A practical synthesis of a novel PPAR alpha agonist

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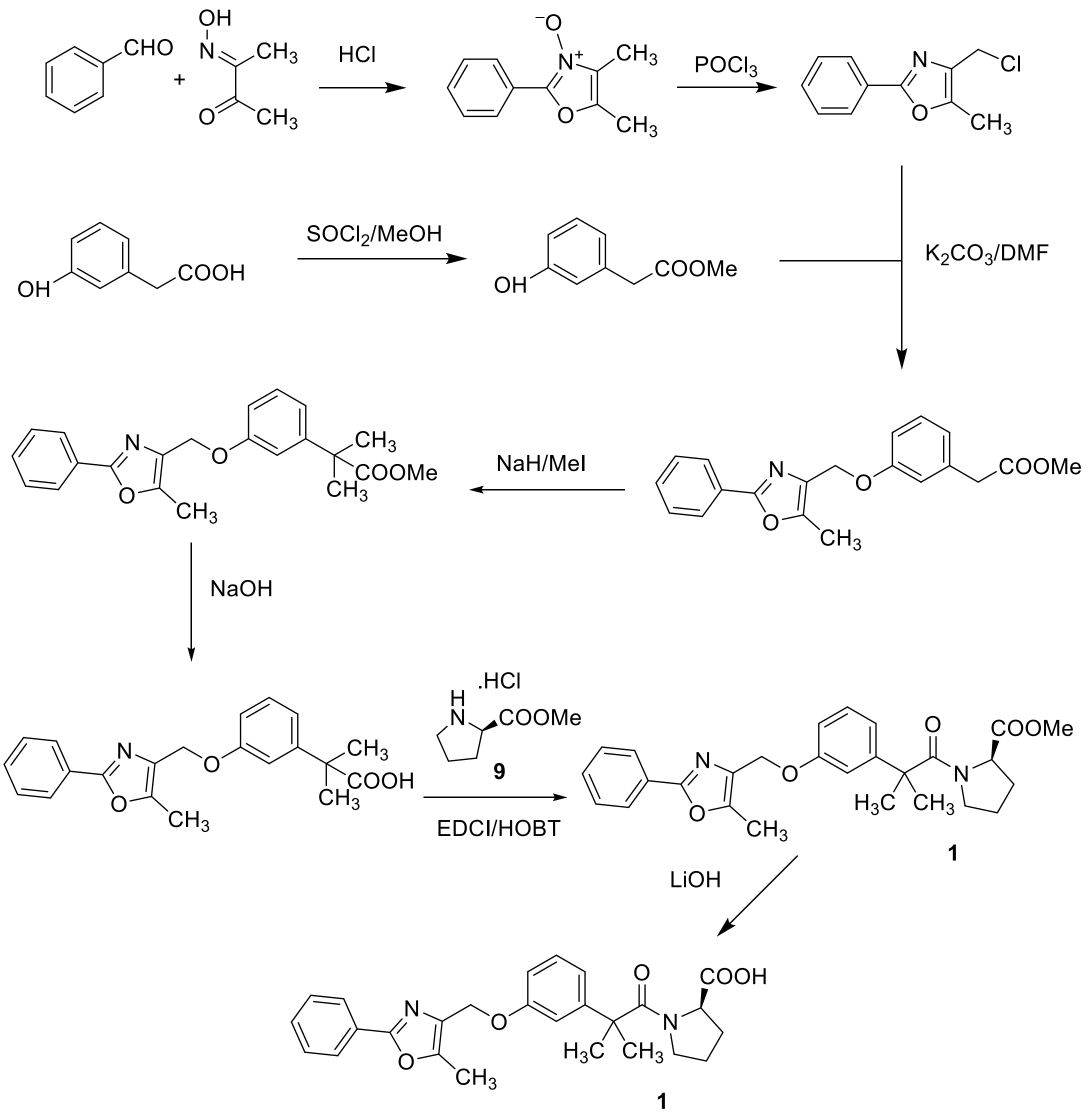
Abstract
An efficient synthesis of a potent PPAR alpha (peroxisome proliferator-activated receptors) agonist is described. The key step in the synthesis is a palladium-catalyzed coupling reaction between a suitably substituted benzene and the anion of methyl isobutyrate. Amide formation with proline provided the drug substance in 62% overall yield based on **2**.

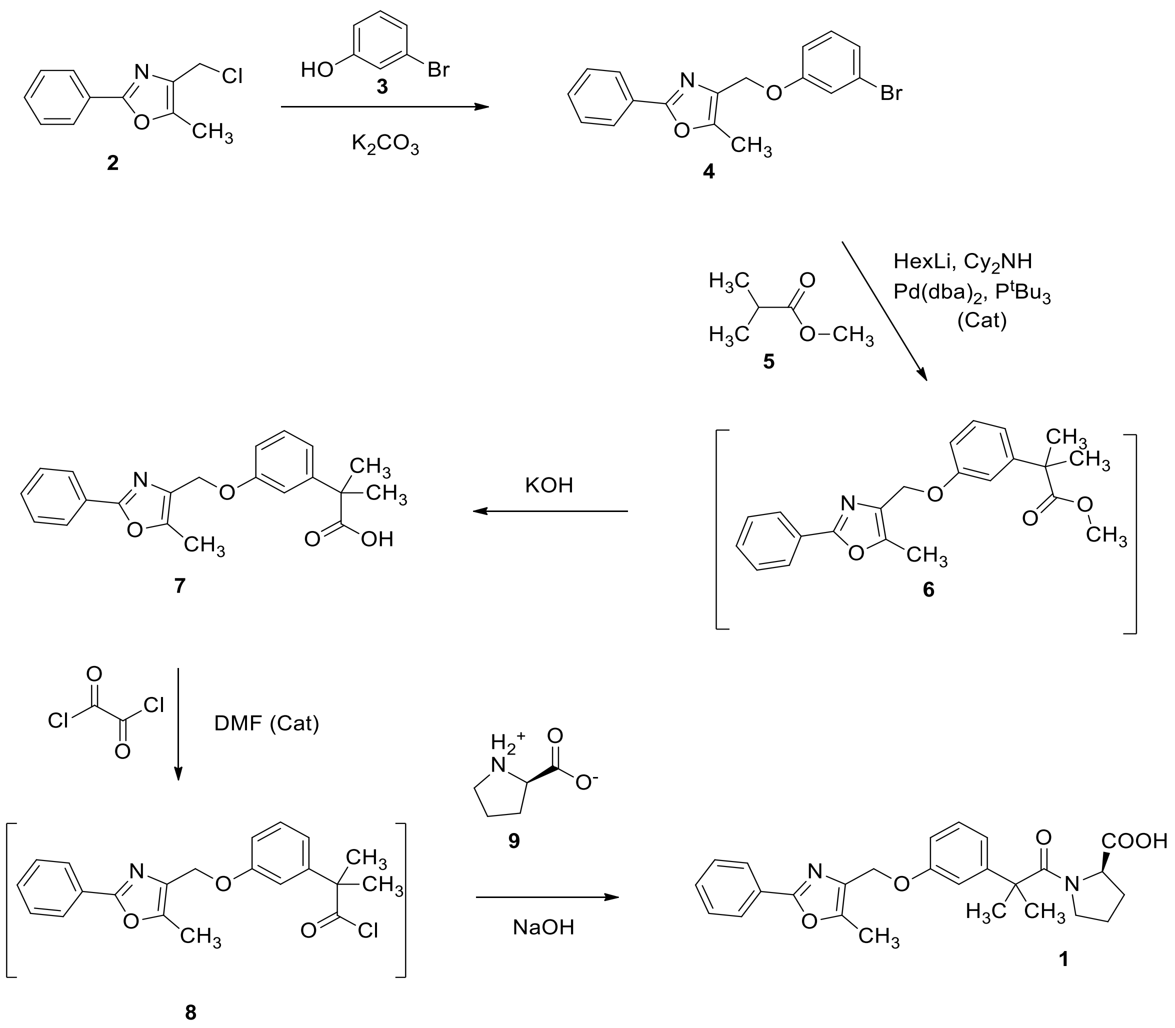
Keywords: Selective PPAR alpha agonist, preparation, Pd-catalyzed C-C bond formation

Introduction

The Discovery synthesis[1] of LBS834 **1**, a potent and selective PPAR alpha agonist,[2] nvolved 8 chemical steps and 3 chromatographic purifications in addition to several lengthy extractions. The overall yield was 6% (see Scheme 1). Although this route proved to be suitable for the preparation of small quantities of drug substance, it was readily apparent that major changes would have to be implemented for scale up in the Pilot Plant. One of our main development goals was to modify the overall strategy to render the entire process more efficient (fewer steps, eliminate chromatography). We felt that the best way to accomplish this was to employ a palladium-catalyzed coupling between a suitably substituted benzene and the anion of methyl isobutyrate. This would provide the basic structure of the molecule and eliminate the undesirable dialkylation step. This strategy had been used successfully in our first scale up in the laboratory (see Scheme 2).



Scheme 1. Discovery synthesis of LBS834.



Scheme 2. Current synthesis.

The palladium-catalyzed coupling between the enolate of methyl isobutyrate **5** and oxazole **4** provided (after saponification) acid **7**, which simply needed to be coupled with D-proline to provide the drug substance. This report provides a detailed discussion of the process development work that was carried out for each step in the preparation of **1** for a Phase I campaign.

Results and Discussion

Coupling of oxazole 2 with phenol 3

In the Discovery procedure, oxazole **2** was prepared in two steps from benzaldehyde and 2,3-butanedione monooxime in an overall yield of 40%. It was condensed with the methyl ester of 3-hydroxyphenylacetic acid. After an aqueous work up, the product was isolated by chromatography in 70% yield. Our main concern was the use of an extractive work-up as well as the need for chromatography. Additionally, this approach required a dialkylation of the product with sodium hydride/methyl iodide, followed by saponification of the ester to afford the coupling partner for the D-proline.

For the Phase I campaign, **4** was synthesized by heating **2** (purchased from an outside vendor)[3] and the potassium salt of **3** (1.2 equiv) in DMF. The work-up was modified to provide a better pilot plant fit. Thus, after the reaction was complete, the batch was cooled to 5 °C, treated with 1.2 equiv of NaOH, and diluted with water at a controlled rate. The batch was seeded to initiate precipitation of the product, and **4** was isolated by filtration in 95% yield and with >99% HPLC purity.

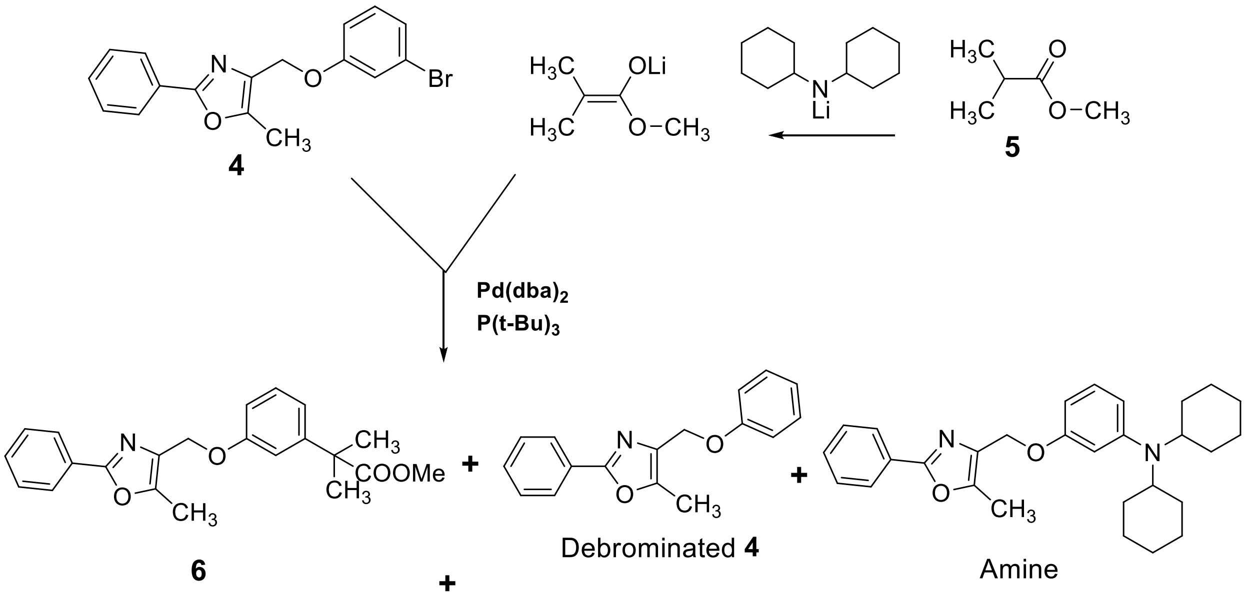
Pd-Catalyzed arylation and hydrolysis

We chose a different approach from that used by Discovery for the preparation of **6** and **7**. This was based on a report[4] in the literature, wherein it was shown that α-aryl esters could be prepared conveniently by a palladium-catalyzed coupling reaction between an aryl halide and an ester enolate. In our case, this involved the reaction between bromophenolic ether **4** and the lithium enolate of methyl isobutyrate **5**. The feasibility of this approach was proven in the laboratory.

For the Phase I campaign, our major goal was to demonstrate the scalability of this step since it would provide a more efficient route to the drug substance. In addition, the possibility of eliminating the chromatographic purifications as well as the undesirable reaction conditions found in some of the steps made the successful implementation of this chemistry a high priority. One of the main development goals associated with this step involved maintaining dry, oxygen-free conditions throughout the process to obtain the highest possible yield. In addition, we wanted to evaluate the time critical operations as well as methods for minimizing the formation of the major side product (de-brominated **4**).

In the laboratory, the coupling reaction was carried out by adding a solution of *n*-hexyllithium in hexane to a solution of dicyclohexylamine in toluene at < –30 °C to form lithium dicyclohexylamide. After warming to 0 °C and recooling to < –30 °C, methyl isobutyrate was added to form the lithium enolate. A total of 1.3 equiv of each reagent with respect to **4** was used. The enolate was then treated with a solution of **4**, the catalyst [$Pd(dba)_2$], and tri-*t*-butylphosphine at –5 °C. The reaction mixture was allowed to warm slowly to 20 °C. Initially, a catalyst loading of 0.0025 equiv was employed, but this was later increased to 0.005 equiv to ensure complete consumption of **4**. Under these conditions, the reaction was complete in 3 h at 20 °C. Analysis of the reaction mixture by HPLC indicated the presence of **6** (90%) and de-brominated **4** (5-10%).

For the Phase I campaign, the amounts of *n*-hexyllithium and dicyclohexylamine were increased slightly. This was done to compensate for the quality of the *n*-hexyl lithium and for any additional water which may have been present. However, when these conditions were used, a new amine impurity was observed in addition to debrominated **4**. The structure of this impurity was confirmed by LC-MS. (Scheme 3). The formation of this compound was attributed to the fact that the amounts of *n*-hexyllithium and dicyclohexylamine were increased without increasing the amount of **5** present. Thus, the excess lithium dicyclohexylamide competed as a nucleophile with the lithium enolate of methyl isobutyrate **5**.



Scheme 3. Formation of **6** and byproducts.

This amine compound, as well as the debrominated **4** could be removed during the work up in the following step. To suppress formation of the amine impurity, the amount of methyl isobutyrate was increased to 1.5 equiv (same as *n*-hexyllithium and dicyclohexylamine) to ensure that no excess amide was present.

The formation of lithium dicyclohexylamide and the enolate were carried out at a higher temperature (–15 to –7 °C) to accommodate the cooling limitations of the pilot plant equipment (–25 °C). Under these conditions, the conversion of **4** to **6** was ~ 81%. Since **6** was not isolated, an aqueous work up was used to ensure that the material obtained was of sufficient quality. Thus, a series of aqueous washes was employed:

- water – removed lithium bromide
- sulfuric acid (2x) – removed dicyclohexylamine
- water – removed last traces of sulfuric acid
- N-acetylcysteine (2x) – removed palladium
- water – removed traces of the N-acetylcysteine.

With regard to the work up and isolation, two major issues were investigated.

(1) Removal of dicyclohexylamine

Removal of dicyclohexylamine and the palladium catalyst was rather challenging. In the laboratory, after the reaction was complete, the batch was treated with dilute aqueous HCl. White solids immediately precipitated, and the batch became a gel. Filtration of the dicyclohexylammonium salt was very sluggish (18 h).

Other acids such citric acid, acetic acid, and sulfuric acid were tested in an attempt to make a solid dicyclohexylammonium salt or one with good water solubility. However, fine particles or gel formed as soon as any of these acids were added, and filtration was still very slow even with filter aids such as cellulose or Celite. To make the gel-like solids dissolve, a large quantity of water (8-10 times the volume of organic solvent) was required. The large volumes were a significant scale-up issue.

However, we soon determined that the problem actually was caused by the presence of lithium bromide, a water-soluble byproduct from the coupling reaction. When acid was added, the lithium bromide reacted with dicyclohexylammonium cation to form the poorly soluble dicyclohexylammonium bromide. Once this was known, the problem was solved by adding water to the batch and separating the aqueous solution of lithium bromide before addition of the acid.

(2) Removal of the palladium catalyst

The palladium present in **6** was soluble in the organic medium and was not removed by the addition of acid. However, we found that the metal would precipitate during the saponification of **6**. In the laboratory, we observed that the precipitated palladium coated the reactor walls and stirring shaft. The coating could only be removed by the addition of concentrated HCl/HNO_3. This presented a problem for the pilot plant since the basic hydrolysis operation was to be carried out in a stainless steel reactor, which is incompatible with strong acids.

After several attempts, we found that removal of the palladium could be effected by an aqueous wash with *N*-acetylcysteine.[5] Washing the toluene solution of crude **6** with aqueous N-acetylcysteine (twice) was carried out at 20 °C. This reduced the palladium content from ~1400 ppm to 400 ppm. Raising the temperature of the wash to 60 °C, reduced the palladium content to less than ~ 70 ppm. In the Phase I campaign, the Pd content in crude **6** was 23 ppm.

Since water was known to have a deleterious effect on the yield of this type of reaction, compound **4** used was analyzed for water content by Karl Fischer titration (see previous step). Based on the final laboratory process sample, the limit for water content was set at $\leq$0.2%. The estimated yield was 81%. Product **6** was obtained as a toluene solution, which was used “as is” in the following step.

In the Discovery synthesis, the ester was isolated and hydrolyzed using sodium hydroxide/water/methanol. Since in our case, a toluene solution of **6** was obtained from the previous reaction, our main development goal was to identify a convenient procedure which would allow us to use this solution directly and allow scale up.

Initially, the hydrolysis (step **6** → **7**) was carried out in methanol-water at 65 °C for 7-12 h. For the Phase I campaign, most of the toluene was removed by distillation and a KOH/methanol solution was added (2 equiv of base were used). The mixture was heated at reflux for 24 h and checked for conversion. The product was isolated by distillation of the methanol followed by the addition of water and toluene. The basic aqueous layer was washed with MTBE and acidified to precipitate product **7**. To further reduce the palladium content, an aqueous solution of N-acetylcysteine was added prior to the precipitation of **7**. The palladium content in the product was thus reduced to 2 ppm.

Amide formation

The procedure used in the Discovery group's preparation of **1** involved coupling of the acid with the D-proline methyl ester using EDCI/HOBt in methylene chloride/DMF. The reaction time was 48 h. After an aqueous work up, the crude product was purified by chromatography. The yield for this step was 60%. In a second step, the methyl ester was saponified to the acid to afford the drug substance.

Our development goals for this step involved simplifying the procedure as much as possible and eliminating the chromatographic purification. We felt that the best way to do this would be to use D-proline instead of the ester. Crystallization of the product directly from the reaction mixture might then be possible. Thus, **7** was treated with 1.2 equiv of oxalyl chloride in THF at 5-10 °C in the presence of 0.02 equiv of DMF. For the peptide coupling, we chose Schotten-Baumann conditions. Thus, the solution of the acid chloride **8** was added slowly to a solution of a large excess of D-proline (5 equiv) in THF-sodium hydroxide at –5 to –10 °C. The reaction was completed by stirring for 15 min after addition of the acid chloride. After removal of the THF and most of the water by distillation (at this point the mixture could be a suspension or a solution), to precipitate the product as the acid, water was added and the solution of the sodium salt of **1** was acidified with 1 N HCl containing N-acetylcysteine (to remove traces of palladium). Filtration afforded wet solids, which contained water trapped in the crystals. Based on the weight of the solids, the amount of water present was equal to or greater than the expected weight of the product. Initially, the wet solids were dried "as is" under vacuum at 50 °C. However, we found that under these conditions, the solids melted in the oven and gave up the water so that a large volume of water was present along with the solids. As an alternative, we decided to re-slurry the wet solids in water at elevated temperature to remove the water trapped in the crystals. To prevent melting, the temperature was maintained below 35 °C. This proved to be an effective method of removing the excess water, since the weight of the isolated **1** was now close to theoretical. After drying, the water content was 0.2% by Karl Fischer.

Conclusions

In conclusion, we have synthesized **1** in five linear steps starting from readily available starting materials. The synthesis is efficient and has been scaled-up to prepare 13 kg of **1**. An efficient method for the palladium-catalyzed coupling of oxazole **4** and the anion of methyl isobutyrate **5** is described. A simplified procedure for the conversion of **7** into the drug substance **1** was also developed.

Experimental Section

General. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AVANCE DPX-500 spectrometer (^{1}H NMR at 500 MHz). Analytical high performance liquid chromatography (HPLC) was carried out using a Waters Alliance 2690 Separations Module, a Waters 996 Photodiode Array Detector (MaxPlot), and a 4.6 mm x 25 cm Waters C18 Symmetry column. Reactions were carried out under an atmosphere of nitrogen. Residual-water content was determined by Karl Fischer titration. The quantities used for each reagent were adjusted for purity.

4-[(3-Bromophenoxy)methyl]-5-methyl-2-phenyl-1,3-oxazole (4). Charge a 400-L glass-lined reactor with 7.8 kg (56.1 mol) of potassium carbonate, 71.3 kg of *N*,*N*-dimethylformamide, and 9.8 kg (55.8 mol) of 3-bromophenol **3**. Rinse the addition line with 8.9 kg of DMF. Stir the heterogeneous reaction mixture for 5 min at 20-24 °C and add 9.8 kg (44.8 mol) of 4-chloromethyl-5-methyl-2-phenyl-1,3-oxazole **2**. Heat the yellow suspension at 65 °C (internal) for 7 h. Cool the reaction mixture to 5 °C and add 11 kg (113.2 mol) of 6 N sodium hydroxide followed by 14.2 kg of water. Seed the batch and stir for 1 h at 5 °C. Warm the mixture to 15 °C and add 174.6 kg of water maintaining the temperature at 10 ± 5 °C. Stir the suspension 18 ± 5 °C for 12 h. Isolate the solid by filtration and wash the cake with 50, then 35 L of water. Dry the solids in a vacuum oven at 30-35 ºC (10 mbar) for 24 h, to yield **4** as a white solid, 14.5 kg (94% yield, corrected); mp 49-53 °C; ^{1}H NMR ($CDCl_3$) δ 8.0 (m, 2H), 7.4 (m, 3H), 7.2-6.9 (m, 4H), 4.9 (s, 2H), 2.4 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.25, 159.46, 147.42, 131.75, 130.73, 130.35, 128.89, 127.54, 126.31, 124.40, 122.94, 118.36, 114.05, 62.61, 10.69.

Methyl α,α-dimethyl-3-[(5-methyl-2-phenyl-4-oxazolyl)methoxy]benzeneacetate (6). Charge a 350-L, glass-lined reactor with 11.7 kg (64.6 mol) of dicyclohexylamine and 47 kg of toluene. Cool the solution to -15 °C and add 18.9 kg (61.5 mol) of 2.3 M *n*-hexyllithium dropwise while maintaining the reaction temperature below – 5 °C. When the addition is complete, stir for 15 min at 0 °C and then cool to –15 °C. Add 5.8 kg (57.1 mol) of methyl isobutyrate **5** while maintaining the temperature below –10 °C. Stir the reaction mixture at –10 °C for 10 min and then warm to 0 °C. Add a solution consisting of 15.3 kg (44.5 mol) of **4** dissolved in 20 kg of toluene. Immediately add a suspension of 128 g (0.23 mol) of bis(dibenzylideneacetone) palladium in 1 L of toluene and 585 g (0.27 mol) of a 10% solution of tri-*tert*-butylphosphine in toluene. Rinse the addition line with 6.7 kg of toluene. Allow the reaction mixture to warm to 20 °C over 3.5 h and then continue stirring for an additional 2 h. Add 101 kg of water and stir for 15 min. Separate the aqueous layer and wash the organic layer twice with a solution of 97 kg of 4% sulfuric acid, followed by 38 kg of water. Add 39 kg of a solution prepared from 1.6 kg (9.9 mol) of *N*-acetyl-ʟ-cysteine in 81 kg of water. Heat the mixture to 60 °C and hold for 30 min. Cool to 30 °C and separate the aqueous layer. Repeat with another 39 kg of *N*-acetyl-L-cysteine solution. Wash the organic layer with 38 L of water. Filter the solution and save for the following step. The yield is approximately 75%. ^{1}H NMR (CDCl$_3$) δ 8.00 (m, 2H), 7.43 (m, 3H), 7.3-6.9 (m, 4H), 5.00 (s, 2H), 3.64 (s, 3H), 2.44 (s, 3H), 1.56 (s, 6H); MS *m/z* 366 (M$^+$).

α,α-Dimethyl-3-[(5-methyl-2-phenyl-4-oxazolyl)methoxy]benzeneacetic acid (7) Charge a 250-L, stainless steel reactor with 97.2 kg of the toluene solution of **6**. Distill the solvent at a batch temperature of 50-65 °C/300-600 mbar until a final volume of approximately 38 L is reached. Cool the residue to 20 °C and add a solution of 5.9 kg of solid potassium hydroxide (85%) in 86.5 kg of methanol. Heat the suspension to 70 °C and stir for 24 h. Cool the mixture to 20 °C and filter using filter aid (Celite Hyflo Supercel). Wash the filter cake with 15.2 kg of methanol. Distill the filtrate at 50-67 °C/300-600 mbar until a volume of 115 L is reached. Charge 82.9 kg of toluene and distill as before to a final volume of 100 L. Add 144 L of water and cool to 20 °C. Add 29 kg of *tert*-butyl methyl ether and stir for 20 min. Separate the organic layer and discard. Add 57 kg of *tert*-butyl methyl ether and stir for 20 min. Separate and discard the organic layer. Distill the aqueous layer at 55-65 °C/100-300 mbar until a final volume of 180 L is reached. Add 107 kg of methanol, 14 kg of 2 N HCl solution, and 1.1 kg on N-acetyl *L*-cysteine dissolved in 9.4 kg (0.018 mol) of water. Stir for 10 min at 20 °C and add 4.2 kg of 2 N HCl solution slowly until cloudiness persists. Stir for 30 min and add 28.6 kg of 2 N HCl over 1 h. The final pH is 2.0. Continue stirring for 1 h. Isolate the solid by centrifugation and wash the filter cake with a mixture of 31 L of water 12.2 kg of methanol. Dry the solids in a vacuum oven at 50-55 °C/10 mbar for 16 h to yield **7** as a pale yellow solid, 18.4 (72% yield); mp 133 °C; ^{1}H NMR (CDCl$_3$) δ 8.01 (m, 2H), 7.42 (m, 3H), 7.24 (m, 1H), 6.95 (m, 3H), 4.99 (s, 2H), 2.43 (s, 3H), 1.58 (s, 6H).

1-[2-Methyl-2-[3-[(5-methyl-2-phenyl-4-oxazolyl)methoxy]phenyl]-1-oxopropyl]-D-proline (1). Charge a 400-L, glass-lined reactor with 11.2 kg (31.6 mol) of **7,** 70.3 kg of THF, and a solution of 53 mL of DMF in 483 mL of THF. Stir until a clear solution is obtained. Cool the resulting solution to 0 °C and add 4.9 kg (38.2 mol) of oxalyl chloride while maintaining the temperature below 5 °C. Warm the resulting the solution to 20 °C over 1 h and hold at this temperature for 30 min. Prepare a solution of 18.4 kg (158.2 mol) *D*-proline **9**, 86.4 kg of THF, and 36.8 kg of 6 N sodium hydroxide solution. Cool the solution to 0 °C and add the solution of the acid chloride **8** while maintaining the temperature between -5 °C and +5 °C. Stir 15 min after the addition is complete. Allow the solution to warm to 20 °C over 1 h. Apply vacuum (20 mm Hg) and warm to 35 °C to remove THF (final volume = 77 L). Add 309 L of water to the resulting white slurry and stir for 30 min at 20 °C. Add 199.6 kg of a solution consisting of 441 g of *N*-acetyl-L-cysteine, 17.5 kg of 37% HCl, and 161.3 kg of water. Add 19.9 kg of 3 N HCl solution. Stir the suspension for 2 h. Remove the aqueous layer. Add 10.7 kg of 3 N NaOH and 180 kg of tetrahydrofuran and stir until the solids dissolve. Apply vacuum (20 mm Hg) and warm to 35 °C to remove THF (final volume = 35-40 L). Cool to 20 °C and add 205 L of water. Stir until solution becomes hazy. Add 166.3 kg of 1 N HCl. Stir the suspension for 2 h. Isolate the solid by centrifugation and wash the filter cake with 75 L of water. Re-slurry the wet solids in 228 L of water and warm to 35 °C. Stir for 45 min, cool to 20 °C, and stir for 3 h. Isolate the solids by centrifugation and wash the filter cake with 250 L of water. Dry the solids at 60 °C/10 mbar for 16 h to yield **1** as a white solid, 13.4 kg (93% yield); mp 81-84 °C; ^{1}H NMR (DMSO, d$_6$) δ 12.41 (br s, 1H), 7.94 (m, 2H), 7.52 (s, 3H), 7.27 (s, 1H), 6.91 (m, 3H), 5.02 (s, 2H), 4.26 (br s, 1H), 3.32 (s, 1H), 2.80 (m, 2H), 2.45 (s, 3H), 2.02 (m, 1H), 1.62 (br s, 1H), 1.40 (m, 7H); ^{13}C NMR (CDCl$_3$) δ 176.24, 175.35, 159.99, 158.75, 147.10, 146.70, 131.67, 130.16, 129.68, 128.66, 127.06, 126.05, 118.12, 112.85, 112.17, 61.76, 77.00, 76.57, 61.76, 60.58, 47.73, 47.06, m27.59, 27.32, 26.62, 25.30, 10.40; MS *m/z* 449 (M$^+$).

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