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Chemical Development of CI-1008, an Enantiomerically Pure Anticonvulsant

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Abstract:

Development of a manufacturing process for (*S*)-3-(aminomethyl)-5-methylhexanoic acid, an anticonvulsant, is described. Initial preparation employed an Evans chiral alkylation on (4*R*,5*S*)-4-methyl-3-(1-oxo-4-methylpentyl)-5-phenyl-2-oxazolidinone, using benzyl bromoacetate. Use of *tert*-butyl bromoacetate proved advantageous for large-scale preparation. Route selection for a low-cost manufacturing process was based on "ideal process" cost projections. Four routes were evaluated in the laboratory. Of the four, two were scaled up in the pilot plant, resulting in selection of a route based on synthesis of racemic 3-(aminomethyl)-5-methylhexanoic acid, followed by resolution with (*S*)-(+)-mandelic acid.

Introduction

CI-1008 is the title assigned by Parke-Davis to (*S*)-3-(aminomethyl)-5-methylhexanoic acid. It is an anticonvulsant believed to have a mechanism of action similar to that of Neurontin, a drug introduced to the market by Parke-Davis in 1994. On the basis of early animal tests, CI-1008 was expected to show several times higher activity and increased duration of action compared to Neurontin.[1] These data indicated the possibility of twice a day dosing for CI-1008, compared to three times a day with Neurontin, an advantage in terms of increased patient compliance. Early animal tests also showed that only the *S* enantiomer of CI-1008 has the desired pharmacological activity; development has proceeded using the pure enantiomer.

Several factors influenced our decisions at the outset of the CI-1008 project. We anticipated that large quantities of product would be needed for toxicity testing, since the toxicity of CI-1008, like that of Neurontin, was expected to be low. Furthermore, the existing regulatory climate was such that settling on a final process early was desirable. That climate included these elements: (1) the requirement by the FDA for evidence that process changes, especially those made late in development, do not introduce new impurities or alter bioavailability of the bulk drug and (2) the requirement for a consistent bulk drug earlier for development and validation of the dosage formulation.

It was clear from the outset that the discovery synthesis[1] would not be a suitable manufacturing process, at least not without extensive modification. An approach was needed which would allow production of significant quantities of material on an early deadline, while developing a final manufacturing process as soon as possible. More specifically this would involve using the discovery synthesis to prepare the initial few kilograms of drug and then modifying as necessary to produce a quantity in the 30−50 kg range. A parallel development program would be aimed at searching out and selecting an ultimate process suitable for manufacturing.

Discovery Synthesis

Prior to beginning our chemical development work the total quantity of CI-1008 prepared was about 50 g. The synthetic route (Scheme 1) used an asymmetric Evans alkylation[2] based on a chiral auxiliary prepared from (+)-norephedrine (**4**). A benzyl ester was employed to mask the carboxylic acid in the alkylation. The optical purity of material issuing from this synthesis was excellent. In general, however, the route in its original form was of limited use for scale-up, owing principally to (1) low temperature (−78 °C) reactions, (2) column chromatography for isolation and purification of three intermediates, (3) side reactions such as lactone and lactam formation, and (4) low overall yield (10%). Moreover, the literature gives little data on recycling of the chiral auxiliary, a recognized necessity for favorable process economics.

Modifying the Discovery Synthesis for Multikilogram Production

Laboratory work resulted in several improvements which put this procedure on a better footing for scale-up. The low-temperature reactions were investigated first, with the result that the acylation reaction used to form **6** was found to be insensitive to temperature. No difference in yield or product purity was seen between reactions run at −78 and 0 °C. Similarly the alkylation to form **7a** could be run at temperatures as high as −35 °C. Above that temperature the yield dropped substantially.

A second area of concern was to avoid the serious product loss caused by formation of lactone **12** in the workup of the borane/DMS reduction of **8a**. Intramolecular displacement of the benzyloxy moiety by the newly formed primary alcohol group took place so readily that this product required careful handling and low-temperature storage to maintain its integrity. Solvent alterations improved this situation somewhat, but it was clear that this side reaction would impede scale-up. Use of the *tert*-butyl ester in place of the benzyl ester showed improved stability. Under pilot plant conditions the benzyl ester gave 16.7% lactone, while the *tert*-butyl ester reproducibly gave 5.8% lactone.

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* Telephone: 616-392-2375. Fax: 616-392-8916.

[1] Yuen, P.; Kanter, G. D.; Taylor, C. P.; Vartanian, M. G. *Bioorg. Med. Chem. Lett.* **1994**, *6*, 823.

[2] Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

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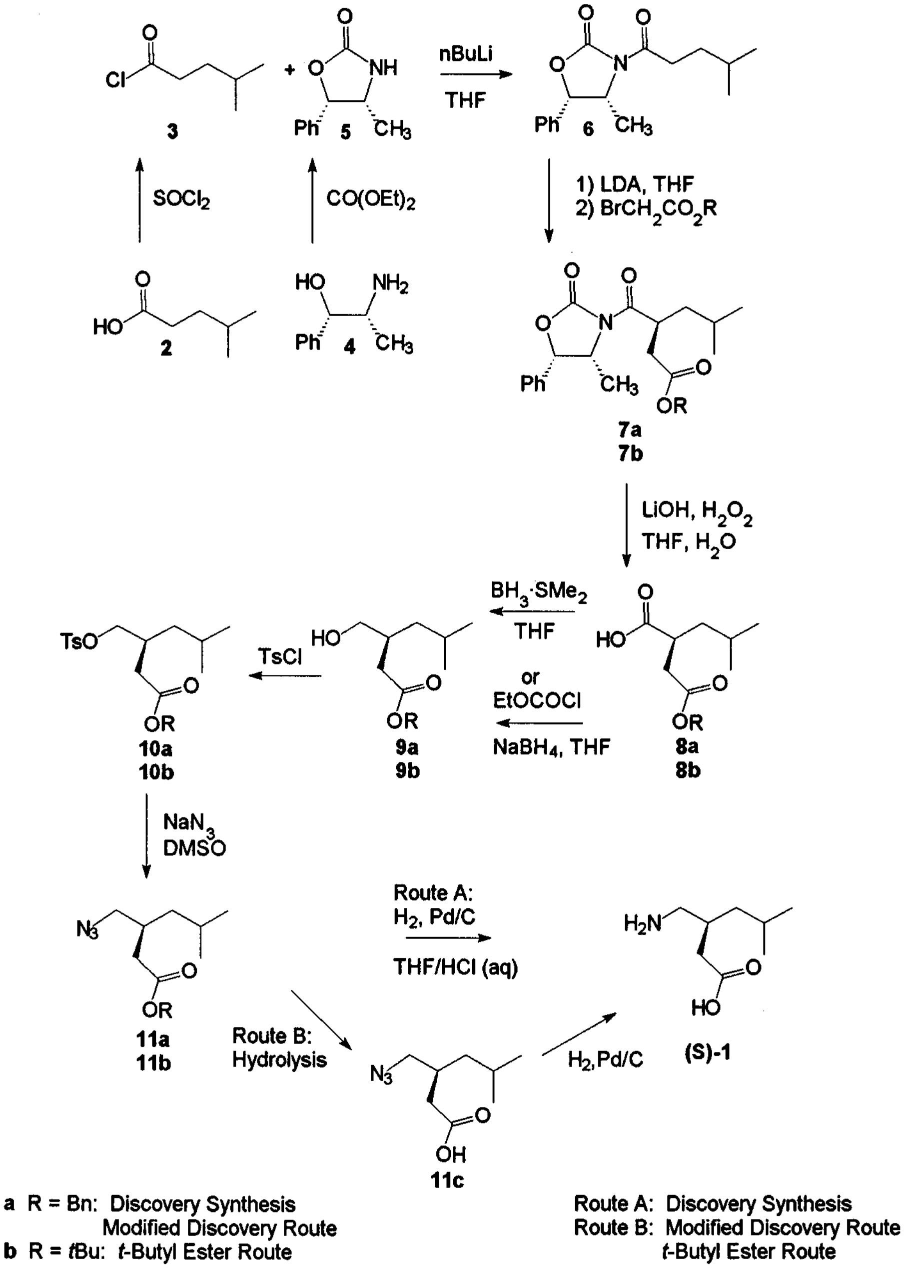
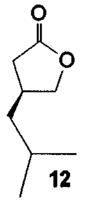
Scheme 1. **Norephedrine-based synthetic routes**

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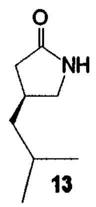
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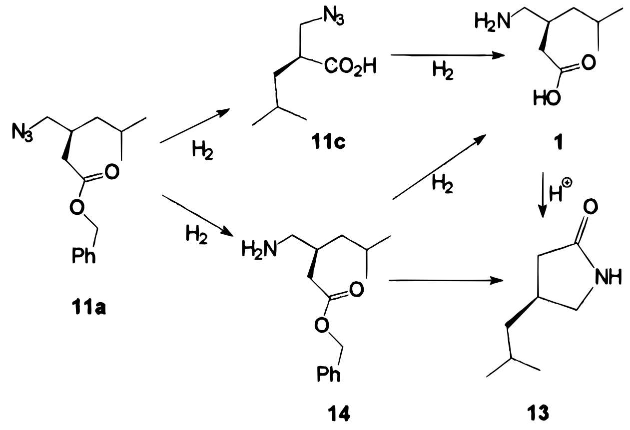
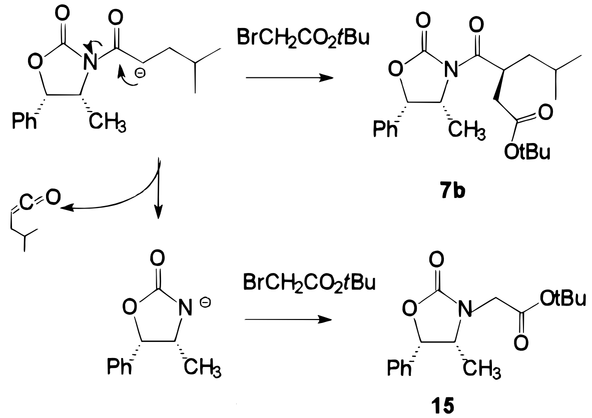
Conversion of the azido benzyl ester **11a** to CI-1008 proceeded in low yield in the original procedure. Hydrogenation in a mixture of aqueous HCl and tetrahydrofuran gave CI-1008 isolated in 33% yield. In part the low yield can be explained by significant formation of lactam **13**. A second cause of the low yield was the inefficient recovery of water soluble CI-1008 by aqueous base treatment of the initially formed hydrochloride. Attempted reduction of **11a** under neutral conditions gave only **13**. Possible routes to **13** are shown in Scheme 2, which indicates that reduction of either the azide or the benzyl ester can occur first. It is probable that reduction of **11a** under acidic conditions gives more CI-1008 than under neutral conditions because the amine group is protonated and cyclization is retarded. In any case, we viewed reduction of **11a** to have a low probability of success on a pilot plant scale. For our first preparation of CI-1008, we needed to find a way to go from the azido benzyl ester **11a** to CI-1008 in synthetically useful yields. The preferred approach was to hydrolyze the **11a** under basic conditions to the azido carboxylic acid **11c**, which could be hydrogenated without significant lactam formation. An added benefit from this approach was that

Scheme 2. **Lactam formation**



Scheme 3. **Alkylation side product**



11c could be separated from several troublesome impurities by extracting it into base and recovering by acidification; this finding enabled us to avoid the chromatographic purification used previously. Hydrogenation of **11c** under neutral conditions gave chloride-free CI-1008 in 55% overall yield from the azido benzyl ester. This yield enabled us to prepare CI-1008 in kilogram quantities.

The benzyl ester route was developed only to the point of preparing the initial multikilogram supplies. Even so the following improvements were achieved, compared to the discovery process: temperatures below −35 °C were avoided; lactam formation was minimized; three chromatographic purifications were circumvented; and the overall yield was improved from 10% to 24%.

After the benzyl ester route was scaled up to make the first 6.4 kg of CI-1008, subsequent supplies were obtained using the *tert*-butyl ester route. Additional experimentation increased our understanding of the asymmetric alkylation. For example, as was the case with the benzyl ester, attempts to raise the temperature of the *tert*-butyl bromoacetate alkylation above −35 °C gave reduced yields. Temperature studies showed that the alkylation achieves identical stereoselectivity (97:3) at either −78 or −35 °C. Reaction mixtures above −35 °C were found to contain a product corresponding to alkylation of **5** at nitrogen with *tert*-butyl bromoacetate (Scheme 3). This product is consistent with loss of isobutylketene from the α-lithio anion of **6**, followed by alkylation of the nascent amide anion with *tert*-butyl bromoacetate. Although Evans[2] has referred to decomposition of the lithium enolates by a ketene pathway at temperatures greater than 0 °C, our results indicate that this side reaction interferes significantly above −35 °C.

Continued scale-up of the acylation of **5** also pointed to an interesting side reaction (Scheme 4). This reaction was discovered when a large-scale batch gave a yield of 80% instead of the expected 95%. Examination of the filtrate showed a substantial fraction of a new impurity. Structural elucidation by proton NMR showed this byproduct to be epimeric to the desired compound at the carbon adjacent to the phenyl ring of **5**. The normal procedure for this reaction is to add *n*-butyllithium in hexane to a solution of **5** in tetrahydrofuran to make the amide anion. Subsequent addition of the acid chloride **3** gives the desired intermediate. A review of the procedure used to make this particular batch showed that a slight excess (<5%) of *n*-butyllithium had been used. Laboratory work showed that such an excess of *n*-butyllithium was associated with the occurrence of epimerization. It was also noted that excess *n*-butyllithium caused a deep red color to appear in place of the yellow color characteristic of the solution containing no excess of *n*-butyllithium. This color implied the presence of a dianionic species containing a carbanionic center adjacent to the phenyl group. Epimerization could occur through degenerate protonation of this species. The acylation product of the unwanted epimer (**6b**) was freely soluble in the reaction medium, and it remained in solution when the desired product was isolated by crystallization, causing the yield loss. The problem was solved by using the red color as an indicator. Careful addition of *n*-butyllithium to the reaction mixture, in such a way that the red color was not allowed to form, prevented epimerization and maintained the expected high yield.

While scaling up the *tert*-butyl ester process, we found that the chiral auxiliary **5** could be recycled. A recovery of 85% of the chiral auxiliary was achieved in the formation of carboxylic acid **8**. Overall recovery of **5** was 64%.

On a pilot plant scale the borane/dimethyl sulfide reduction of carboxylic acid **8b** to alcohol **9b** required careful engineering, processing, and scrubbing to contain the odor of dimethyl sulfide. Our response was to develop an alternative which consisted of preparing the mixed anhydride of **8b** with ethyl chloroformate and reducing with sodium borohydride.[3] The yields for the two reduction routes are similar.

The *tert*-butyl ester process represented a significant advance over the modified benzyl ester chemistry and was used to prepare several hundred kilograms of CI-1008. This process incorporated three noteworthy improvements: (1) Lactone formation was reduced by 66%. (2) Recycling of 64% of chiral auxiliary **5** was achieved. (3) The overall yield was increased to 33%.

Searching for Low-Cost CI-1008

Having supplied bulk chemical for the initial stages of the CI-1008 development program, we turned our attention to cost objectives for full-scale manufacturing. Based on

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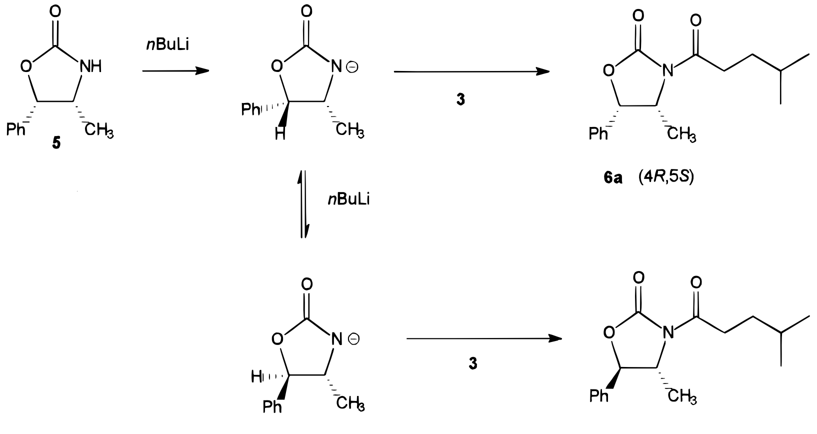
(3) Ishizumi, K.; Koga, K.; Yamada, S.-I. *Chem. Pharm. Bull. Jpn.* **1968**, *16*, 492. Rodriguez, M.; Llinares, M.; Doulut, S.; Heitz, A.; Martinez, J. *Tetrahedron Lett.* **1991**, *32*, 923.

Scheme 4. **Epimerization of 6**



the overall economics of the CI-1008 program, the estimated manufacturing cost using the *tert*-butyl ester route exceeded the required cost by a factor of 6. Most of this high cost was related to the expense of the (+)-norephredrine-based chiral auxiliary **5**, which contributes only to the chirality of the final molecule, not to the carbon skeleton. Recovery of **5** was high (85%) from the step in which it is cleaved from **8b**, but much of it was lost as byproducts in previous steps. Other materials contributing to the excessive cost were 4-methylpentanoic acid and *tert*-butyl bromoacetate. In general, despite extensive optimization (average yield: 90% per step), the length (10 steps) and linearity of the synthesis resulted in high cost. In response we initiated a program to identify and explore several of the most promising potential routes to CI-1008.

The challenge was to identify which of the many possible synthetic routes to CI-1008 would be superior in a commercial application. In the absence of experimental data we decided to compare several of the proposed synthetic procedures using what we refer to as "ideal process" cost projections. These included the assumptions of (1) 100% yields, (2) no labor or overhead cost, (3) no waste disposal costs, and (4) bulk prices for raw materials. On the basis of this analysis we estimated the following relative costs for the most promising alternate routes compared to the *tert*-butyl ester route:

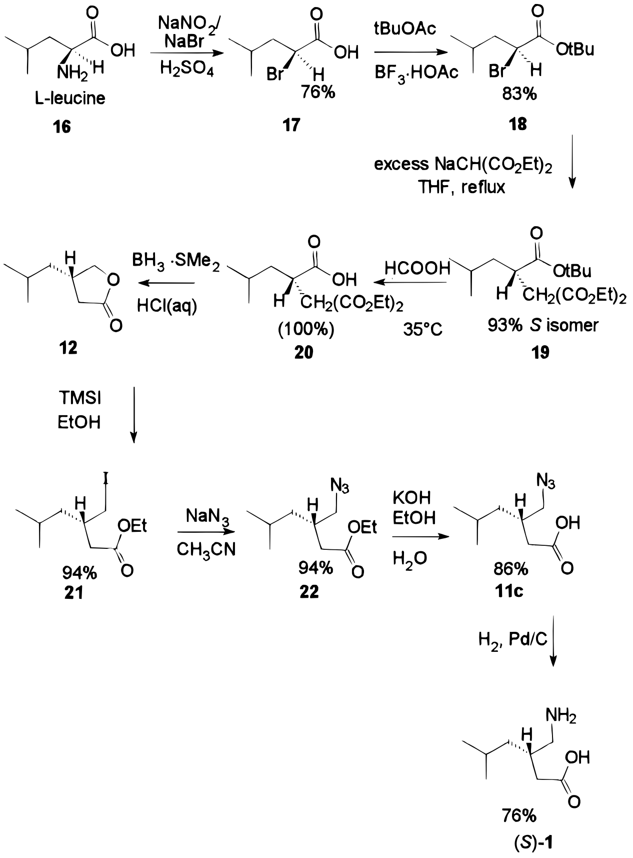
synthetic route	relative cost
tert-butyl ester route	12.2
L-leucine approach	6.1
Stobbe condensation	2.2
malonate route	1.5
resolution of γ-isobutylglutaric acid derivatives	1.0

We ultimately evaluated all four of the alternate processes in the laboratory and found that, even with better yield data and processing information in hand, the order of expected manufacturing cost did not change.

L-Leucine Approach

We found that L-leucine could be converted to CI-1008 using the synthetic route illustrated in Scheme 5. The α-bromo acid **17** was produced as previously reported[4] and transesterified to give ester **18** using *tert*-butyl acetate. Displacement of bromide with excess diethyl sodiomalonate gave **19** in good yield. This intermediate was not easily purified and was carried into the next step as a mixture with excess diethyl malonate. The chiral lactone **12** was opened with trimethylsilyl iodide and elaborated to CI-1008 via the azide. The primary attraction of this route in comparison to the other routes under consideration was that the chirality is built right into the starting substance. However, in spite of the initially favorable outlook for this reaction sequence, L-leucine was found not to be low enough in cost to compensate for the relatively long synthesis (nine steps). After exploring this route to the point of preparing gram quantities of (*S*)-**1**, it was set aside in favor of other, more advantageous sequences.

Scheme 5. **L-Leucine approach**



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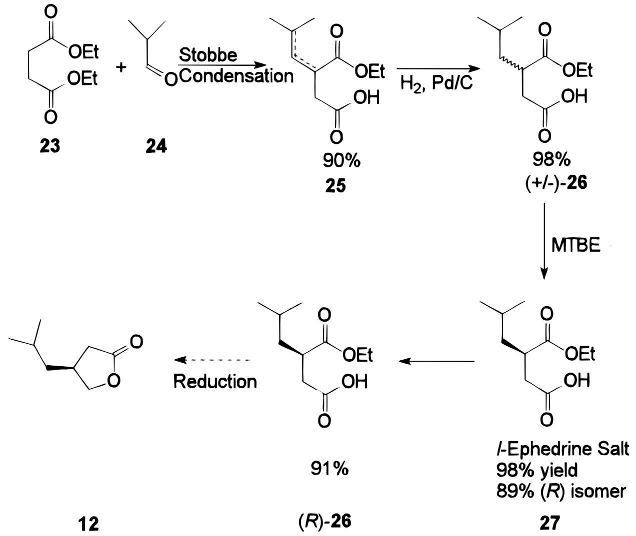
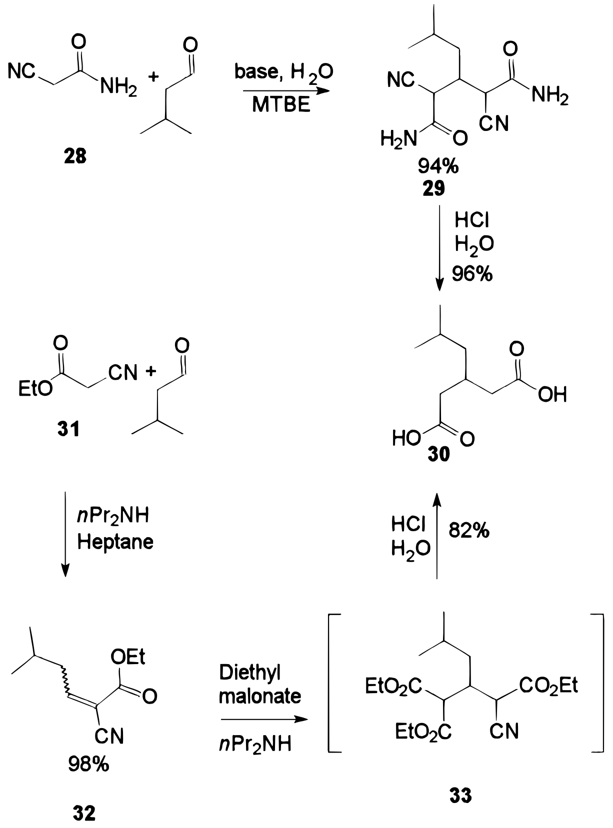
[4] Dutta, A. S.; Giles, M. B.; Gormley, J. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 111.

Scheme 6. **Stobbe approach**



Scheme 7. **Synthesis of γ-isobutylglutaric acid**



Stobbe Condensation

A second route based on Stobbe condensation of isobutyraldehyde (Scheme 6) with diethyl succinate[5] was worked out through the same chiral lactone intermediate (**12**) as was used in the L-leucine approach. The key chirality-inducing step in this route was classical resolution of the monoester **26** with *l*-ephedrine. With the addition of the four-step conversion of lactone **12** to CI-1008, the overall sequence consisted of nine steps. The length of the synthesis, in combination with an unsatisfactory overall yield, caused us to set it aside to explore others.

Enzymatic Resolution of a γ-Isobutylglutaric Acid Derivative

On the basis of earlier work,[1] we recognized the opportunity of achieving a very efficient synthesis by converting prochiral γ-isobutylglutaric acid to an appropriate chiral intermediate using an enzyme. Two routes were developed for the synthesis of γ-isobutylglutaric acid (Scheme 7). Initially the condensation of 2 equiv of cyanoacetamide with isovaleraldehyde[6] was used. This reaction is followed by hydrolysis with aqueous hydrochloric acid to give the desired diacid. Disadvantages of this route included (1) high cost for cyanoacetamide, (2) low throughput, and (3) an unavoidable isolation of a solid intermediate. The latter two factors were occasioned by the low solubility and emulsifying tendencies of the intermediate condensation product **29**, which caused large amounts of solvent to be used to keep the reaction mixture fluid. The preferred method proved to be initial di-*n*-propylamine catalyzed condensation of isovaleraldehyde with ethyl cyanoacetate[7] to give **32**, followed by a second condensation with diethyl malonate to give triester **33**. Hydrolysis of **33** yielded γ-isobutylglutaric acid. No isolation of either intermediate was required. An advantage of this route is that the intermediates are liquids, resulting in high throughput. The lower costs of ethyl cyanoacetate (ca. 30% of the cost of cyanoacetamide) and diethyl malonate were further advantages. Ethyl cyanoacetate was used as starting point for all large-scale pilot plant work.

After screening of a number of γ-isobutylglutarate diesters with several different enzymes, our chosen intermediate–enzyme combination was diisopropyl γ-isobutylglutarate (**34**) with porcine liver esterase (Scheme 8). The monoester **35** was isolated in 98% yield with a maximum of 85% enantiomeric purity. Contrary to what we would have expected from the literature,[1] the *S* enantiomer predominated. The *S* enantiomer could be used by applying a conversion of the ester to the primary amide (*R*)-**36** using lithium methoxide and formamide in a mixed solvent system.[8] The Hofmann rearrangement was used to convert (*R*)-**36** to (*S*)-**1**. The enzymatic reactions were only successful at low concentrations, a factor which did not lend this chemistry to large-scale work. Then, too, conversion of the monoester **35** to monoamide **36** is a transformation of only moderate yield. Nonetheless, the short, direct synthesis of CI-1008 by this route inspired us to look into other alternatives to the enzymatic resolution.

Classical Resolution of a γ-Isobutylglutaric Acid Derivative

Our work with the monoamide (**36**) of γ-isobutylglutaric acid alerted us to the concept of using classical resolution on this intermediate. The resolved (*R*)-**36** could then be converted to CI-1008 using the Hofmann rearrangement.[9] We found an improved synthesis of (±)-**36** from the diacid

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[5] Andruskiewicz, R.; Barrett, A. G. M.; Silverman, R. B. *Synth. Commun.* **1990**, 159.

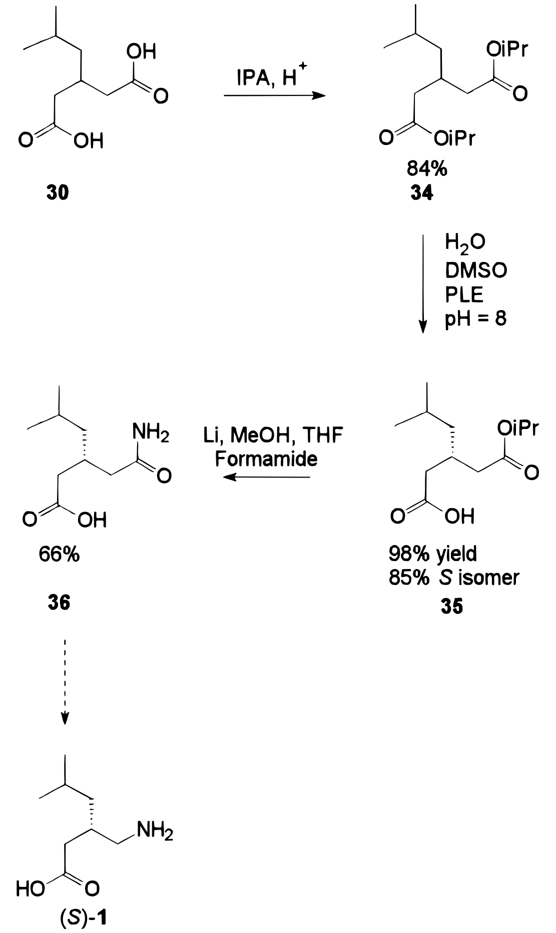
[6] Day, J. N. E.; Thorpe, J. F. *J. Chem. Soc.* **1920**, *117*, 1465.

[7] Thiesen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 142.

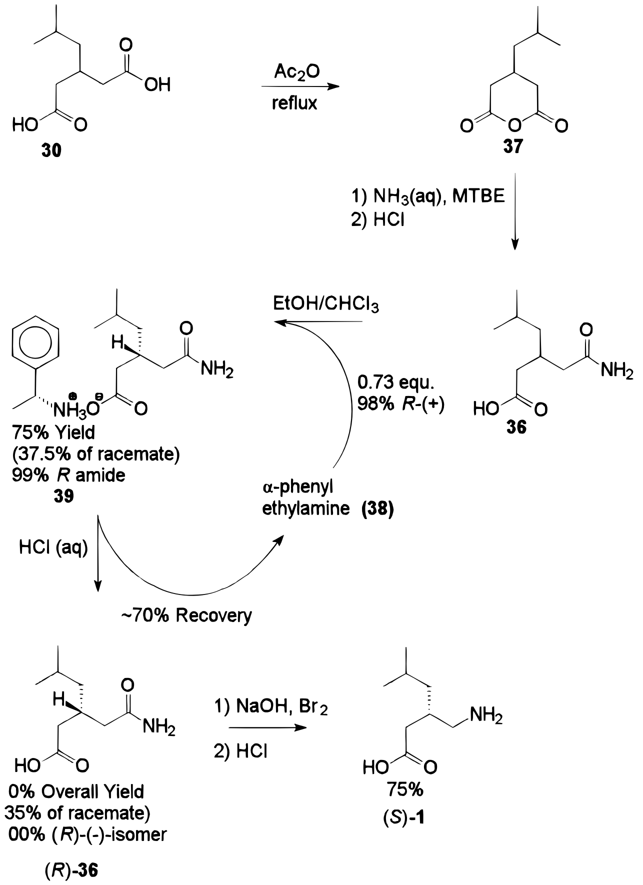
[8] Hackbart, W.; Hartman, M. *J. Prakt. Chem.* **1961**, *14*, 1.

[9] Wallis, E. S.; Lane, J. F. *Organic Reactions*; Wiley: New York, 1946; Vol. III, pp 267–306.

Scheme 8. **Enzymatic resolution route**



Scheme 9. **γ-Isobutylglutaric acid route**



(**30**) by converting first to the cyclic anhydride with acetic anhydride[10] and then opening the ring with aqueous ammonia[11] (Scheme 9).

To develop a method for resolving the amido carboxylic acid **36**, a number of possible resolving agents were screened. From these efforts, (+)-α-phenylethylamine emerged as a clear favorite. A subsequent solvent selection screen showed ethanol/chloroform to be the best solvent system for this resolution. Intensive efforts to develop an alternative solvent system comparable to or better than ethanol/chloroform were not successful. Other optimization work led to the choice of a 0.73:1.0 mole ratio of amine to **36**. The best result for the diastereomeric salt was a single crystallization giving a 37.5% yield (based on racemate) of salt containing 99% *R* enantiomer of **36**. Splitting of that salt gave an overall 35% yield of 100% (*R*)-**36**. Mixtures of the *R* and *S* enantiomers of **36** can be recovered from filtrates, hydrolyzed to γ-isobutylglutaric acid in 95% yield, and recycled into the process.

Hofmann Rearrangement

Hofmann rearrangements can be problematic on scale-up because the reaction is exothermic. Attempts to control the exotherm by gradual reagent addition often lead to byproducts. In the case of amido carboxylic acid **36**, the exotherm proved to be quite controllable, even though the required procedure called for combining the reagents at once and heating the mixture. An evaluation of the Hofmann rearrangement in a Mettler RC-1 calorimeter showed the adiabatic heat rise of the reaction mixture to be 58 °C. This data predicted that in a worst case scenario on scale-up, involving complete loss of cooling, a maximum temperature of 80 °C could be expected. A temperature rise of this magnitude was considered to be quite manageable in large-scale equipment.

Using sodium hypobromite as oxidant, the isolated yield of (*S*)-**1** in the Hofmann rearrangement was 70%. Conversion as indicated by HPLC was significantly higher than 70%, but separating the moderately water soluble (*S*)-**1** from sodium halides inevitably resulted in the loss of some product. Other methods for separating (*S*)-**1** from salts were investigated; none was found to be superior to simple crystallization from water. In our hands sodium hypochlorite gave poor conversions in the Hofmann reaction.

Malonate Route

While work on the γ-isobutylglutaric acid route was in progress, we began to look again at the potential advantages of using malonate chemistry[12] (Scheme 10) to prepare (±)-**1** and then applying a traditional resolution to obtain the final product. Disadvantages of this approach included the lack of a known resolution and the complexity of some of the reaction mixtures.

Condensation of isovalderaldehyde with diethyl malonate using di-*n*-propylamine/acetic acid as catalyst gave the α,β-

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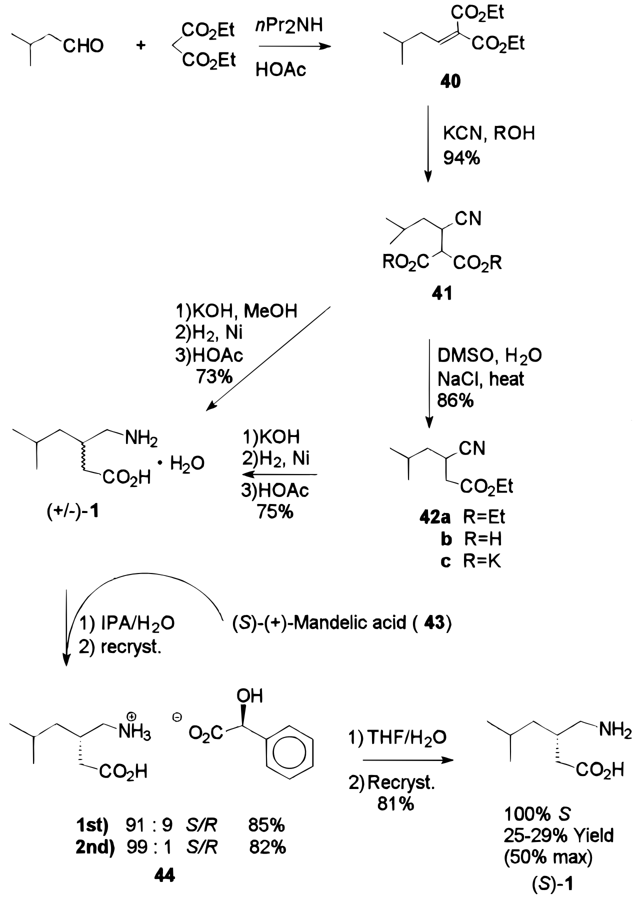
[10] Carson, J. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, pp 630−632.

[11] Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1969**, *91*, 3075.

[12] Griffiths, G.; Mettler, H.; Mills, L. S.; Previdoli, F. *Helv. Chim. Acta* **1991**, *74*, 309.

Scheme 10. **Malonate route**



unsaturated diester **40** in high yield. The β-cyano diester **41** was prepared in high yield by addition of potassium cyanide. The challenge was to convert β-cyanodiester **41** to (±)-**1a**, a transformation which formally consists of hydrolysis, decarboxylation, and reduction. Our first attempts used the free cyano carboxylic acid **42b** as the reduction substrate. Yields were poor because **42b** is unstable. We did, however, discover that the potassium salt of the cyano carboxylic acid (**42c**) can be reduced without decomposition. The instability of the free acid **42b** meant that a nonacidic environment would be needed for decarboxylation. This was initially provided by the Krapcho reaction,[13] in which cyano diester **41** is converted directly to the cyano ester **42a** in 86% yield using sodium chloride as a nucleophile. Saponification followed by hydrogenation under basic conditions with a sponge nickel catalyst[14] gave racemic CI-1008 in 80% yield. The desire for a direct route from the cyano diester **41** to (±)-**1** prompted us to attempt hydrolysis, decarboxylation, and reduction in one pot under basic conditions. This ultimately proved successful, giving racemic CI-1008 in 73% overall yield, an advantage over the 64% overall yield of the combined steps of the Krapcho route.

Having bridged the gap from the cyano diester **41** to the racemate (±)-**1**, we turned our attention to the resolution step. In the absence of a known resolution procedure, a screen[15] with a variety of commercially attractive chiral carboxylic acids was set up. The preferred agent which emerged from this screen was (*S*)-(+)-mandelic acid. In two recrystallizations, a salt having a diastereomer ratio of 99:1 was obtained in 70% yield. Although standard acid or base treatments could presumably be used, we were concerned about inorganic salt contamination as had been observed in the workup of the Hofmann rearrangement. Further experimentation led to the discovery that the diastereomeric salt could be split with wet tetrahydrofuran under neutral conditions to give CI-1008 having an *S*:*R* ratio of 99.1:0.1. A final crystallization from isopropyl alcohol brought the enantiomeric purity up to 100% *S* with an overall yield of 25−29%.

Comparison of the γ-Isobutylglutaric Acid and Malonate Routes

Both the γ-isobutylglutaric acid and malonate routes were scaled up successfully in the pilot plant. Costs for the two routes were comparable. Throughput and waste disposal costs were in close agreement for the two routes. The question remained how to discriminate between the processes and to make a choice for future commercial production. The key to this question was the unavoidable use of chloroform as a solvent in the resolution step of the γ-isobutylglutaric acid process. To avoid operator exposure to chloroform meant that the work would have to be performed in isolated equipment. By contrast, the malonate process could be run using available equipment. Use of the γ-isobutylglutaric acid route would require a capital investment in equipment, whereas use of the malonate route would not. Complete engineering analyses of the two processes indicated a preference for the malonate process based on the difference in capital outlay.

Summary

Throughout development of CI-1008, requirements for bulk drug supplies were met with the benzyl ester, *tert*-butyl ester, and malonate routes. The chosen malonate route has met intermediate cost goals in the pilot plant. The CI-1008 project has been a success in terms of both material supply and development of a commercial process. As a tool for evaluating the potential of alternate routes when little experimental data is available, we have found the ideal process cost projection to be very useful. In this particular work as well as in others we have found it to be true that the discovery route, even if inefficient, is usually the fastest route to prepare the first small batch of product.

It may come as a surprise that the two lowest cost processes for CI-1008 use classical resolution, rather than enantioselective synthesis. The reason is that, although high enantiospecificity was achieved in asymmetric synthesis, this advantage did not compensate for low overall yield or high material costs. In order to be truly of commercial value, the step which introduces chirality must be an integral part of an otherwise low cost process, as was the case with both routes using classical resolution.

Experimental Section

General. Experimental work is described only for the routes which were developed and run at pilot plant scale.

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(13) Krapcho, A. P. *Synthesis* **1982**, *805*, 893.

(14) Bergeron, R. J.; Garlich, J. R. *Synthesis* **1984**, 782.

(15) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*; Kreiher Publishing Co.: Malabar, FL, 1991; pp 251−262, 378−396.

Reactions at multikilogram scale were run in glass-lined steel reactors or stills, unless otherwise noted; basket centrifuges were used to isolate crystalline products. 2B ethanol is alcohol which has been denatured with 0.3−0.8% v/v toluene. Unless otherwise noted, all ^{1}H NMR spectra were obtained at 200 MHz using tetramethylsilane as a reference. ^{13}C NMR spectra were obtained at 50 MHz with the solvent as reference. All melting points are uncorrected. The abbreviation wt/wt % indicates analysis compared to a reference standard.

HPLC Enantiomer Determination for 1. The derivative was prepared with Marfey's reagent (*N*α-(2,4-dinitro-5-fluorophenyl)-L-alaninamide) and chromatographed on Hypersil BDS, 0.05 M aqueous triethylamine (adjusted to pH 3 with phosphoric acid)−acetonitrile, 62:38.

4-Methylpentanoyl Chloride (3). 4-Methylvaleric acid (**2**, 105 kg, 904 mol) was added slowly to a solution of thionyl chloride (144 kg, 1210 mol), the batch temperature being maintained at 30−35 °C. The solution was stirred for at least 1 h at 30−35 °C and then heated to 70−75 °C for at least 30 min. The batch was distilled at atmospheric pressure to remove ca. 20 L of distillate. The remaining contents were cooled to 30 °C or less, 52 L of hexane was added, and the batch was distilled under vacuum until the pressure stabilized for 30 min (batch temperatures 52 °C/60 mmHg). The low-boiling distillates (SO_2, $SOCl_2$ and hexane) were removed, and the product was distilled under vacuum (batch temperature 70 °C/pressure 55 mmHg) to obtain **3** (107.4 kg, 88.3%) as a colorless liquid: gas chromatography 95.0 wt/wt % as methyl ester derivative; ^{1}H NMR ($CDCl_3$) δ 2.88 (dd, 2 H, $J = 7.3$ Hz), 1.70−1.50 (m, 3H), 0.91 (d, 6H, $J = 6.6$ Hz).

(4*R*,5*S*)-4-Methyl-5-phenyl-2-oxazolidinone (5). (1*S*,2*R*)-(+)-Norephedrine (52.0 kg, 344 mol), potassium carbonate (5.9 kg, 43 mol), diethyl carbonate (52.0 kg, 440 mol), and toluene (106 L) were combined. The batch was stirred and heated to reflux. When the batch temperature fell to 85 °C, the toluene was distilled off until the batch temperature reached ≥100 °C. The batch was monitored for the presence of norephedrine and the toluene addition/reflux/distillation procedure repeated until the HPLC assay showed less than 2% norephedrine. The batch was cooled to 65−70 °C and was given two hot washes with water (44 L) to remove the salts. The solvent was removed by atmospheric distillation to a volume of about 150 L. The product was crystallized by cooling of the batch, filtered, and dried at 35−40 °C under vacuum to obtain **5** as off-white crystals (54.1 kg, 88%): HPLC 99.5 area %; ^{1}H NMR ($CDCl_3$) δ 7.45−7.20 (m, 5H), 6.07 (br s, 1H), 5.72 (d, 1H, $J = 7.7$ Hz), 4.21 (dt, 1H, $J = 14.3, 6.2$ Hz), 0.81 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 159.4, 135.0, 128.5, 126.0, 81.0, 52.4, 17.5; $[\alpha]^{25}{}_D = 163.9°$ ($c = 1.0$, $CHCl_3$). Anal. Calcd for $C_{10}H_4NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.66; H, 6.26; N, 7.89.

(4*R*,5*S*)-4-Methyl-3-(1-oxo-4-methylpentyl)-5-phenyl-2-oxazolidinone (6). Oxazolidinone **5** (135.6 kg, 765 mol) was dissolved in tetrahydrofuran (1150 L). The resulting solution was cooled to below 0 °C, and *n*-BuLi (203 kg of a 24% solution in hexane, 760 mol) was added slowly, the batch temperature being maintained below 0 °C, to a distinct end point. The critical end point is reached when the *n*-BuLi solution forms a 1 ft streak of dark red color as it mixes into the batch. Immediately after the *n*-BuLi addition, **3** (107.6 kg, 799 mol) was added slowly, the batch temperature being maintained below 5 °C. The batch was stirred for 2 h at 0 °C and then quenched with water (190 L). Heptane (292 kg) was added, and the product was extracted into the organic layer, which was washed with a sodium bicarbonate solution (10 kg in 190 L of water) and with water (100 L). The separated organic layer was distilled at atmospheric pressure until about 290 L of solution remained. Heptane (325 kg) was added, and the distillation was continued until a vapor temperature of about 95 °C was reached. The product was crystallized by cooling of the batch to 0 °C, filtered, rinsed with cold heptane (180 kg), and dried at 35−40 °C under vacuum to obtain **6** (198.6 kg, 94.3%) as a white solid: HPLC 98.2 area %; ^{1}H NMR δ 7.48−7.25 (5H, m), 5.66 (d, 1H, $J = 7.3$ Hz), 4.76 (dt, 1H, $J = 13.4, 6.7$ Hz), 3.08−2.81 (m, 2H), 1.72−1.50 (m, 2H), 0.94 (d, 6H, $J = 6.2$ Hz), 0.90 (d, 3H, $J = 6.6$ Hz); $[\alpha]^{25}{}_D = 46.12°$ ($c = 1.0$, $CHCl_3$). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.66; H, 7.62; N, 5.02.

[4*R*-(3*S,4α,5α)]-4-Methyl-*β*-(2-methylpropyl)-*γ*,2-dioxo-5-phenyl-3-oxazolidinebutanoic Acid, 1,1-Dimethylethyl Ester (7b).** In a reactor constructed of Hastelloy C, acyl oxazolidinone **6** (99.0 kg, 360 mol) and tetrahydrofuran (298 L) were cooled to below −40 °C. A solution of diisopropylamine (36.4 kg, 360 mol) in tetrahydrofuran (50 L) was cooled to less than 0 °C. *n*-Butyllithium (95.9 kg of a 24% solution in hexane, 359 mol) was added slowly to the amine/tetrahydrofuran solution, the temperature of the solution being maintained at 0 °C, and the solution was stirred for 30 min. The resulting LDA solution was transferred slowly into the solution of **6** in tetrahydrofuran, the batch temperature being maintained below −35 °C during the addition, and the solution stirred for 30 min. *tert*-Butyl bromoacetate (70.1 kg, 359 mol) was slowly added to the batch, the temperature of the solution being maintained below −35 °C. A batch temperature of −35 °C or less was maintained for 30 min; the temperature was then allowed to rise slowly to −15 °C over 2.5−3.5 h. The reaction was quenched with aqueous ammonium chloride (45.4 kg in 152 L of water), the mixture was warmed to 25 °C, and the layers were separated. The organic layer containing the product was washed with water (40 L), and the tetrahydrofuran solvent was distilled off and replaced with heptane (145 kg).

A second part lot was prepared by repeating the entire alkylation procedure in duplicate fashion. The two product solutions were combined; heptane (360 kg) was added, and the solution was concentrated to about 400 L by atmospheric distillation. More heptane (360 kg) was added and the solution concentrated to about 575 L. Isopropyl alcohol (150 L) and heptane (605 kg) were added, the batch temperature being maintained above 55 °C. The product was crystallized by cooling of the solution to 35−40 °C and holding at this temperature for 1 h, followed by slow cooling to 0 °C. The product was stirred overnight at 0 °C, filtered, rinsed with a cold solution of isopropyl alcohol/heptane (23 kg/160 kg) and dried under vacuum at 37−47 °C overnight to obtain **7b** as an off-white solid (208 kg, 74.3%): HPLC 99.3 wt/

wt %; ^{1}H NMR ($CDCl_3$) δ 7.47−7.25 (m, 5H), 5.66 (d, 1H, $J = 7.3$ Hz), 4.75 (dt, 1H, $J = 13.6$, 6.7 Hz), 4.36−4.18 (m, 1H), 2.70 (ddd, 1H, $J = 2.2$, 10.1, 16.5 Hz), 2.44 (ddd, 1H, $J = 2.1$, 4.8, 16.7 Hz), 1.72−1.50 (m, 3H), 1.41 (s, 9H), 0.95 (dd, 6H, $J = 2.7$, 6.0 Hz), 0.90 (d, 3H, $J = 6.0$ Hz); $[\alpha]^{25}_D = 25.48°$ ($c = 1.0$, $CHCl_3$). Anal. Calcd for $C_{22}H_{34}NO_5$: C, 67.84; H, 8.02; N, 3.60. Found: C, 67.61; H, 8.04; N, 3.64.

(*S*)-2-(2-Methylpropyl)-1,4-butanedioic Acid, 4-(1,1-Dimethylethyl) Ester (8b). A solution of $LiOH{\cdot}H_2O$ (24.7 kg, 589 mol) in water (250 L) was cooled to 5 °C. Separately **7b** (208 kg, 534 mol) and tetrahydrofuran (750 L) were combined and cooled to about 3 °C. Hydrogen peroxide (103 kg of 35%) was slowly added to the LiOH solution, the batch temperature being maintained below 11 °C. The peroxide solution was transferred slowly to the tetrahydrofuran solution, the batch temperature being maintained below 8 °C, and the oxygen level being maintained at less than 8% by use of a nitrogen purge. Oxygen measurement was made with an MSA Model 261 portable combustible gas and oxygen indicator. The batch was cooled to 3 °C and stirred for 4 h. The reaction was quenched by addition of a bisulfite solution (116 kg of $NaSO_3$/600 L of water), a batch temperature of less than 30 °C being maintained. The product was extracted into methyl *tert*-butyl ether (175 kg). The water layer was back washed with methyl *tert*-butyl ether (154 kg). The organic layers were combined and washed with a brine solution (155 kg of NaCl/435 L of water). The solvent was removed by vacuum distillation. Heptane (245 L) was added and distillation continued until no more distillate was removed. Heptane (730 L) was added and the batch cooled to −7 °C. The resulting solid was filtered, rinsed with cold heptane (50 L), and dried under vacuum at 38 °C (88.6 kg of oxazolidinone **5** was recovered). A brine solution (3 kg of NaCl/670 L of water) was added to the mother liquor containing the product, and the mixture was heated to 60 °C. The hot organic layer was separated and washed twice with brine solution (3 kg of NaCl/670 L of water). The solvent was removed by vacuum distillation. The residue was cooled, and tetrahydrofuran (110 L) was added to store the product as a 56% solution. Alternatively the product could be dissolved in methyl *tert*-butyl ether (see method A for **9b**). A 96.8% yield was established by removing the solvent from a sample and calculating the weight of the oil to be 119.0 kg: HPLC 95.5 area %; ^{1}H NMR ($CDCl_3$) δ 10.00 (br s, 1H), 2.93−2.75 (m, 1H), 2.58 (dd, 1H, $J = 9.1$, 16.5 Hz), 2.34 (dd, 1H, $J = 5.1$, 16.5 Hz), 1.75−1.21 (m, 3H), 1.43 (s, 9H), 0.91 (dd, 6H, $J = 6.6$, 6.3 Hz); $[\alpha]^{25}_D = -14.68°$ ($c = 1.0$, $CHCl_3$).

(*S*)-3-(Hydroxymethyl)-5-methylhexanoic Acid, 1,1-Dimethylethyl Ester (9b). *Method A.* A solution of **8b** (341.0 kg, 1481 mol) in methyl *tert*-butyl ether (813 kg) was cooled to about 5 °C. Borane/dimethyl sulfide (130.8 kg, 1721 mol) was added slowly, the batch temperature being maintained below 5 °C, followed by a rinse of methyl *tert*-butyl ether (14.8 kg). The batch was cooled to about 5 °C and stirred for 3 h. The solution was warmed to about 25 °C and stirred for 16 h. The solution was cooled to about 0 °C and quenched with water (240 L), the batch temperature being maintained below 5 °C. The organic layer was washed twice with sodium bicarbonate solution (30 kg of $NaHCO_3$/360 L of water) and once with water (160 L). The solvent was removed by distillation under vacuum. Heptane (800 L) was added, and the vacuum distillation continued until no more distillate was removed. The product was taken directly on into the next step; the yield of **9b** was estimated to be 320 kg (99.9%): ^{1}H NMR δ 3.64 (dd, 1H, $J = 4.4$, 11.0 Hz), 3.46 (dd, 1H, $J = 7.0$, 11.0 Hz), 2.29 (d, 1H, $J = 2.6$ Hz), 2.26 (s, 1H), 2.20−1.95 (m, 2H), 1.77−1.49 (sept, 1H, $J = 6.6$ Hz), 1.45 (s, 9H), 1.31−1.03 (m, 2H), 0.89 (dd, 6H, $J = 3.0$, 6.6 Hz).

Method B. A solution of **8b** (187.4 kg, 814 mol) in tetrahydrofuran (176 kg), *N*-methylmorpholine (90.5 kg, 895 mol), and tetrahydrofuran (650 L) were combined and cooled to −10 °C. Ethyl chloroformate (89 kg, 820 mol) was added to the tetrahydrofuran solution, the batch temperature being maintained below 0 °C. The batch was stirred at −5 °C for 45 min and the resulting slurry filtered. The solids were rinsed with tetrahydrofuran (50 L), and the rinse was combined with the filtrate. A borohydride solution was prepared (46.2 kg, 1221 mol, $NaBH_4$ in 3.3 kg of 50% NaOH and 442 L of water) and was added to the mixed anhydride solution while the batch temperature was maintained about 0 °C. The batch was warmed to about 22 °C, stirred for an hour, and filtered to remove solids. The solid was rinsed with tetrahydrofuran (50 L). The combined filtrate and rinse were distilled under vacuum to remove the tetrahydrofuran, the temperature being kept below 20 °C. Heptane (564 kg) was charged as the extraction solvent. The organic layer was washed with dilute acid (24.5 kg of concd HCl/226 L of water), with base (20 kg of $NaHCO_3$/245 L of water), and with water (160 L). The solvent was removed by vacuum distillation, and heptane (68 L) was added to the remaining organic layer. To the heptane solution was added dilute acid (17.8 kg of concd HCl, 120 L of water) until the pH of the aqueous layer was 5. The aqueous layer was then separated and discarded. The solvent was removed under vacuum from a sample of the product solution to give **9b** as an oil. From the sample, the yield of **9b**, taken directly into the next step, was estimated to be 158 kg (90% yield): HPLC 96.2 area % (refractive index detection).

(*S*)-5-Methyl-3-[[[(4-methylphenyl)sulfonyl]oxy]methyl]hexanoic Acid, 1,1-Dimethylethyl Ester (10b). *p*-Toluenesulfonyl chloride (158 kg, 829 mol) was added to a 24 °C solution of **9b** (158 kg, 730 mol) in heptane (68 kg), taken directly from the previous step run as method B. Triethylamine (77.1 kg, 763 mol) was added slowly, a batch temperature of about 27 °C being maintained. After stirring for 2.5 h, a dilute acid solution (25 kg of concd HCl/280 L of water) and methyl *tert*-butyl ether (225 kg) were added. The organic layer was separated and washed with ammonium hydroxide (150 kg of 28% NH_4OH/150 L of water), sodium hydroxide (30 kg of 50% NaOH/275 L of water), sodium bicarbonate (24 kg of $NaHCO_3$/280 L of water), and brine (15 kg of NaCl/275 kg of water). The organic layer was distilled under vacuum to remove the solvent and used directly in the next step. A sample was taken and stripped more carefully under vacuum to remove solvents, giving **10b** (estimated 250 kg, 92%) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.77

(d, 2H, $J = 8.4$ Hz), 7.34 (d, 2H, $J = 8.1$ Hz), 4.01 (dd, 1H, $J = 9.5$, 4.0 Hz), 3.92 (dd, 1H, $J = 9.5$, 5.2 Hz), 2.44 (s, 3H), 2.39−2.08 (m, 3H), 1.60−1.30 (m, 1H), 1.39 (s, 9H), 1.25−1.00 (m, 2H), 0.82 (dd, 6H, $J = 6.4$, 2.4 Hz); HPLC 96.4 area %.

(*S*)-3-(Azidomethyl)-5-methylhexanoic Acid, 1,1-Dimethylethyl Ester (11b). DMSO (560 kg) was added to **10b** (250 kg, 675 mol) and stirred. Sodium azide (43.8 kg, 674 mol) was added, and the batch was stirred overnight at 60 °C. The batch was cooled to about 20 °C, water (430 L) and heptane (360 kg) were added, and the layers were separated. The organic layer was washed with additional water (200 L) and concentrated under vacuum to give 205.6 kg of a solution of **11b**. A sample was stripped of solvent under vacuum to obtain **11b** (estimated 155 kg, 95%) as a light yellow oil: ^{1}H NMR δ 3.36 (dd, 1H, $J = 5.8$, 12.1 Hz), 3.26 (dd, 1H, $J = 5.0$, 12.3 Hz), 2.25 (d, 1H, $J = 4.4$ Hz), 2.22 (d, 1H, $J = 1.8$ Hz), 2.25−2.00 (m, 1H), 1.75−1.50 (sept, 1H, $J = 6.6$ Hz), 1.45 (s, 9H), 1.36−1.06 (m, 2H), 0.89 (dd, 6H, $J = 1.1$, 6.6 Hz); $[\alpha]^{25}_{D} = 0.75°$ ($c = 1.0$, $CHCl_3$); HPLC 96.0 area % (refractive index detection).

(*S*)-3-(Azidomethyl)-5-methylhexanoic Acid (11c). A solution of **11b** (166 kg, 688 mol) in heptane (119 kg) was added to a clean, dry 1900 L glass-lined vessel. The heptane was removed by vacuum distillation. The **11b** was cooled to 5 °C, and formic acid (669.3 kg) and sulfuric acid (6.9 kg) were added. The acidic solution was warmed to about 23 °C, stirred for 2 h, and concentrated to about 530 L by distillation. After stirring for 2 h, the reaction was quenched with brine (195 kg of NaCl/615 L of water) and 230 kg of methyl *tert*-butyl ether was added. The layers were separated, and the aqueous layer was extracted with 225 kg of methyl *tert*-butyl ether. The organic layers were combined, washed with 110 L of water, and distilled to remove the solvent. Isopropyl alcohol (100 L) was added to the concentrated product to obtain a solution of **11c** (89.6% pure by HPLC, wt/wt), which was carried directly into the next step. A sample was stripped under vacuum to remove solvents, giving **11c** (estimated 131 kg, 102%) as a light yellow oil: ^{1}H NMR δ 3.43 (dd, 1H, $J = 5.1$, 12.1 Hz), 3.31 (dd, 1H, $J = 6.2$, 12.1 Hz), 2.40 (d, 1H, $J = 4.4$ Hz), 2.37 (d, 1H, $J = 2.2$ Hz), 2.28−2.10 (m, 1H), 1.74−1.54 (sept, 1H, $J = 6.8$ Hz), 1.40−1.14 (m, 2H), 0.91 (dd, 6H, $J = 1.1$, 6.6 Hz); $[\alpha]^{25}_{D} = 3.73°$ ($c = 1.8$, $CHCl_3$); HPLC, 89.6 wt/wt %.

(*S*)-3-(Aminomethyl)-5-methylhexanoic Acid (1) from 11c. A solution was prepared from **11c** (82.1 kg, HPLC 89.4%, 396 mol) and isopropyl alcohol (150 L) and added to a stainless steel reactor containing 5% palladium on carbon (8.6 kg, 50% water wet). Additional isopropyl alcohol (270 L) was added as a rinse. The unit was purged three times with 50 psi of nitrogen and then purged twice with 50 psi of hydrogen. After pressurizing again to 50 psi with hydrogen, the reaction temperature was maintained below 40 °C by cooling. After 30 min the pressure was released and the unit was repressurized to 50 psi with hydrogen, the reaction temperature being kept below 40 °C. The repressurization was repeated five times at intervals of 1 h and then twice at intervals of 0.5 h. The unit was then purged three times with nitrogen. Water (250 L) was added, and the solution was heated to 80−85 °C. The hot mixture was filtered to remove the catalyst. The catalyst was rinsed with a hot (80−85 °C) solution of water (9.1 kg) and isopropyl alcohol (58 L). The combined aqueous isopropyl alcohol solutions were concentrated by vacuum distillation to 400−450 L, the solution temperature being kept below 40 °C. The resulting slurry was heated to 80−85 °C to dissolve the solids and cooled to 48−60 °C to begin crystallization. Using slow agitation the solution was kept at 37−42 °C for 2 h; then it was cooled to 0 °C, and isopropyl alcohol (400 L) was added. The solids were collected on a centrifuge, rinsed with cold isopropyl alcohol (85.4 L), and dried at 50 °C for 48 h in a vacuum oven to obtain white crystalline **1** as a solid (38.8 kg, 61.5% yield, corrected for purity of **11c**): HPLC 99.8 wt/wt %; ^{1}H NMR (D_2O) δ 2.99 (dd, 1H, $J = 12.8$, 5.5 Hz), 2.90 (dd, 1H, $J = 12.8$, 6.2 Hz), 2.35−2.00 (m, 3H), 1.72−1.52 (sept, 1H, $J = 6.8$ Hz), 1.18 (dd, 2H, $J = 6.9$, 7.0 Hz), 0.85 (dd, 6H, $J = 2.2$, 6.6 Hz); $[\alpha]^{25}_{D} = 10.1°$ ($c = 1.1$, H_2O); mp 175−176 °C. Anal. Calcd for $C_8H_{17}NO_2$: C, 60.35; H, 10.76; N, 8.80. Found: C, 60.62; H, 10.65; N, 8.78. Chiral HPLC: 99.99 % (*S*)-**1**.

A second crop of material was obtained by concentration of the filtrates by vacuum distillation to about 60 L. The resulting residues were dissolved in isopropyl alcohol (505 L) at 70−85 °C and then cooled to 0 °C. The resulting solids were filtered, rinsed with cold isopropyl alcohol (20 L), and dried at 50 °C for 27 h under vacuum to obtain an additional 5.8 kg (9.2%) of **1** (HPLC, 97.8 wt/wt %).

3-Isobutylglutaric Acid (30). A mixture of ethyl cyanoacetate (62.4 g, 552 mmol), hexane (70 mL), isovaleraldehyde (52.1 g, 605 mmol), and di-*n*-propylamine (0.55 g, 5.4 mmol) was placed under reflux. Water was collected azeotropically using a water separator. When no additional water was being collected from the reaction, the reaction mixture was cooled and subjected to vacuum distillation to remove the solvent. Diethyl malonate (105.7 g, 660 mmol) and di-*n*-propylamine (5.6 g, 55 mmol) were added to the remaining oil. The mixture was stirred at 50 °C for 1 h and then poured into an aqueous solution of hydrochloric acid (300 mL of 6 N). The mixture was placed under reflux. The reaction mixture was maintained at reflux until ^{1}H NMR indicated that the hydrolysis and decarboxylation were complete (approximately 72 h). The reaction mixture was cooled to 70−80 °C, and the aqueous mixture was extracted with toluene (1 × 250 mL, 1 × 150 mL). The toluene extracts were combined, and solvent was removed by distillation to give **30** (88.7 g, 85.4%) as an oil: ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 6H, $J = 6.6$ Hz), 1.23 (dd, 2H, $J_1 = 6.6$ Hz, $J_2 = 6.5$ Hz), 1.64 (m, 1H), 2.25−2.40 (m, 1H), 2.40−2.55 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 22.4, 25.1, 29.5, 38.4, 43.4, 179.2; IR (KBr) 680.7, 906.4, 919.9, 1116.6, 1211.1, 1232.3, 1249.6, 1301.7, 1409.7, 1417.4, 1448.3, 1463.7, 1704.8, 2958.3, 3047.0 cm^{-1}.

3-Isobutylglutaric Anhydride (37). 3-Isobutylglutaric acid (156 g, 829 mmol) and acetyl chloride[16] (130 g, 1.66 mol) were combined and placed under reflux for 16 h. The mixture was placed under atmospheric distillation until a distillate temperature of 135 °C was reached. The mixture was cooled and placed under vacuum distillation to give **37**

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(16) Bose, N. K.; Chaudhury, D. N. *Tetrahedron* **1964**, *20*, 49.

(129 g, 91.5%): bp 128 °C (1 mmHg); ^{1}H-NMR (CDCl$_3$) δ 0.91 (d, 6H, $J = 6.6$ Hz), 1.20−1.24 (m, 2H), 1.52−1.78 (m, 1H), 2.10−2.45 (m, 3H), 2.79−2.91 (m, 2H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ 166.53, 43.99, 36.48, 26.79, 25.08, 22.57; IR (neat) 559.3, 592.0, 609.4, 659.5, 837.0, 954.6, 1033.7, 1070.3, 1184.1, 1241.9, 1288.2, 1369.2, 1388.5, 1411.6, 1425.1, 1469.5, 1760.7, 1810.8, 2873.4, 2958.3, 3552.2 cm^{-1}. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.50; H, 8.30.

(±)-3-(Carbamoylmethyl)-5-methylhexanoic Acid (36). Aqueous ammonia (308 g of 28%, 5.06 mol), water (431 g), and methyl *tert*-butyl ether (200 g) were combined and cooled to 15 °C. 3-Isobutylglutaric anhydride (391 g, 2.3 mol) was added, and the reaction mixture was allowed to warm to 55 °C. The reaction mixture was cooled to 20−25 °C. The organic solvent was evaporated, and the pH of the remaining aqueous solution was adjusted to 1.0 with concentrated hydrochloric acid. Water (200 mL) was added, and the mixture was filtered. The solid was washed with water (200 mL). The solid was dried under reduced pressure to give (±)-**36** (408 g, 94.8%) as an off-white solid: ^{1}H-NMR (DMSO-d_6) δ 0.84 (d, 6H, $J = 6.5$ Hz), 1.07−1.17 (m, 2H), 1.50−1.72 (m, 1H), 1.98−2.25 (m, 5H), 6.75 (s, 1H), 7.30 (s, 1H), 11.6 (s, 1H); IR (KBr) 592.0, 655.7, 700.0, 1010.5, 1133.9, 1214.9, 1241.9, 1278.6, 1294.0, 1427.1, 1461.8, 1585.2, 1668.1, 1700.9, 2514.7, 2622.7, 2962.1, 3220.5, 3367.1 cm^{-1}. Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.93; H, 9.37; N, 7.50.

Preparation of 3-Isobutylglutaric Anhydride (37) Followed by Preparation of (±)-3-(Carbamoylmethyl)-5-methylhexanoic Acid (36). 3-Isobutylglutaric acid (68.8 kg, 366 mol) and acetic anhydride (44.5 kg, 436 mol) were combined and placed under reflux for 2.5 h. The mixture was placed under atmospheric distillation followed by vacuum distillation to remove acetic acid and acetic anhydride. The undistilled 3-isobutylglutaric anhydride was dissolved in methyl *tert*-butyl ether (63 kg) and added to a solution of aqueous ammonia (49 kg of 28%) and water (92 kg) at a temperature of 25 °C or less. The mixture was stirred for 35 min, and the layers were separated. The aqueous layer was placed under vacuum distillation to remove any remaining volatile nonaqueous solvent. Concentrated hydrochloric acid (51 kg) was added to the aqueous mixture to obtain a pH of 1.5. The mixture was cooled to 0−10 °C and filtered. The solid was washed with water (50 L) and dried under reduced pressure. The solid was then dissolved in hot (70 °C) ethyl acetate (237 kg) and filtered. The solution was cooled to 0−5 °C, and the product was collected by filtration. The solid was washed with cold ethyl acetate (45 kg) and dried under reduced pressure to give (±)-**36** (47.5 kg, 69.3%) as an off-white solid.

(*R*)-(−)-3-(Carbamoylmethyl)-5-methylhexanoic Acid (*R*)-(+)-α-Phenylethylamine Salt (39). (±)-**3** (17.0 g, 90.8 mmol) was placed in chloroform (292 g, ACS reagent), and ethanol (3.2 g) was added. The mixture was heated to 55 °C, and (*R*)-(+)-α-phenylethylamine (6.0 g) was added. After a solution formed, additional (*R*)-(+)-α-phenylethylamine (2.0 g) and (*R*-(−)-3-(carbamoylmethyl)-5-methylhexanoic acid seed crystals (50 mg) were added. The mixture was cooled to 32 °C and filtered. The solid was washed with chloroform (30 mL) and dried under reduced pressure to give (*R*,*R*)-**39** (10.5 g, 75.0%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 0.83 (d, 6H, $J = 6.4$ Hz), 1.1−1.4 (m, 2H), 1.32 (d, 3H, $J = 6.6$ Hz), 1.50−1.75 (m, 1H), 2.0−2.3 (m, 5H), 4.11 (q, 1H, $J = 6.6$ Hz), 6.0 (br s, 3H), 6.72 (s, 1H), 7.2−7.5 (m, 6H); IR (KBr) 700.0, 763.7, 1091.5, 1270.9, 1400.1, 1523.5, 1633.4, 1660.4, 2869.6, 2933.2, 2956.3, 3187.8, 3376.7 cm^{-1}. Anal. Calcd for $C_{17}H_{28}N_2O_3$: C, 66.20; H, 9.15; N, 9.08. Found: C, 66.22; H, 9.28; N, 9.03. Chiral HPLC: >99% (*R*)-(−)-**36** (Chiralcel OD-H, hexane/isopropyl alcohol/formic acid, 96:4:0.1).

(*R*)-(−)-3-(Carbamoylmethyl)-5-methylhexanoic Acid (36). (*R*,*R*)-**39** (10.9 g, 35.3 mmol), was placed into water (35 mL). The mixture was acidified to pH 1.7 at 31 °C with concentrated hydrochloric acid. The mixture was cooled to 4 °C and filtered. The solid was washed with cold (4 °C) 1 M hydrochloric acid (10 mL) and dried under reduced pressure to give (*R*)-(−)-**36** (6.2 g, 93.8%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 0.84 (d, 6H, $J = 6.5$ Hz), 1.09−1.15 (m, 2H), 1.50−1.65 (m, 1H), 2.01−2.27 (m, 5H), 6.76 (s, 1H), 7.30 (s, 1H), 12.0 (s, 1H); IR (KBr) 624.8, 954.6, 1168.7, 1207.2, 1236.1, 1294.0, 1411.6, 1592.9, 1643.1, 1712.5, 2873.4, 2931.3, 2958.3, 3224.4, 3332.4, 3434.6 cm^{-1}. Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.84; N, 9.34; N, 7.48. Chiral HPLC: >99% (*R*)-(−)-**36** (Chiralcel OD-H, hexane/isopropyl alcohol/formic acid, 96:4:0.1).

Preparation of (*R*)-(−)-3-(Carbamoylmethyl)-5-methylhexanoic Acid (36) Followed by Regeneration of 3-Isobutylglutaric Acid (30). (±)-3-(Carbamoylmethyl)-5-methylhexanoic acid (47 kg, 251 mol) was placed into chloroform (807 kg) and ethanol (8.8 kg). The mixture was heated to 55 °C, and (*R*)-(+)-α-phenylethylamine (16.7 kg) was added. After a solution formed, additional (*R*)-(+)-α-phenylethylamine (5.5 kg) and (*R*)-(−)-3-(carbamoylmethyl)-5-methylhexanoic acid seed crystals (100 g) were added. The mixture was cooled to 32 °C and filtered. The solid was washed with chloroform (100 kg) and dried under reduced pressure to give (*R*,*R*)-**39**. The solid was dissolved in water (138.5 kg), and concentrated hydrochloric acid (9.4 kg) was added. The mixture was cooled to 0−10 °C and filtered. The solid was washed with cold water (20 L) and dried under reduced pressure to give (*R*)-(−)-**36** (17.7 kg, 75.3%) as a white solid.

The chloroform filtrate was extracted with aqueous sodium hydroxide solution (25 kg of 50% sodium hydroxide dissolved in 106 kg of water). The aqueous extract was acidified with concentrated hydrochloric acid (94 kg) and heated under reflux for approximately 24 h. The aqueous mixture was extracted with methyl *tert*-butyl ether (70.5 kg). The methyl *tert*-butyl ether solution was concentrated under reduced pressure to give 3-isobutylglutaric acid (27.4 kg).

(*S*)-3-(Aminomethyl)-5-methylhexanoic Acid (1) from 36. (*R*)-(−)-**36** (30 g, 160 mmol) was dissolved in water (28 g) and 50% sodium hydroxide (12.6 g) and cooled to 5 °C. In a separate flask were combined water (85 g), 50% sodium hydroxide (53 g), and bromine (30.6 g) while a temperature of less than 10 °C was maintained. The bromine solution was added to the solution of (*R*)-(−)-**36** and warmed until a temperature of 80 °C was reached. The solution was cooled to 45 °C and quenched into 37% hydrochloric acid (42 g). The mixture was heated to 89 °C and then cooled to 3 °C. The mixture was filtered, and the solid was washed with water (30 mL). The solid was dried under reduced pressure to give (*S*)-**1** (16.7 g). Chiral HPLC: 99.8% (*S*)-**1**. The solid (16.3 g) was recrystallized from a mixture of isopropyl alcohol (54 g) and water (54 g) to give 14.7 g (59.1%) of recrystallized (*S*)-**1**: ^{1}H NMR (D_2O) δ 0.88 (d, 3H, $J = 6.5$ Hz), 0.90 (d, 3H, $J = 6.5$ Hz), 1.21 (t, 2H, $J = 7$ Hz), 1.52−1.75 (m, 1H), 2.1−2.4 (m, 3H), 2.89−3.06 (m, 2H); IR (KBr) 700.0, 823.5, 860.1, 1278.6, 1334.5, 1369.2, 1417.4, 1645.0, 2210.0, 2603.4, 2690.2, 2775.1, 2844.5, 2873.4, 2896.6, 2923.6, 2956.3 cm^{-1}.

2-Carbethoxy-5-methylhex-2-enoic Acid, Ethyl Ester (40). Isovalderaldehyde (362 kg, 4200 mol) was combined with diethyl malonate (641 kg, 4000 mol), hexane (1000 L), di-*n*-propylamine (20.0 kg, 198 mol), and glacial acetic acid (24.0 kg, 400 mol) in a 4000 L vessel. The mixture was heated to reflux (jacket temperature set at 90 °C) with continuous removal of water until the rate of water collection slowed significantly (69.4 kg of water collected versus 72.0 kg expected by theory). The mixture was cooled to below 60 °C, and a second catalyst addition was carried out by charging di-*n*-propylamine (20.0 kg, 198 mol) and glacial acetic acid (24.0 kg, 400 mol) to the mixture. Reflux was resumed for 22.5 h or until the reaction was >90% complete by GC assay. The mixture was cooled to <40 °C and washed with water (2 × 800 L). The organic layer was concentrated by atmospheric pressure distillation until most of the hexane was removed. The remaining oil was further concentrated under vacuum at 40 °C for 2 h. The product was obtained as a colorless to yellow liquid (810 kg, 88.7 yield) containing a mixture of olefin isomers (both of which are converted to the same product in the next synthetic step). The major isomer (74−76% by GC) is **40**: proton NMR of the mixture shows resonance for the minor isomer (typically 10−13% by GC) consistent with the structure 2-carbethoxy-5-methylhex-3-enoic acid ethyl ester: ^{1}H NMR ($CDCl_3$) δ 0.91−1.02 (m, 6H), 1.23−1.37 (m, 6H), 1.78−1.85 (m, 1H), 2.16−2.23 (m, 2H), 4.19−4.36 (m, 4H), 7.02 (t, 1H, $J = 7.9$ Hz).

2-Carbethoxy-3-cyano-5-methylhexanoic Acid, Ethyl Ester (41). Compound **40** (692.7 kg, 3034 mol) was charged to a 4000 L vessel containing potassium cyanide (172.6 kg, 2650 mol) and 2B ethanol (700 kg). The resulting slurry was stirred at 25−40 °C for at least 18 h or until in-process HPLC assay indicated less than 5% **40** (typically 22−24 h). Hexane (890 L) was charged to the slurry. Glacial acetic acid (175 kg, 2914 mol) was slowly added, the temperature kept below 35 °C. To the resulting thick slurry was added water (820 L) with stirring. The layers were separated. The aqueous layer was extracted with hexane (890 L). The organic layers were combined and washed with water (420 L). The water layer was separated, and the remaining organic solution was distilled at atmospheric pressure until most of the hexane was removed. The oil was then further concentrated under vacuum at 40 °C for 2−19 h. The product was obtained as a colorless to orange liquid (752.6 kg, 93.8%): HPLC 83−86%; ^{1}H NMR (DMSO-d_6) δ 0.92 (t, 6H, $J = 6.1$ Hz), 1.15−1.21 (m, 6H), 1.23−1.36 (m, 1H), 1.54−1.68 (m, 2H), 3.25−3.33 (m, 1H), 3.97 (d, 1H, $J = 6.5$ Hz), 4.10−4.25 (m, 4H).

3-Cyano-5-methylhexanoic Acid, Ethyl Ester (42). An 800 L still was charged with sodium chloride (21 kg, 359 mol), **41** (80.0 kg, 313 mol), dimethyl sulfoxide (238 kg), and water (10.8 kg, 600 mol). The mixture was heated to 137−148 °C for 8.5 h. The mixture was cooled to below 50 °C and treated with methyl *tert*-butyl ether (125 kg). The mixture was cooled to 0−10 °C and treated with water (160 L) in portions to maintain the temperature below 40 °C. After stirring for 15−30 min, the phases were separated. The aqueous phase was extracted with methyl *tert*-butyl ether (125 kg). The organic extracts were combined with a vessel rinse (25 kg of methyl *tert*-butyl ether) and extracted with water (110 L). The aqueous phase was discarded. The methyl *tert*-butyl ether phase was concentrated by atmospheric pressure distillation to a batch temperature of about 65 °C. The batch was cooled to 30−40 °C and further concentrated by vacuum distillation until GC indicated <5% methyl *tert*-butyl ether. The product was obtained as a brown oil (51.3 kg, 85.7%): GC 86.20 area %; ^{1}H NMR ($CDCl_3$) δ 0.88−0.99 (m, 6H), 1.19−1.40 (m, 4H), 1.57−1.69 (m, 1H), 1.72−1.84 (m, 1H), 2.53 (dd, 1H, $J = 6.8$, 16.6 Hz), 2.70 (dd, 1H, $J = 7.4$, 16.5 Hz), 2.99−3.10 (m, 1H), 4.21 (q, 2H, $J = 7.1$ Hz).

(±)-3-(Aminomethyl)-5-methylhexanoic Acid (1) from 42. An 800 L still was charged with **42** (50.1 kg, 273 mol) and ethyl alcohol (53 kg). A solution of potassium hydroxide (17.8 kg) in water (56 L) was added, the addition rate being controlled so as to maintain the batch temperature below 25 °C. The mixture was stirred at 20−25 °C for 1.5 h. The batch was transferred to a stainless steel hydrogenator containing sponge nickel catalyst (15.0 kg, 50% water wet), followed by a rinse of ethyl alcohol (27 kg). The mixture was treated with hydrogen at 50 psi for 19 h (hydrogen uptake stopped). The nickel catalyst was removed by filtration, and the filter cake was rinsed with a mixture of 39 kg of ethyl alcohol and 111 L of water. Glacial acetic acid (22.8 kg, 380 mol) was added to the filtrate, the batch temperature being maintained at less than 40 °C. The batch was heated to 70−75 °C to dissolve the solids and slowly cooled to 0−5 °C to crystallize the product. The solid was collected on a centrifuge and rinsed with 160 L of cold (0−5 °C) isopropyl alcohol. The solid was dried in a vacuum tray drier under vacuum at 35−45 °C (28 h). The water content for this product is variable, depending on the length of drying, but typically is in the range of a monohydrate (10.2% water by theory). The product (±)-**1** was obtained as a white solid (31.4 kg, 75.1%): mp 166.0−167.5 °C; water (Karl Fischer) 9.51% by weight; HPLC 102 wt/wt %; ^{1}H NMR (D_2O) δ 0.86−0.90 (m, 6H), 1.21 (t, 2H, $J = 7.0$ Hz), 1.62−1.69 (m, 1H), 2.12−2.35 (m, 3H), 2.94−3.00 (m, 2H).

Direct Preparation of (±)-3-(Aminomethyl)-5-methylhexanoic Acid (1) from 41. A 2000 L still was charged with **41** (286 kg, 1120 mol) and methyl alcohol (100 L). A solution of potassium hydroxide (60.8 kg, 1046 mol) in methyl alcohol (260 L) was added, the addition rate being controlled so as to keep the batch temperature at 20−35 °C. A rinse of 40 L of methyl alcohol was added to the batch, and the mixture was heated to reflux for 4−5 h. The batch was cooled to 25−30 °C, and a solution of potassium hydroxide (121.6 kg, 2167 mol) in water (200 L) was added while the batch temperature was maintained below 50 °C. The batch was concentrated by vacuum distillation to about 580 L volume. Water (100 L) was added, and the distillation continued to a volume of about 510 L. The batch was transferred to an 800 L stainless steel hydrogenator containing 44.8 kg of sponge nickel (50% water wet), along with a mixture of 20 L of water and 30 kg of ethyl alcohol as a rinse. The mixture was treated with hydrogen at about 50 psi until hydrogen uptake stopped (18−19 h). Ethyl alcohol (58 kg) was added, and the nickel catalyst was removed by filtration. The filter cake was rinsed with a mixture of 100 kg of ethyl alcohol and 270 L of water. The filtrates were transferred to a 2000 L still containing 222 kg (3697 mol) of glacial acetic acid at 50−60 °C. The addition rate was monitored to control gas evolution and to maintain the temperature at 50−60 °C. A rinse of 40 L of water was added to the batch, and the temperature was increased to 70−75 °C to dissolve the solids. The batch was slowly cooled to 0−5 °C to crystallize the product. The solid was collected on a centrifuge and rinsed with 570 L of isopropyl alcohol. The solid was dried under vacuum at 35−45 °C (22 h) to give (±)-**1** (108.1 kg, 72.7%) as a white solid: water (Karl Fischer) 1.68% by weight; HPLC 99.67 wt/wt %; ^{1}H NMR (D_2O) δ 0.88−0.92 (m, 6H), 1.23 (t, 2H, $J = 6.9$ Hz), 1.64−1.70 (m, 1H), 2.13−2.37 (m, 3H), 2.96−3.01 (m, 2H). Recrystallization from water/isopropyl alcohol gave an analytical sample as the monohydrate. Anal. Calcd for $C_8H_{17}NO_2 \cdot H_2O$: C, 54.21; H, 10.81; N, 7.90. Found: C, 54.50; H, 10.98; N, 7.90.

(*S*)-3-(Aminomethyl)-5-methylhexanoic Acid, (*S*)-Mandelic Acid Salt (44). A solution of 3% v/v water in isopropyl alcohol was prepared by mixing water (18 kg) and isopropyl alcohol (582 L) in a 400 L reactor. The solvent was stored in plastic drums and used as necessary. A 400 L still was charged with (±)-**1** (29.7 kg, 168 mol), (*S*)-(+)-mandelic acid (39.3 kg, 258 mol), and 3% v/v water/isopropyl alcohol solution (244 kg) prepared earlier. The mixture was heated to dissolve the solids (about 65−80 °C), cooled, and seeded with **44** to crystallize the enriched mandelate salt (Chiral HPLC 93.7% *S*: 6.3% *R*). The solid was collected on a centrifuge and rinsed with 3% water/isopropyl alcohol (21.5 kg). The solid may optionally be dried but is typically carried on as a solvent-wet solid. The damp salt was charged to a 400 L still along with (*S*)-(+)-mandelic acid (5.8 kg, 38 mol) and 3% water/isopropyl alcohol (121 kg) and the crystallization and isolation procedure repeated. The solid may optionally be dried at this stage but is typically carried on as a solvent-wet solid. The dried *S,S* salt was isolated as a white solid: mp 133−134 °C; ^{1}H NMR (D_2O) δ 0.87−0.92 (m, 6H), 1.24 (t, 2H, $J = 7.2$ Hz), 1.55−1.76 (m, 1H), 2.11−2.52 (m, 3H), 3.00 (d, 2H, $J = 6.2$ Hz), 5.07 (s, 1H), 7.43 (s, 5H). Anal. Calcd for $C_{16}H_{25}NO_5$: C, 61.72; H, 8.09; N, 4.50. Found: C, 61.91; H, 8.05; N, 4.34. Chiral HPLC: 99.5% *S*, 0.5 *R*.

(*S*)-3-(Aminomethyl)-5-methylhexanoic Acid (1) from 44. The solvent-wet salt **44** was transferred to a 400 L reactor with tetrahydrofuran (195 L) and water (10 kg). The mixture was warmed to 60−65 °C and cooled to 0−5 °C. The solid was collected on a centrifuge and rinsed with a mixture of tetrahydrofuran (28 L)/water (1 kg). The solid (crude **1**, <0.05% *R*) may optionally be dried at this stage or carried on as a solvent-wet solid. The damp solid was transferred to a 200 L still with isopropyl alcohol (113 L) and water (38 kg). The mixture was heated to dissolve the solids (about 75−80 °C), filtered while hot, and cooled to 0−5 °C to crystallize. The solid was collected on a centrifuge and rinsed with 25 L of isopropyl alcohol. The solid was dried in a vacuum tray drier under vacuum at 35−45 °C to give (*S*)-**1** (7.4 kg, 55.6%) as a white crystalline solid: mp 177−179 °C (dec); water (Karl Fischer) 0.04% by weight; HPLC 99.4 wt/wt %; chiral HPLC 100% (*S*)-**1**, no *R* isomer detected (limit of detection 0.05%); ^{1}H NMR (D_2O) δ 0.88−0.92 (m, 6H), 1.23 (t, 2H, $J = 6.9$ Hz), 1.64−1.70 (m, 1H), 2.13−2.32 (m, 3H), 2.96−3.01 (m, 2H). Anal. Calcd for $C_{16}H_{25}NO_5$: C, 61.72; H, 8.09; N, 4.50. Found: C, 61.91; H, 8.05; N, 4.34.

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