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Development of a Scalable Synthesis of a Serotonin Receptor Antagonist

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ABSTRACT: An efficient process was developed for the manufacture of MSA100, a serotonin receptor antagonist, via a five-step synthetic route furnishing a high quality of active pharmaceutical ingredient. Highlights of this synthesis include: (1) replacing carcinogenic methyl iodide with methyl *p*-toluenesulfonate as the methylating reagent; (2) a hydrogenation protocol with optimized temperature, pressure, and mass-transfer conditions that avoided one side product and reduced the other one effectively; (3) chemical resolution employing *D*-camphoric acid in a mixed-solvent system; (4) amidation under anhydrous conditions for controlling a Michael adduct impurity; and (5) plausible mechanisms for the formation of side products.

INTRODUCTION

It was reported that the (*S*)-enantiomer of 2′-[2-(1-methyl-2-piperidyl)ethyl]cinnamanilide (MSA100, **1**) (Figure 1) is an

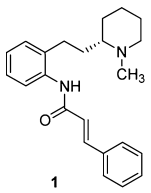

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Figure 1. MSA100, a serotonin receptor antagonist.

active 5-HT (5-hydroxytryptamine or serotonin) receptor antagonist; however, its (*R*)-isomer is totally or substantially devoid of the same activity.[1] Because we had interests in investigating its therapeutic potential in humans, we needed to develop a scalable synthesis allowing the production of kilogram quantities of this active pharmaceutical ingredient (API). The original synthesis of **1** established the molecule's chirality by chemical resolution using dibenzoyl-*L*-tartaric acid as the resolving agent (Scheme 1).[1a] Use of chemical resolution for the synthesis of enantiomerically pure drug substances has been extensively demonstrated in the pharmaceutical industry[2] as well as in our lab.[3] Since this approach is practical and reliable, we decided to utilize this strategy and explore its potential in making enantiomerically pure **1** on kilogram scale. During the course of exploring the feasibility of the original synthetic route, we found several drawbacks. First, methyl iodide is not a desirable methylating agent for **4**, because it is a potential carcinogen.[4] Second, resolution with dibenzoyl-*L*-tartaric acid afforded diastereomeric salt **7** in only 28.6% yield and resulted in an overall yield of 10.7% for the original synthesis. Herein, we disclose an improved synthesis that was employed successfully on plant-scale.

RESULTS AND DISCUSSION

Synthesis of Phenethylpiperidine 11. Our manufacturing synthesis of MSA100 (**1**) began with the preparation of 2-styrylpyridine **4** by reacting 2-nitrobenzaldehyde **2** with 2-picoline **3** in acetic anhydride at 140 °C.[1,5] Upon completion, the reaction mixture was cooled to 15 °C and adjusted to pH 11 with 50% NaOH resulting in the formation of a granular solid, which was collected by filtration. This process was scaled-up on a 40-kg scale in the plant to afford 47.3 kg of **4** (79% yield) with 99% purity.

To prepare the methylpiperidine fragment of the target molecule, the original synthesis treated **4** with methyl iodide leading to methylpyridinium salt **5**, which was then hydrogenated to methylpiperidinium salt **6**.[1] We were concerned about the carcinogenic property of methyl iodide and decided to replace it with a less toxic methylating reagent. We found that methyl *p*-toluenesulfonate is an excellent alternative. Methylation of **4** with methyl *p*-toluenesulfonate in acetonitrile at 82 °C for 24 h cleanly generated tosylate salt **10** (Scheme 2). This salt precipitated out from the reaction mixture by adding isopropyl acetate and was isolated by filtration. This simple and efficient process was employed on a 47-kg scale in the plant to furnish 80 kg of **10** (93% yield) with 99% purity.

Conversion of pyridinium salt **10** to the subsequent piperidinium salt **11** by catalytic hydrogenation employing platinum as the catalyst could generate side products **12** and **13** (Figure 2), about 25% each, if the hydrogen concentration and its mass-transfer rate are not sufficient. Both side products were isolated and characterized by NMR. The plausible mechanism for their formations is shown in Scheme 3.

We postulated that the conversion of nitropyridinium tosylate **10** to piperidinium salt **11** by hydrogenation went by pathway A involving both nitroso **10a** and aniline **10b** (Scheme 3). Both intermediates can be detected and characterized by LC/MS analyses. As suggested by HPLC analysis of the reaction mixture, reductions of the double bond and the pyridinium ring of **10b** to piperidine **11** were much slower than that of the nitro group of **10a** to aniline **10b**. If conditions were not optimum for pathway A, such as low hydrogenation

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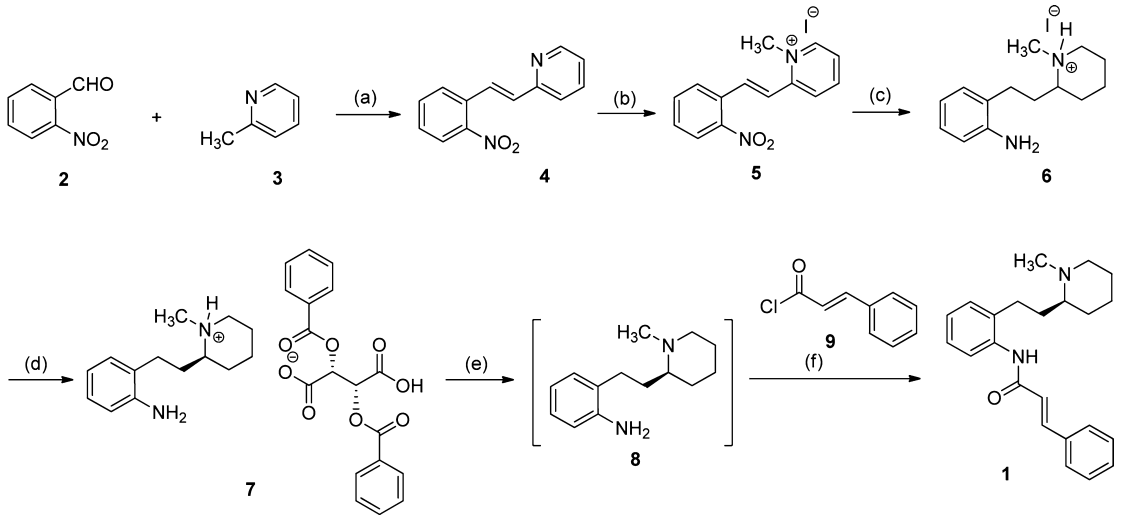
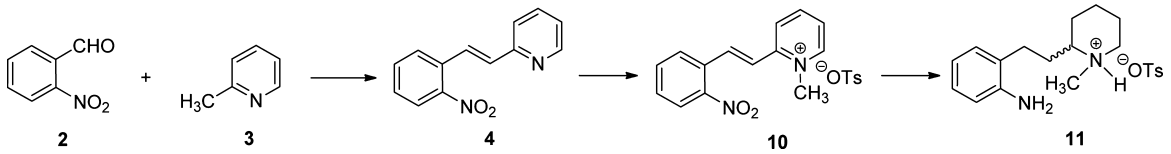
Scheme 1. Original Synthesis[a] of 1



[a]Reagents and conditions: (a) Ac_2O, 140 °C, 100% as is (b) MeI, acetone, reflux, 80%; (c) H_2, Pt/C, MeOH, 25 °C; 59%; (d) NaOH, then dibenzoyl-*L*-tartaric acid, MeOH, 25 °C, 28.6%; (e) $NaHCO_3$, EtOAc, 100% as is (f) K_2CO_3, EtOAc, 79%. Overall yield: 10.7%.

Scheme 2. Synthesis of Piperidinium Salt 11



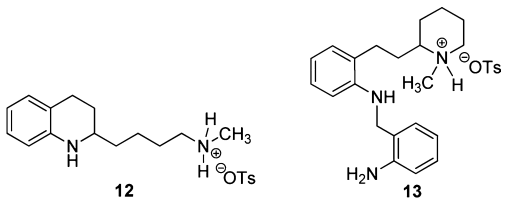


Figure 2. Two hydrogenation side products.

concentration or slow agitation rate (mass transfer), both pathways B and C could compete with pathway A. Through pathway B, an intramolecular cyclization reaction of aniline **10b** could give a spiro-intermediate **10c**. After subsequent three transformations: hydrogenation to **10d**, rearrangement to **10e**, and hydrogenation of **10e**, **10b** could lead to side product **12**. Under another scenario, a thermal [2 + 2]-cycloaddition reaction between nitroso intermediate **10a** and starting material **10** via pathway C is conceivable.[6] The four-membered ring intermediate **10f** thus formed could undergo a retro [2 + 2]-cycloaddition reaction to afford an imine intermediate **10g**. Further hydrogenation of **10g** could generate side product **13**. To prove that **13** could be formed under hydrogen-deficient conditions, an experiment was conducted in which the hydrogen supply was interrupted as soon as **10** was converted to the nitrosopyridium tosylate **10a**. The reaction mixture was then heated to 65 °C in the absence of hydrogen gas and stirred for an additional 1.5 h. At this point, hydrogen supply was resumed and the hydrogenation reaction was allowed to go to completion. As expected, we observed more than 25% side product **13**.

Because we noticed that both hydrogen concentration and mass-transfer rate had significant impacts on the profiles of product and side products during the hydrogenation of **10**, efforts were focused on optimizing these conditions. Employing the improved conditions (30 °C, 75 psi, and 450 rpm), we were able to generate **11** containing no detectable amount of **13** and 14% (by area relative to **11**) of **12**. Side product **12** was not a problem because it was easily removed from **11** by crystallization. This protocol was utilized on 20-kg scale three times in the plant to afford a total of 40.6 kg (71% yield) of **11** with 99% purity.

Chemical Resolution. Dibenzoyl-*L*-tartaric acid was utilized in the original synthesis as the resolving agent for separating the free base of racemic **11** and resulted in the isolation of the desired diastereomeric salt in 28.6% yield (57.2% theory).[1a] To increase the throughput, alternative resolving agents were investigated. We found that *D*-camphoric acid (*D*-CA) consistently gave superior results under various conditions (Scheme 4). The best diastereomeric ratio of 98.6:1.4 for salt **14** was obtained in 47% yield (94% theory) when the resolution was conducted in a mixture of ethanol and isopropyl alcohol. Further recrystallization of **14** in the same solvent system can enhance the diastereomeric ratio to 99.9:0.1 in 94% recovery, an overall yield of 44% (88% theory) from **11**. This process was scaled up on 40-kg scale in the plant to produce 17.4 kg (41% yield) of **14** with 99.9% diastereomeric purity.

Amidation. To synthesize the final active pharmaceutical ingredient **1**, diastereomaric salt **14** was liberated to free-base **8** by treating it with an aqueous NaOH solution in isopropyl acetate (Scheme 5). Amidation of **8** with cinnamoyl chloride **9** employing a biphasic system was problematic. For instance, treating the isopropyl acetate solution of **8** with **9** employing the Schotten–Baumann conditions[7] with an aqueous solution

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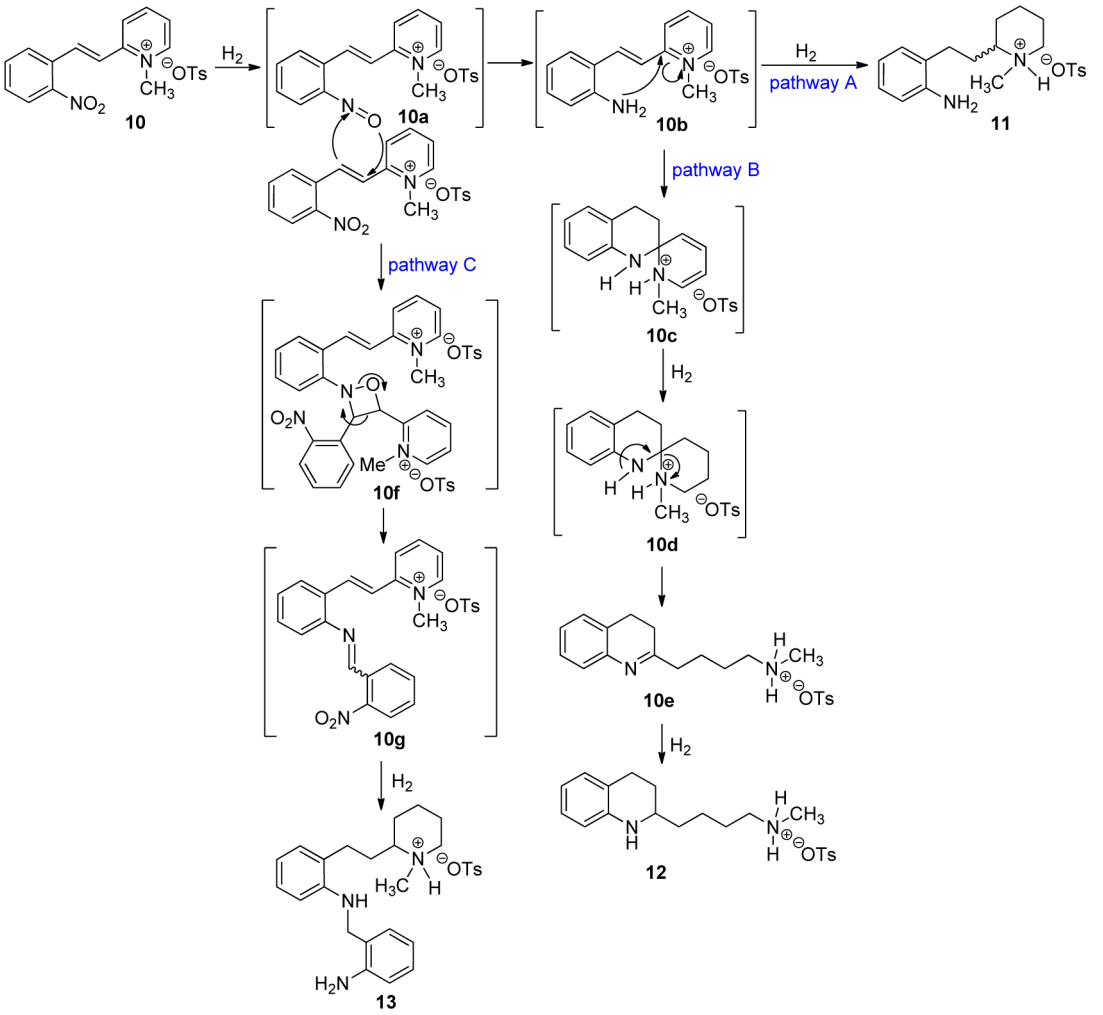
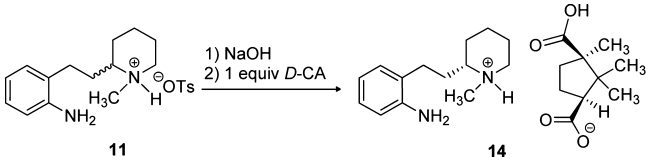
Scheme 3. Plausible Mechanism for the Formation of Side Products 12 and 13



Scheme 4. Chemical Resolution

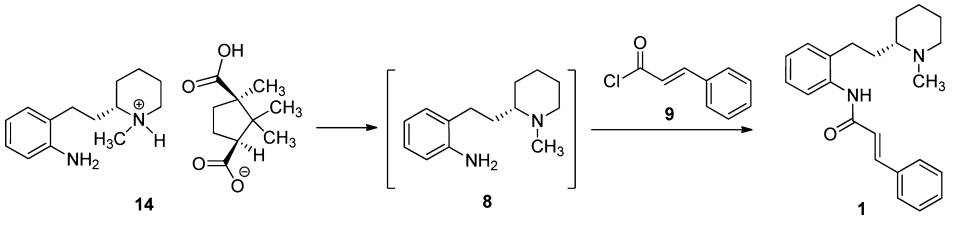


of either K_2CO_3 or $NaHCO_3$ resulted in the formation of a side product in 33−42% range. This side product was characterized by NMR and LC/MS as a Michael adduct **15**, arising from Michael addition of aniline **8** to product **1** (Scheme 6). Replacing the above biphasic solution with an anhydrous system employing K_2CO_3 as the acid scavenger, similar conditions used in the original synthesis,[1a] the side product **15** was decreased to 1.3%. Further reduction of **15** to less than 0.1% was achieved by crystallization. To obtain the anhydrous solution of **8** without using any drying agent, the isopropyl acetate solution of **8** containing residual amounts of water was concentrated by azeotropic distillation to ensure a complete removal of water. As a result, amidation of **8** with cinnamoyl chloride in the presence of solid K_2CO_3 was carried out on 16-kg scale in the plant to produce **1** (10.9 kg, 83% yield) with 99.1% purity and 99.8% ee.

CONCLUSIONS

An efficient process was developed for the manufacture of MSA100 (**1**), a serotonin receptor antagonist, via a five-step synthetic route furnishing a high quality of active pharmaceutical ingredient. The overall yield of the manufacturing synthesis

Scheme 5. Amidation



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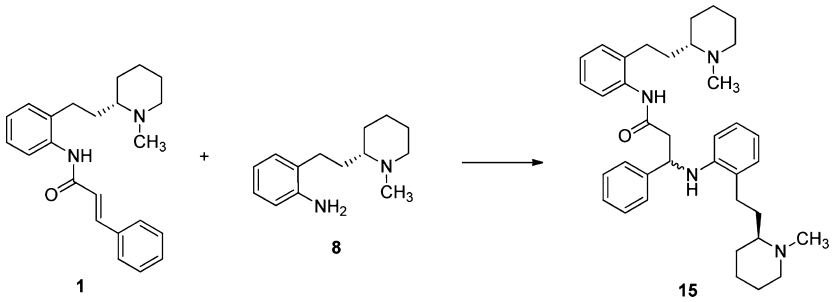
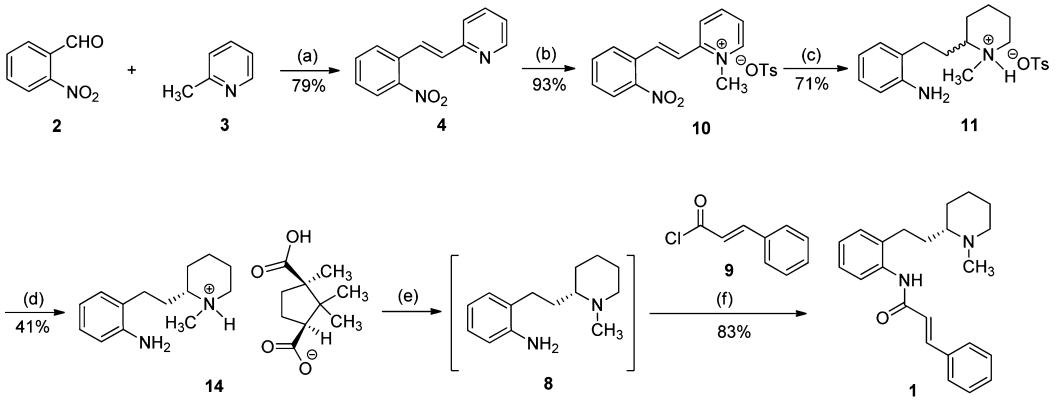
Scheme 6. Formation of Side Product 15



Scheme 7. Manufacturing Synthesis of 1



[a]Reagents and conditions: (a) Ac_2O, 140 °C; (b) methyl *p*-toluenesulfonate, CH_3CN, 82 °C; (c) H_2 (75 psi), 10% Pt/C, MeOH, 30 °C, 450 rpm; (d) NaOH, then (1*R*, 3*S*)-(+)-camphoric acid, EtOH-*i*PrOH, 65−23 °C; (e) NaOH, *i*PrOAc; (f) K_2CO_3, *i*PrOAc, 85 °C. Overall yield: 17.8%.

of **1** (Scheme 7) was increased from the original 10.8 to 17.8%. Highlights of this synthesis include the following: (1) replacing carcinogenic methyl iodide with methyl *p*-toluenesulfonate as the methylating reagent; (2) a hydrogenation protocol with optimized temperature, pressure, and mass-transfer conditions that avoided one side product and reduced the other one effectively; (3) chemical resolution employing *D*-camphoric acid in a mixed-solvent system; (4) amidation under anhydrous conditions for controlling a Michael adduct impurity; and (5) plausible mechanisms for the formation of side products.

EXPERIMENTAL SECTION

General. Reverse phase HPLC analyses were performed on an Agilent HPLC system with a DAD detector (area normalization).

*2-[(E)-2-(2-Nitrophenyl)ethenyl]-pyridine (**4**).* A mixture of 2-nitrobenzaldehyde **2** (150 g, 0.99 mol), 2-picoline **3** (130 g, 1.39 mol), and acetic anhydride (282 mL) was heated to 140 °C and stirred for 28 h. The resulting dark mixture was cooled to 10 °C. Water (750 mL) was added while maintaining the batch temperature below 35 °C. The mixture was cooled to 15 °C. A 50% (w/w) aqueous NaOH solution (263 g) was added while maintaining the batch temperature below 35 °C. Seeds (**4**, 120 mg) were added. More 50% (w/w) aqueous NaOH solution (263 g) was added while maintaining the batch temperature below 35 °C. The resulting suspension was stirred at 35 °C for 1 h. The precipitate was filtered, rinsed with water (4 × 375 mL), and dried under reduced pressure (15−40 mbar) at 70 °C for 16 h to afford **4** (195 g, 87% yield) as a solid: mp 95−96 °C (lit. ref 5, mp 98−99 °C); HPLC for **4** (t_R = 4.60 min, identical to authentic sample) 99.5% purity; **2** (t_R = 8.64 min); **3** (t_R = 1.63 min): Waters Symmetry-C18 150 × 4.6 mm, flow rate = 1 mL/min, 25 °C, gradient elution from 25:75 A−B (held for 5 min) to 90:10 A−B over 2 min, and held at 90:10 A−B (5 min); A = acetonitrile; B = 0.1% TFA in water; UV λ = 254 nm.

*1-Methyl-2-[(E)-2-(2-nitrophenyl)-ethenyl]-pyridinium 4-methylbenzenesulfonate (**10**).* A mixture of **4** (80 g, 0.354 mol), methyl *p*-toluenesulfonate (98.8 g, 0.530 mol), and acetonitrile (400 mL) was heated to 82 °C and stirred for 24 h. Isopropyl acetate (400 mL) was added at 82 °C. The suspension was cooled to 25 °C over 1 h and stirred for 4 h. The precipitate was filtered, rinsed with isopropyl acetate (2 × 160 mL), and dried under reduced pressure (15−40 mbar) at 60 °C for 16 h to afford **10** (135 g, 93% yield) as a solid: mp 172−173 °C; HPLC for **10** (t_R = 2.60 and 3.47 min) 99.7% purity; **4** (t_R = 4.60 min); methyl *p*-toluenesulfonate (t_R = 9.33 min): Waters Symmetry-C18 150 × 4.6 mm, flow rate = 1 mL/min, 25 °C, gradient elution from 25:75 A−B (held for 5 min) to 90:10 A−B over 2 min, and held at 90:10 A−B (5 min); A = acetonitrile; B = 0.1% TFA in water; UV λ = 254 nm.

*2-[2-(1-Methyl-2-piperidinyl)ethyl]-benzenamine 4-methylbenzenesulfonate (1:1) (**11**).* To an inert hydrogenation vessel was charged **10** (43.9 g, 0.106 mol), 10% Pt/C (1.87 g, 62.4% wet), and methanol (396 g) under N_2 atmosphere. The headspace was purged with N_2, and the vessel was charged with H_2 by pressurizing with H_2 to 65 psi, followed by depressurizing to 14.5 psi. The H_2 pressurization/depressurization cycle was repeated 4 times. After the final depressurization, the reactor's temperature, hydrogen pressure, and agitation speed were set at 30 °C, 75 psi, and 450 rpm, respectively. Hydrogenation was maintained under these conditions for an

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additional 6 h. The batch was cooled to 25 °C. The vessel was depressurized, purged with N_2 by pressurizing to 65 psi, and depressurized. The pressurizing−depressurizing cycle was repeated five times. The mixture was filtered over a pad of Celite (8 g) and rinsed with methanol (2 × 45 g). The combined filtrate was concentrated at 35−45 °C under reduced pressure (80−160 mbar) until a final volume of ∼150 mL was reached. 2-Propanol (353 g) was added and the mixture was concentrated at 35−45 °C under reduced pressure (80−160 mbar) until a final volume of ∼150 mL was reached. 2-Propanol (353 g) was added one more time and the mixture was concentrated at 35−45 °C under reduced pressure (80−160 mbar) until a final volume of ∼150 mL was reached. The residue was heated to 60 °C and isopropyl acetate (44 g) was added while maintaining the temperature at 55−65 °C. The mixture was cooled to 40 °C over a period of 20 min and seeded with **11** (160 mg). The mixture was cooled to 20 °C over a period of 1 h and stirred for 4 h. The precipitate was filtered, rinsed with a solution of 2-propanol/isopropyl acetate (1:2 v/v) (2 × 42 g), and dried under reduced pressure (15−40 mbar) at 60 °C for 16 h to afford **11** (26.3 g, 64% yield) as a solid: mp 133−135 °C; HPLC for **11** (t_R = 5.20 min) 98.8% purity: Waters YMC ODS-AQ S-3 120 A, 150 × 3.0 mm, flow rate = 0.8 mL/min, 25 °C, gradient elution from 90:10 A−B to 40:60 A−B over 22 min; A = 10 mM NH_4OAc in water ; B = acetonitrile; UV λ = 240 nm.

*(S)-2-[2-(1-Methyl-2-piperidinyl)ethyl]-benzenamine (1R,3S)-(+)-camphoric acid salt (1:1) (**14**).* To a mixture of **11** (30 g, 76.8 mmol) and isopropyl acetate (200 mL) was added a solution of NaOH (4 g, 100 mmol) in water (50 mL). The suspension was stirred until a solution was obtained. The organic layer was separated and saved. The aqueous layer was extracted with isopropyl acetate (67 mL). The combined organic layer was washed with water (50 mL) and concentrated at 20−40 °C under reduced pressure (20−100 mbar) until a final volume of ∼25 mL was reached. 2-Propanol (50 mL) was added and concentrated at 20−40 °C under reduced pressure (20−100 mbar) until a final volume of ∼25 mL was reached. More 2-propanol (50 mL) was added and concentrated at 20−40 °C under reduced pressure (20−100 mbar) until a final volume of ∼25 mL was reached. The residue was dissolved in 2-propanol (100 mL) and added to a solution of (1*R*,3*S*)-(+)-camphoric acid (15.4 g, 76.8 mmol) in anhydrous ethanol (100 mL) at 65 °C. More 2-proponol (100 mL) was added and seeded with **14** (10 mg). The mixture was cooled to 23 °C over a period of 2 h and stirred for an additional 2 h. The precipitate was filtered, rinsed with 2-proponol (2 × 50 mL), dried at 45−50 °C under reduced pressure (13−40 mbar) for 16 h to obtain crude **14** (15.1 g) as a white solid (enantiomeric purity of free base **8**: 98.6:1.4 er).

Recrystallization. A mixture of crude **14** (15.1 g), anhydrous ethanol (40 mL), and 2-propanol (50 mL) was heated to 78 °C and stirred for 1 h. The mixture was cooled to 25 °C over a period of 2 h. The resulting slurry was cooled to 5 °C over a period of 30 min and diluted with 2-propanol (40 mL) at 5 °C. The precipitate was filtered, rinsed with 2-propanol (2 × 30 mL), dried at 45−50 °C under reduced pressure (13−40 mbar) for 16 h to obtain **14** (14.2 g, 44% yield) as a white solid: mp 139−142 °C; Chiral HPLC for **8S** free base (t_R = 7.80 min), 99.9:0.1 er; **8R** free base (t_R = 10.3 min): Chiralcel AD-H, 250 × 4.6 mm, flow rate = 1.0 mL/min, 25 °C, 900:100:1 A−B−C isocratic; A = hexanes; B = ethanol; C = diethylamine; UV λ = 230 nm.

*(2E)-N-[2-[2-[(2S)-1-Methyl-2-piperidinyl]ethyl]phenyl]-3-phenyl-2-propenamide (**1**).* To a mixture of **14** (6.28 g, 15 mmol) and isopropyl acetate (60 mL) was added a solution of NaOH (1.6 g, 40 mmol) in water (20 mL). The suspension was stirred until a solution was obtained. The organic layer was separated and saved. The aqueous layer was extracted with isopropyl acetate (20 mL). The combined organic layer was washed with water (20 mL) and concentrated at 20−40 °C under reduced pressure (20−100 mbar) until a final volume of ∼65 mL was reached to obtain a solution of free base **8**. Potassium carbonate (6.22 g) and cinnamoyl chloride **9** (3.75 g, 22.5 mmol) was added. The suspension was stirred at 85 °C for 2 h and cooled to 25 °C. Water (50 mL) was added and stirred for 30 min to obtain a biphasic solution. The organic layer was separated and stirred with 0.5 *N* aqueous HCl solution (80 mL, 40 mmol). The aqueous solution was separated, diluted with isopropyl acetate (60 mL), and treated with a solution of NaOH (2 g, 50 mmol) in water (25 mL). The organic layer was separated and saved. The aqueous layer was extracted with isopropyl acetate (60 mL). The combined organic layer was washed with water (40 mL) and concentrated at 20−40 °C under reduced pressure (20−100 mbar) until a final volume of ∼22 mL was reached. The residue was heated to 85 °C, and heptane (96 mL) was added while maintaining temperature at 85 °C. The mixture was cooled to 25 °C over a period of 1 h, and stirred for 2 h. The precipitate was filtered, rinsed with a solution of heptane/isopropyl acetate (6/1 v/v) (2 × 14 mL), dried at 45−50 °C under reduced pressure (13−40 mbar) for 16 h to obtain **1** (4.06 g, 78% yield) as an off-white solid: mp 125−127 °C (lit. ref 1a, mp 128 °C); Chiral HPLC for (***S***)-**1** (t_R = 19.3 min), >99.9% ee; (***R***)-**1** (t_R = 18.5 min): Chiralcel AD-H, 250 × 4.6 mm, flow rate = 1.0 mL/min, 25 °C, 900:100:1 A:B:C isocratic; A = hexanes; B = ethanol; C = diethylamine; UV λ = 230 nm. HPLC for **1** (t_R = 11.2 min) 99.8% purity; **8** (t_R = 5.4 min); **9** (t_R = 12.3 min): Waters Symmetry-C18 150 × 4.6 mm, flow rate = 1 mL/min, 25 °C, gradient elution from 93:7 A−B to 85:15 A−B over 5 min, to 10:90 A−B over 10 min and held for 2 min, to 93:7 A−B over 1 min; A = 0.1% TFA in water; B = acetonitrile; UV λ = 230 nm.

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Notes

The authors declare no competing financial interest.

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