the temperature at 5 °C throughout the addition. The reaction mixture was then allowed to warm to 24 °C and stirred at this temperature for at least 1 h, or until reaction completion by HPLC. Water (700 L) was added to the mixture and stirred for at least 20 min, before allowing the layers to separate, the aqueous layer was removed, and a solution of conc. hydrochloric acid (30 kg) in water (750 L) was added to the mixture and stirred for at least 30 min before allowing the two layers to separate. The aqueous layer was removed, and the organic layer was washed with a sodium bicarbonate solution (40 kg) in water (480 L); the layers were allowed to separate, and the aqueous layer was removed. The organic layer was distilled under vacuum to give the mesylate as an oil; DMSO (100 kg) was added to the oil to give a solution. Meanwhilem to a separate reactor were charged DMSO (1560 kg) and sodium azide (70.8 kg, 1090 mol), and the mixture was stirred under nitrogen. This mixture was heated to 62 °C, the DMSO solution of mesylate was added to the azide solution, and the resulting mixture was stirred at 62 °C for at least 10 h or until reaction completion by HPLC analysis. The reaction was cooled to 20 °C, water (920 L) and hexane (1360 L) were added, and the mixture was stirred for at least 20 min before allowing the layers to separate. The reaction mixture was then washed with water (460 L). The organic layer was distilled under vacuum, a distillate of 750 ± 50 L was collected to leave a hexane solution of the title compound **12** (258.6 kg, 91.9% yield). $[\alpha]_D = -8.3$ ($c = 1$ in $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 172.01, 80.73, 54.89, 39.73, 39.46, 39.00, 33.40, 29.85, 28.30, 20.15, 19.82, 14.52.

(3S,5R)-3-Aminomethyl-5-methyloctanoic Acid tert-Butylester ***13***. To a stirred reactor was charged a solution of **12** in hexane (477.2 kg); the solution was cooled to 0−5 °C. Formic acid (90%) (450 kg, 8799 mol) was added to the solution, maintaining a batch temperature of 0−5 °C, followed by sulphuric acid (94%), (21.8 kg, 208.9 mol), again maintaining the reaction temperature of 0−5 °C. The reaction mixture was then distilled under vacuum, maintaining a batch temperature of no more than 30 °C until the batch volume reached 780 ± 15 L. The reaction mixture was then stirred at 23 °C for at least 10 h or until HPLC analysis showed reaction completion. TBME (485 L) and water (185 L) were added to the reaction mixture and stirred for at least 15 min, before allowing the layers to separate. The aqueous layer was removed, and the organic layer washed with water (90 L); the mixture was stirred for at least 15 min and then allowed to settle for 20 min. The aqueous layer was removed and the organic layer washed with water (2 × 90 L). The organic layer was distilled under vacuum until the batch volume reached 400−420 L, ensuring the batch temperature remained below 35 °C throughout the distillation. Hexane (200 kg) was added to the reaction and the mixture washed with sodium hydroxide solution, (665 kg, of a 50% sodium hydroxide solution, 134 kg in water 690 L); the reaction mixture was stirred for 20 min, (ensuring the pH of the reaction mixture was at least pH 12). The layers were then separated, and the sodium hydroxide wash was repeated. The combined aqueous layers were then combined and washed with TBME (750 L) and hydrochloric acid 37% (160 kg) (ensuring the reaction pH was <3) then the layers were separated and the aqueous layer was washed with TBME (375 L) and the layers separated. The organic layers were combined and distilled under vacuum maintaining the batch temperature less than 35 °C until the reaction volume was 350−400 L. Isopropyl alcohol (1000 L) was added to the mixture, and the mixture was distilled under vacuum, maintaining the internal temperature below 35 °C, until the reaction volume reached 350−400 L to afford the title compound **13** as a IPA solution (161.3 kg, 78.8%), which was used directly in the next step.

(3S,5R)-3-(Aminomethyl)-5-methyloctanoic Acid ***3***. To a hydrogenation vessel was charged 20% palladium hydroxide on carbon (50% wet; 10 kg) the reactor was evacuated under nitrogen. An IPA solution of **13** (67.3 kg, 196.9 mol) was added to the vessel, followed by IPA (1105 L). The resulting mixture was hydrogenated under 50 psi of hydrogen at 10 °C until hydrogen uptake ceased. Water (200 L) was added to the mixture, and the mixture was heated to 70−75 °C and filtered through a 0.2 μm filter. The filter cake was washed with warm IPA/water solution, (10:1, 120 L). The combined filtrates were distilled under vacuum, maintaining a batch temperature less than 40 °C until the reaction mixture reached a volume of 120−140 L. The mixture was cooled to 0−5 °C and granulated for at least 1 h, then filtered, washing with isopropyl alcohol (50 L). The product was dried under vacuum at 35−40 °C, then reslurried in isopropyl alcohol (395 L); the slurry was heated to reflux and held at reflux for 30 min before cooling to 0−5 °C and granulating for 1 h before filtering. The filter cake was washed with cold IPA (120 L) and the product dried under vacuum at 40−45 °C to afford **3** as a white solid (34.8 kg, 68.1% yield). Chiral purity of the product **3** was obtained by derivatisation with Marfey's reagent[12] (1-fluoro-2,4-dinitrophenyl-5-L-alanine amide; 5 mg/mL in acetonitrile) as follows: 20 mg of sample, diluted with water (10 mL), take 500 μL of the solution, add Marfey's reagent (500 μL), add 50 μL of 1 M $NaHCO_3$, seal the vial and mix at 40 °C for 1 h, quench with 1N HCl (50 μL); to (200 μL) of the mixture, dilute with (800 μL) mobile phase, inject the sample. Samples were analyzed on a Hitachi L-6200 instrument according to the following conditions: column BDS Hypersil C18, 100 mm × 4.6 mm i.d, 5 μm; eluent 38: 62 acetonitrile: 1% triethylamine (pH 3.0 water/H_3PO_4); wavelength, diode array (340 nm); column temperature, 60 °C; injection volume, 20 μL, flow rate 2 mL/min. The quasimolecular ion (MH+) of the title compound was observed at 188.1653 amu; IR (KBr) 2955. 8, 2212.1, 1643.8, 1551.7, 1389.9; ^1H NMR (400 MHz, CD_3OD) δ 4.91 (bs, 2H), 3.01−2.73 (m, 2H), 2.45−2.22 (m, 2H), 1.60−1.48 (m, 1H), 1.45−1.04 (m, 6H), 0. 98−0.86 (m, 6H); ^{13}C NMR (110.6 MHz, CD_3OD) δ 181.04, 45.91, 44.30, 42.13, 40.65, 33.42, 31.24, 21.39, 20.49, 15.1; de 99.4%. Anal. Calcd. For $C_{10}H_{21}NO_2$: C, 64.13; H, 11.30; N, 7.48, found C, 64.22; H, 11.32; N, 7.43.

Mandelic Acid Resolution Route: (*R*)-2-Methyl-1-pentanol. A 2000-L reactor was charged with vinyl decanoate (526.7 kg, 2.66 mol, 0.87 equiv), 2-methyl-1-pentanol (312 kg, 3.05 mol), methylene chloride (1006.8 kg), and Amano Lipase PS-C1 (3.75 kg, 1.2 wt %). The reaction was stirred at room temperature for approximately 19 h (until reaction completion, 96% ee, calculated by gas chromatography after derivatisation to 2-methylvaleric acid), the enzyme was removed by filtration, and the reaction mixture was distilled under atmospheric pressure to remove the methylene chloride and then placed under vacuum

(275 mmHg pressure). The fraction with a boiling range of 109−110 °C was collected, to afford the *title compound* as a colorless oil, (75.5 kg, 24% yield, 92% chemical purity, enantiomeric purity 96% ee). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 68.10, 35.50, 35.36, 19.98, 16.72, 14.12.

(R)-2-Methylpentyl methanesulfonate. A 4000 L reactor was charged with (*R*)-2-methylpentan-1-ol (260 kg, 2545 mol), TBME (2000 L), and cooled to −10 to 0 °C. Methanesulfonyl chloride (310 kg, 2705 mol) was charged, and then Et_3N (310 kg, 3063 mol) was added while maintaining the internal temperature at 0 to 10 °C. After the addition was complete, the reaction mixture was warmed to 15 to 25 °C and stirred at this temperature for at least 1 h until complete by GC analysis. A solution of aq HCI (88 kg of conc. HCl in 700 L of water) was then added to the reaction mixture. The resulting mixture stirred for at least 15 min, settled for at least 15 min and then the lower aqueous phase was removed. The upper organic phase was washed with water (790 L) and aqueous sodium bicarbonate (67 kg of sodium bicarbonate in 840 L of water). The solution was then concentrated under vacuum to remove the TBME to afford the *title compound* as an oil (472 kg, 95% yield). ^{1}H NMR (400 MHz, $CDC1_3$) δ 4.07−3.93 (m, 2H), 2.97 (s, 3H), 1.91−1.80 (m, 1H), 1.42−1.09 (m, 4H), 0.94 (d, J = 6.57 Hz, 3H), 0.87 (t, J = 6.56 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 74.73, 37.01, 34.81, 32.65, 19.71, 16.29, 14.04.

(2′R)-2-Cyano-2-(2′-methyl-pentyl)succinic Acid Diethyl Ester ***15***. A 4000 L reactor was charged with (*R*)-2-Methylpentyl methanesulfonate (245 kg, 1359 mol), 2-cyanosuccinic acid diethylester (298 kg, 1495 mol) and anhydrous EtOH (1300 kg). Sodium ethoxide (506 kg, 21 wt % in EtOH) was added. The resulting solution was heated to 70−75 °C and the mixture stirred at this temperature for at least 18 h until complete by GC analysis. After the reaction was complete, a solution of aqueous HCl (32 kg of conc. HCl in 280 L of water) was added to the reaction mixture until the pH was <2. Additional water (400 L) was added, and the reaction mixture was then concentrated under vacuum to remove the ethanol. TBME (1000 kg) was added and the mixture was stirred for at least 15 min, settled for at least 15 min and then the lower aqueous layer was back extracted with TBME (900 kg). The combined organic phases were concentrated under vacuum to afford the product **15** as a dark oil (294 kg, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (q, J = 7.07 Hz, 2H), 4.18 (q, J = 7.07 Hz, 2H), 3.03 (dd, J = 6.6, 7.1 Hz, 2H), 1.93−1.61 (m, 3H), 1.40−1.20 (m, 10H), 0.95−0.82 (m, 6H); ^{13}C NMR (100.6 MHz, $CDC1_3$) δ 168.91, 168.67, 168.59, 168.57, 119.08, 118.82, 62.95, 62.90, 44.32, 44.19, 42.21, 42.02, 39.77, 39.64, 30.05, 29.91, 20.37, 19.91, 19.66, 13.99.

Method A (5R)-3-Cyano-5-methyloctanoic Acid Ethyl Ester ***16***. A 4000-L reactor was charged with NaCl (175 kg, 3003 mol), tetrabutylammonium bromide (33.1 kg, 103 mol), water (87 L), and DMSO (1000 kg). (2′*R*)-2-Cyano-2-(2′-methylpentyl)succinic acid diethyl ester (243 kg, 858 mol) was charged, and the mixture was heated to 135−138 °C and stirred at this temperature for at least 48 h, until complete by GC analysis. After the reaction was cooled to 25−35 °C, heptane (590 kg) was added, and the mixture stirred for at least 15 min and settled for at least 15 min, and then the lower aqueous phase was removed. The upper organic phase was washed with water (800 L). The heptane solution containing the product was decolorized with carbon and concentrated under vacuum to afford the title compound as an orange oil (133.9 kg, 74% yield corrected for purity). ^{1}H NMR (400 MHz, $CDC1_3$) δ 4.20 (q, J = 7.07 Hz, 2H), 3.13−3.01 (m, 1H), 2.75−2.49 (m, 2H), 1.80−1.06 (m, 10H), 0.98−0.86 (m, 6H); ^{13}C NMR (100.6 MHz, $CDC1_3$) δ 169.69, 169.65, 121.28, 120.99, 61.14, 39.38, 39.15, 38.98, 37.67, 37.23, 36.95, 30.54, 30.47, 25.67, 25.45, 19.78, 19.61, 19.53, 18.56, 14.13, 14.05.

Method B (5R)-3-Cyano-5-methyloctanoic Acid Ethyl Ester ***16***. A 250-mL flask was charged with LiCl (3. 89 g, 0.09 mol), water (7 mL), and DMSO (72 mL). (2′*R*)-2-Cyano-2-(2′-methylpentyl)succinic acid diethyl ester (25.4 g, 0.07 mol, 78.74% by GC) was charged, and the mixture was heated to 135−138 °C and stirred at this temperature for at least 24 h, until complete by GC analysis. After the reaction was cooled to 25−35 °C, heptane (72 mL), saturated NaCl (72 mL) and water (72 mL) were added, and the mixture stirred for at least 15 min, settled for at least 15 min, and then the lower aqueous phase was washed with heptane (100 mL). The combined organic phases were concentrated under vacuum to afford the title compound as an orange oil (13.0 g, 85% yield).

(5R)-3-Cyano-5-methyloctanoic Acid Sodium Salt ***17***. A 4000-L reactor was charged with (5*R*)-3-cyano-5-methyloctanoic acid ethyl ester (250 kg, 1183 mol) and THF (450 kg). An aqueous solution of NaOH was prepared (190 kg of NaOH in 350 L of water) and then added to the THF solution. The resulting solution was stirred at 20−30 °C for at least 2 h, until the reaction was complete by GC analysis. After this time, THF was removed by vacuum distillation to afford an aqueous solution of the product **17**, which was used immediately in the next step.

(5R)-3-Aminomethyl-5-methyloctanoic Acid Sodium Salt. A 120-L autoclave was charged with sponge nickel catalyst (3.2 kg, Johnson Matthey A7000) followed by an aqueous solution of (5*R*)-3-cyano-5-methyloctanoic acid sodium salt (15 kg in 60 L of water,) and the resulting mixture was hydrogenated under 50 psi of hydrogen at 30−35 °C for at least 18 h, or until hydrogen uptake ceased. The reaction was then cooled to 20−30 °C, and the spent catalyst was removed by filtration through a 0.2 μm filter. The filter cake was washed with water (2 × 22 L), and the resulting aqueous solution of the title compound was used directly in the next step without isolation.

(5R)-3-Aminomethyl-5-methyloctanoic Acid ***14***. A 4000-L reactor was charged with an aqueous solution of (5*R*)-3-aminomethyl-5-methyloctanoic acid sodium salt (150 kg in 1000 L of water) and cooled to 0−5 °C. Glacial acetic acid was added until the pH was 6.3−6.8. To the mixture was added anhydrous EtOH (40 kg). The resulting slurry was heated to 65−70 °C for less than 20 min and was cooled to 0−5 °C over 3 h. The product was collected by filtration to afford the product **14** as a water-wet cake (76 kg, 97% yield corrected for purity, 10% water by KF), which was used directly in the next step. ^{1}H NMR (400 MHz, CD_3OD) δ 4.97 (bs, 3H), 3.00−2.74 (m, 2H), 2.48−2.02 (m, 3H), 1.61−1.03 (m, 7H), 0.94−086 (m, 6H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 181.10, 181.07, 46. 65, 45.86, 44.25, 43.15, 42.16, 41.64, 41.35, 33.45, 31.25, 31.20, 21.45, 21.41, 20.52, 20.12, 15.15, 15.12.

(3S,5R)-3-(Aminomethyl)-5-methyloctanoic Acid ***3*** *via (S)-Mandelic Acid Resolution.* A 4000-L reactor was charged with water wet (10%) (5*R*)-3-aminomethyl-5-methyloctanoic acid (76 kg, 365 mol), (*S*)-mandelic acid (34. Eight kg, 229 mol), anhydrous EtOH (1780 kg), and water (115 L). The resulting mixture was heated to 65−70 °C and stirred until the solids dissolved. The solution was then cooled to 0−5 °C over 2 h and stirred at this temperature for an additional 1 h. The product was collected by filtration, and the cake was washed with cooled EtOH (3 × 60 kg). The crude damp product (18 kg, 24% yield)

and EtOH (167 kg) were charged to a reactor. The mixture was cooled to 0−5 °C and stirred at this temperature for 1.5 h. The product was then collected by filtration, and the cake was washed with cold EtOH (3 × 183 kg) to afford the title compound (17 kg, 94% yield).

Orthoester Route. *Methyl (5R)-3-Cyano-5-methyloctanoate **21***. A reactor was charged with toluene, (227.5 L), (*R*)-2-methylpentan-1-ol (35 kg, 342.5 mol), and Et_3N (38.1 kg, 376.8 mol) cooled to 0 °C. Methanesulfonyl chloride (41.2 kg, 359.6 mol) was added while maintaining the internal temperature at 0−10 °C. After the addition was complete, the slurry was warmed to 25 °C and stirred at this temperature for at least 1 h until complete by GC analysis. Water (105 L) was then added to the reaction and the resulting mixture stirred for at least 40 min, settled for at least 15 min and then the lower aqueous phase was removed. Water (24.5 kg) was added, followed by sodium bromide (35.2 kg, 342.5 mol) and tetrabutylammonium bromide (22.1 kg, 68.5 mol), the mixture was heated to 90 °C and stirred at this temperature for at least 3 h or until reaction completion by GC analysis. The reaction mixture was then cooled to 25 °C, and water (185.5 L) was added. The mixture was stirred for at least 30 min and settled for at least 30 min, and then the lower aqueous layer was removed. 4,4,4-Trimethoxybutyronitrile (65.4 kg, 411 mol) was added portion wise to the reaction mixture followed by toluene (30.2 kg, 35 L), the reaction mixture was cooled to −10 °C. Meanwhile in a separate vessel, THF (236.4 kg, 266 L) was added to precooled (−10 °C) potassium *tert*-butoxide (134.5 kg, 1198.8 mol). The premixed toluene solution of 4,4,4-trimethoxybutyronitrile and (*R*)-1-bromo-2-methylpentane was then added to the base over a minimum of 2 h, maintaining the temperature throughout the addition between −2 °C and −10 °C, followed by a line wash of THF (10 kg, 11.2 L). The reaction mixture was stirred for a further 18 h or until reaction completion by GC analysis, maintaining the reaction temperature between −2 °C and −10 °C, throughout this period. Water (280 L) was added to the reaction mixture maintaining the temperature between −10 and 25 °C. The reaction mixture was stirred at 25 °C and a solution of 4 M HCl (118 kg conc. HCl in 228 L water) was added to the reaction mixture over 1 h until a final pH of 1−2 was achieved. The reaction mixture was stirred at 25 °C for a period of at least 2 h or until reaction completion by GC, settled for at least 20 min and then the lower aqueous layer was removed. Water (280 L) was added to the reaction mixture, the mixture was stirred for at least 20 min, settled for at least 20 min and then the lower aqueous layer was removed. The mixture was then distilled under reduced pressure down to a volume of 60 L to give the product **21** as a solution in toluene (54 kg, 79.9% yield) which was used directly in the next step.

*Methyl (3S,5R)-3-Cyano-5-methyloctanoate **22***. A reactor was charged with water (486 L) and sodium bicarbonate (17.3 kg, 205.5 mol), the mixture was stirred at 25 °C until a solution was formed, whereupon Lipase PS-SD (10.8 kg, ∼23,000 U/g) was charged, and the mixture was stirred until a solution was formed. The solution was transferred to a vessel containing the toluene solution of **21** from the previous step, and the reaction mixture was warmed to 45 °C with vigorous stirring. The reaction was stirred at this temperature for 48 h or until reaction completion by GC analysis, (NMT 2% (3*R*,5*R*)-3-cyano-5-methyloctanoate remaining). Sodium chloride (162 kg) was added to the reaction mixture and stirred for at least 30 min. The reaction was cooled to 25 °C. TBME (159.8 kg) was added to the mixture, stirred for at least 30 min, and settled for at least 1 h; then, the lower aqueous phase was separated, and the upper TBME layer was filtered through a 1.2 μm filter to give **22** as a TBME solution (202.4 kg, which equates to 24.6 kg, 45.6% of **22**). This was taken through to the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (q, J = 7.83 Hz, 2H), 3.13−3.06 (m, 1H), 2.71−2.58 (m, 2H), 1.75−1.64 (m, 10H), 0.95(d, J = 6.34, 3H), 0.92, (t, J = 6.83, 3H). ^{13}C NMR (110.6 MHz, $CDCl_3$) δ 170.4, 121.8, 61.1, 39.6, 38.6, 37.0, 31.0, 25.9, 20.0, 18.5, 13.9.

*Crude (3S,5R)-3-(Aminomethyl)-5-methyloctanoic Acid **3***. A reactor was charged with water (80 L) and 40% sodium hydroxide (13.7 kg, mol), the mixture was stirred at 25 °C and a solution of **22** in TBME (202.4 kg, (24.6 of **22**), 24.7 mol) from the previous step was added, maintaining the temperature at 25 °C. Additional charges of 40% sodium hydroxide (13.7 kg, 137.2 mol) and water (10 kg) were then added to the reaction mixture, and the reaction stirred for at least a further 4 h at 25 °C, or until reaction completion. Agitation was stopped, and the two phases settled for at least 30 min; the lower aqueous phase was transferred directly to a loop reactor and purged with nitrogen. The loop reactor was charged with water (8 L) and sponge nickel catalyst (5 kg, Johnson Matthey A7603), and the resulting mixture was hydrogenated under 50 psi of hydrogen at 30−35 °C for at least 18 h, or until hydrogen uptake ceased. The reaction was then cooled to 20−30 °C, and the spent catalyst was removed by filtration through a 1.2 μm filter. The filter cake was washed with water (2 × 45 L). The combined aqueous washes were treated with aqueous citric acid (16 kg in 16 L water) until the pH of the reaction was between pH 5.5 and 6.5. To the resulting slurry was added anhydrous ethanol (77.6 kg), and the slurry was heated to reflux and stirred at this temperature until a solution was obtained. The reaction was then cooled to 0−2 °C over 3.5 h and then granulated at this temperature for 18 h. The solid was washed with EtOH (2 L) and water (2 L) and dried under vacuum at 35 °C to give the crude product **3** (18.09 kg, 77.3% yield), which was taken directly into the next step.

*Recrystallisation of **3***. A reactor was charged with water (250 L), anhydrous ethanol (197.2 kg, 250 L), and crude **3** (25 kg, 133.5 mol), the mixture was heated to 75 °C at a rate of 0.5 °C/min, and the mixture was held at his temperature for 1 h and then cooled at a rate of 0.5 °C/min to 0 °C. The slurry was granulated at this temperature for 2 h, then washed with cold anhydrous ethanol (98.6 g), and dried under vacuum at 50 °C to give the product **3** (21.84 g, 87.4% yield).

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