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Process Development for (*S,S*)-Reboxetine Succinate via a Sharpless Asymmetric Epoxidation

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Abstract:

Reboxetine mesylate is a selective norepinephrine uptake inhibitor (NRI) currently marketed as the racemate. The (*S,S*)-enantiomer of reboxetine is being evaluated for the treatment of neuropathic pain and a variety of other indications. (*S,S*)-Reboxetine has usually been prepared by resolution of the racemate as the (−)-mandelate salt, an inherently inefficient process. A chiral synthesis starting with a Sharpless asymmetric epoxidation of cinnamyl alcohol to yield (*R,R*)-phenylglycidol was developed. (*R,R*)-Phenylglycidol was reacted without isolation with 2-ethoxyphenol to give 4, which was isolated by direct crystallization. Key process variables for the asymmetric epoxidation were investigated. Conversion of (*R,S*)-4 to reboxetine parallels the racemic synthesis with streamlined and optimized processing conditions. (*S,S*)-Reboxetine free base was converted directly to the succinate salt without isolation as the mesylate salt.

Introduction

Reboxetine mesylate is a selective norepinephrine uptake inhibitor (NRI) currently marketed as the racemate. The (*S,S*)-enantiomer is significantly more active than the racemate in a number of assays, and studies are currently underway for the use of (*S,S*)-reboxetine succinate **1** for the treatment of neuropathic pain and a variety of other indications.[1] Enantioselective syntheses have also been described,[2] but (*S,S*)-reboxetine is usually prepared by resolution of the racemate as the (−)-mandelate salt.[3] This process is inherently inefficient due to the throughput limitations of a classical resolution.

To sustain a future supply of (*S,S*)-reboxetine succinate an enantioselective synthetic route was developed utilizing a Sharpless asymmetric epoxidation.[4] Cinnamyl alcohol **2** was epoxidized to yield (*R,R*)-phenylglycidol (**3**) which was reacted without isolation with 2-ethoxyphenol to give **3**, which was isolated by direct crystallization. Key process variables for the asymmetric epoxidation were investigated.

Changes were made to the racemic process to optimize and simplify the following steps: (1) in step **5**, methylene chloride was substituted for ethyl acetate due to the low solubility of **4** in ethyl acetate; (2) intermediate **6** was crystallized as the free base form rather than as the mesylate salt; (3) a process was developed for the conversion of **6** to **9** using toluene as the single solvent for these three steps, eliminating dimethyl carbonate and a series of solvent exchanges; (4) the acylation of **6** was done under Schotten−Baumann conditions which gives a much cleaner reaction; (5) *S,S*-reboxetine succinate was obtained directly via crystallization of the free base, eliminating the need for the intermediate formation of its mesylate salt (Scheme 1).

Results and Discussion

The synthesis starts with a Sharpless asymmetric epoxidation of cinnamyl alcohol, establishing the two chiral centers early in the process. Sharpless asymmetric epoxidation of cinnamyl alcohol is reported to give **3** with >98% enantiomeric excess and in 89% yield after product crystallization.[4,5] We found the enantiomeric excess of crude **3** to be about 92%. Intermediate **4** is upgraded to >98% ee by crystallization, eliminating the need to recrystallize the relatively low-melting (2*R*,3*R*)-phenylglycidol. **3** was obtained as a solution in methylene chloride which was reacted with 2-ethoxyphenol and sodium hydroxide under phase transfer conditions. The resulting **4** was extracted into MTBE, washed with sodium hydroxide solution to remove unreacted 2-ethoxyphenol and phenylglycerol, precipitated, and then recrystallized from MTBE/isooctane. Enantiomeric excess at this point was about 98%. Further enantiomeric upgrading occurred in the crystallizations of **6** and (*S,S*)-reboxetine succinate.

The catalyst load, reaction concentration, and the equivalents of TBHP in asymmetric epoxidation reaction were varied to find the optimal conditions for performing this transformation, and most observations were in agreement with the published data on this reaction.[4] The tolerable limits for water in the TBHP solutions were established by running reactions with TBHP solutions containing 0.2, 0.3, 0.4, and 0.5% of water. The reactions were run in MultiMax experiments, monitoring heat flow; all these reactions performed

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(5) All compounds in this process are single enantiomers and diastereomers as shown. Commercial cinnamyl alcohol is typically >99.5% *trans*.

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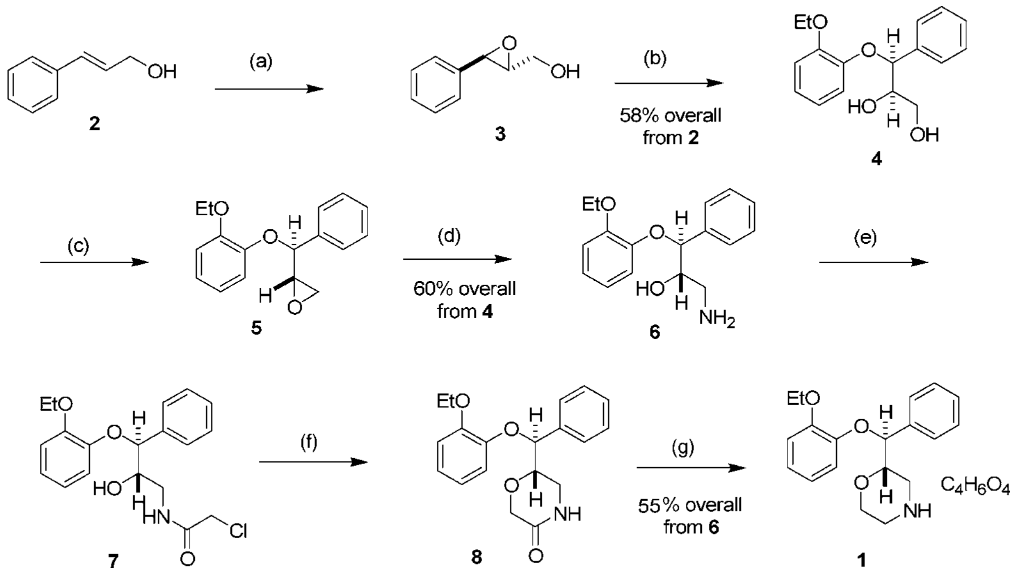
Scheme 1[a]



[a] Reagents and conditions: (a) L-DIPT, Ti(i-PrO)$_4$, TBHP, EtOAc. (b) 2-Ethoxyphenol, NaOH. (c) i. TMSCl, Et$_3$N; ii. MsCl, Rt$_3$ N; iii HCl, H$_2$O; iiii. NaOH. (d) CH$_3$OH. (e) ClCH$_2$COCl, Na$_2$CO$_3$. (f) t-AmONa. (g) i. Vitride; ii. C$_4$H$_6$O$_4$.

about the same as the reference reaction, containing no additional water in the TBHP.

These experiments demonstrate the importance of molecular sieves in the asymmetric epoxidation reaction since the calculated amount of water in the reaction solutions exceeds the equivalents of titanium isopropoxide used. For optimal reaction performance, 10 mol % titanium isopropoxide and 15 mol % of DIPT were used. Two equivalents of TBHP were needed for this reaction to go to 97% completion in 3 h. An unexpected result from these experiments was the observation of a significant induction period and exotherm at the outset of the TBHP addition. To maintain process control, a portion of the TBHP was added initially. The addition was stopped until the exotherm was observed, and the TBHP was then added slowly, maintaining the reaction temperature below −15 °C.

The quench to destroy the excess TBHP was critical. The standard TBHP quench with Fe^{II} sulfate was unsuitable for this application due to epoxide decomposition. Under these quench conditions, the mixture became acidic, leading to decomposition of the very acid-sensitive epoxide; the pH of the Fe^{II} sulfate solution by itself was initially about 3.5 and dropped to 1.5 after the quench.

A search for a new quenching reagent was done. The main difficulty in evaluating TBHP quenches is the fact that TBHP is not effectively detected by standard peroxide test strips. Iodometric titration, although effective at determining TBHP concentration, lacks adequate sensitivity at <100 ppm level. We found that 4-aminophenol is a very sensitive TBHP color indicator at ppm level; after reaction mixtures are resolved on TLC plates, it stains the TBHP spot pink.

A variety of reducing agents were examined. Aqueous sodium thiosulfate and sodium sulfite gave only a slight reduction of the TBHP concentration. Fe^{II} salts of weak organic acids were also considered: Fe^{II} oxalate was tried, but its poor solubility in water precludes its use. Conditions resembling the peroxide titration procedure were also tried. Aqueous solutions of NaI, NaCl, KBr, and NaBr with sodium thiosulfate were used, but even in the presence of carbon dioxide as a weak acid to enhance reduction of TBHP these condition gave negative results. TBHP was not effectively reduced by dimethyl sulfide, DMSO, or by diethylphosphite. In contrast, trimethylphosphite and triethylphosphite were found to be very effective at reducing TBHP, and both exothermically reduced TBHP even at −20 °C to the corresponding phosphates.

In situ reactions of Sharpless epoxidation products are well-known;[6] however, the procedures invariably involve a hydrolysis step to destroy the phosphates and phosphites before product isolation. We found that **4** crystallized from MTBE−isooctane without hydrolyzing the phosphate. Intermediate **4** is soluble in both trimethylphosphate and triethylphosphate. Since triethyl phosphate is miscible with isooctane while trimethylphosphate is immiscible, triethylphosphite was chosen as the TBHP quench reagent. Crude **4** was concentrated to oil still containing triethylphosphite, and isooctane or branched octanes were added to cause product crystallization. After a short stir period, **4** crystallized as an easily stirrable slurry. The solids were filtered and recrystallized from MTBE. This produced small, easily filtered white crystals of **4** in 48% yield from cinnamyl alcohol and with 98% ee. **4** could be further upgraded by recrystallization to >99% ee.

Because the physical properties of the (S,S)-enantiomer of **4** vary significantly from the racemic diol, modifications were made to the racemic reboxetine process. In the reaction leading to the formation of **5**, ethyl acetate was replaced with methylene chloride due to the low solubility of **4** in EtOAc. In the original process the crude free base of **6** was converted to its mesylate salt before it was crystallized, but in the (S,S) process **6** was crystallized from an EtOAc−heptane mixture as a free base, eliminating two chemical steps.

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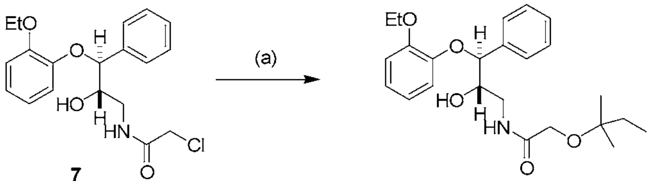
Scheme 2[a]



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[a] Regents and conditions: (a) *t*-AmONa.

Rationalization of the process for the conversion of **6** to reboxetine was examined. The process currently used was a relic of the original racemic process, which was not substantially changed when the process was redeveloped. It used two reactive solvents (dimethyl carbonate and IPA), had multiple solvent exchanges, proceeded in relatively low overall yield, and gave **7** that was darkly colored, requiring a carbon treatment for decolorization of the final product.

Changing the solvent for the acylation from dimethyl carbonate to methylene chloride improved the workability but still gave **7** that was highly colored with multiple impurities. The colored impurities presumably arise from the polymerization of chloroketene formed by reaction of chloroacetyl chloride and triethylamine. Acylation under Schotten−Baumann conditions (aqueous Na_2CO_3−toluene) gave a clean reaction and eliminated the formation of highly colored byproducts. The reaction started with a slurry of **6** and went to completion in essentially quantitative yield to give a colorless **7**.

Step **7** was run in the racemic process with *t*-BuOK in IPA. With purified **7**, reactions were done with *t*-BuOK in THF, KHMDS in toluene, and sodium *tert*-amylate in toluene. All of these reactions performed well. Since the **8** reduction was performed in toluene, sodium *tert*-amylate in toluene was selected for a further study. A temperature study showed that an impurity increases as the reaction temperature increases. This was isolated and shown to be the *tert*-amylate displacement product (Scheme 2). In practice, the **7** solution was dried by azeotropic distillation and taken directly into the cyclization step to produce **8**. After an aqueous workup, the toluene solution of **8** was used directly in the Vitride step.

No changes were made to the Vitride reduction (step **9**) except that the carbon treatment was omitted since the material was already colorless. Formation of the succinate salt was done after solvent exchange from toluene to IPA. Only one crystallization was required to obtain **1** of very high purity in 55% overall yield from **6**, and intermediate isolation of the methanesulfonate salt was found to be unnecessary.

Conclusion

An efficient enantioselective process for the synthesis of (*S*,*S*)-reboxetine was developed. The conditions for the key asymmetric epoxidation were optimized and defined. The processing for the remaining steps was simplified and streamlined to allow efficient processing. (*S*,*S*)-Reboxetine succinate was produced with high chemical and enantiomeric purity. The overall yield of (*S*,*S*)-reboxetine succinate by this process is about 19% from cinnamyl alcohol, compared to <10% overall yield via resolution. The asymmetric process described reduces solvent use and waste generation by approximately 50% compared to the resolution route to (*S*,*S*)-reboxetine, resulting in a greener process.

Experimental Section

Materials were obtained from commercial suppliers and used without purification. Melting points were run in open tube capillaries and are uncorrected. IPA refers to 2-propanol; MTBE refers to methyl-*tert*-butyl ether. NMR spectra were run on Varian INOVA operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Mass spectra were recorded on a Micromass Platform LC mass spectrometer.

(2*S*,3*R*)-3-(2-Ethoxyphenoxy)-2-hydroxy-3-phenyl-1-propanol (4). Cinnamyl alcohol (150 g, 1.12 mol), 60 g of activated 4Å molecular sieves, and methylene chloride (2.25 L) were charged to a 5 L, three-necked, jacketed flask equipped with a mechanical stirrer and a 500-mL addition funnel. D-DIPT (39 g, 0.17 mol) was added to the flask via syringe, and the mixture was cooled to −15 to −20 °C. When the temperature was below −15 °C, $Ti(OiPr)_4$ (33.2 mL, 0.11 mol) was added via a syringe. The mixture was stirred for 30 min, maintaining the reaction temp at −20 °C to −25 °C. TBHP solution[7] (500 mL, 4.47 M, 2.24 mol) in isooctane was added to the addition funnel. After about 20% of the TBHP solution had been added, an exothermic reaction was noted, and the addition was stopped. The solution exothermed to about −12 °C (from −20 °C), and then the temperature fell. After the temperature of the reaction mixture was again −20 °C, addition of the TBHP solution was resumed. Total time for addition of the TBHP solution was about 90 min. The reaction mixture was stirred for 3 h at about −20 °C. When the reaction was complete, $P(OEt)_3$ (210 mL, 1.23 mol) was added slowly, allowing the mixture to exotherm to +20 °C. The mixture was filtered through a Celite 545 cake. *The filtered solution of* ***3*** *was used immediately in the next step.*

Sodium hydroxide (49.2 g, 1.23 mol), tetrabutylammonium chloride (15.53 g, 0.056 mol), 2-ethoxyphenol (169.9 g, 1.23 mol), and 1080 mL of water were charged to a 5-L three-necked round-bottom flask. The solution of **3** from above was added, and the mixture was gradually heated to distill the methylene chloride. The distillation was continued until the internal temperature was 65 °C. Heating was continued for 3 h after completion of the methylene chloride removal.

The mixture was cooled to 30 °C, MTBE (1.5 L) was added, and the mixture was stirred for 30 min. The phases were separated, and the organic layer was washed with 1 M NaOH solution (2 × 1 L). The organic layer was washed with 1 L of water and with 1 L of brine. The solution was heated to reflux with an attached Dean−Stark trap and refluxed until the KF was <1%. The solution was distilled

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(7) **Caution:** A serious explosion occurred during engineering development of this process when TBHP was dried by azeotropic distillation using the published procedure.[4] The explosion is believed to have been caused by an inadvertent heating of a very concentrated TBHP solution. The use of commercial anhydrous TBHP solutions in hydrocarbons or material dried over molecular sieves is recommended.

until about 950 mL of distillate was collected. Isooctane (200 mL) was added, and the solution was cooled to about 20 °C. Once crystallization had initiated, 700 mL of isooctane was added in portions. The slurry was cooled to −20 °C. The solids were filtered and washed with 500 mL of isooctane. The solids were redissolved in 300 mL of MTBE with heating. The solution was cooled to rt. Isooctane (400 mL) was added in portions, the slurry was cooled to −15 °C, and the solids were filtered, washed with 300 mL of isooctane, and dried with rt nitrogen. Yield of **4**: 187.3 g, (58%) mp 93.5−95.1 °C (lit. mp 87−89 °C).[3] ^{1}H NMR (399.76 MHz, $CDCl_3$) δ 0.09 (s, 9H), 1.48 (t, $J = 7.0$ Hz, 3H), 3.23−3.26 (m, 1H), 3.63−3.70 (m, 1H), 3.86−3.98 (m, 2H), 4.1 (q, $J = 7.0$ Hz, 2H), 5.25 (d, $J = 4.1$ Hz, 2H), 6.61−6.4 (m, 1H), 6.68−6.74 (m, 1H), 6.86−6.92 (m, 2H), 7.27.7.42 (m, 5H). ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 15.0. 62.4, 64.4, 74.6, 86.3, 112.8, 116.5, 121.0, 122.59, 126.66, 128.3, 128.9, 138.19, 147.3, 149.3. LRMS-APCI *m/z* calcd for $C_{17}H_{21}O_4$ $(M + H)^+$: 289. Found: $m/z = 289$ $[M + 1]^+$. Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.68; H, 7.02. $[\alpha]^{32.8}_{D}$ +18.98° (*c* 0.5, EtOH); (lit $[\alpha]^{20}_{D}$ +7.8° (*c* 1, EtOH)).[3] Chiral HPLC: Chiracel OD-H; 90:10 hexanes−IPA; 1 mL/min; 215 nm; *2R,3S* 5.9 min; 2*S*,3*R* 5.3 min.

(2*S*,3*S*)-3-Amino-1-(2-ethoxy-phenoxy)-1-phenylpropan-2-ol (6). Intermediate **4** (40.0 g, 0.138 mol), triethylamine (17.0 g, 0.168 mol, 23.4 mL), and 400 mL of methylene chloride were charged to a 1-L, three-necked Morton flask. The solution was cooled to about −20 °C. Chlorotrimethylsilane (16.0 g, 0.147 mol) was dissolved in 28 mL of methylene chloride, and this solution was added to the **4** solution, keeping the internal temperature below −15 °C. After the addition was complete, the mixture was stirred for 15 min when the temperature reached less than −15 °C.

Methanesulfonyl chloride (19.5 g, 0.17 mol, 13.2 mL) was added to the solution, keeping the temperature between −20 and −15 °C. Triethylamine (14.1 g, 0.14 mol, 19.5 mL) was, added keeping the temperature below −15 °C. The mixture was stirred for 15 min after completion of triethylamine addition. HCl (141 mL, 1 M) was added to the mixture, which was allowed to warm to rt and was stirred until the hydrolysis was complete (about 3 h). The phases were separated, and the organic phase was washed with 131 mL of 5% (w/v) solution of sodium bicarbonate.

Sodium hydroxide (25 g, 0.62 mol), 1.92 g of tetrabutylammonium chloride, and 100 mL of water were charged to a 1-L, three-necked Morton flask. The methylene chloride solution was added, and the mixture was stirred at rt. When reaction was complete, the phases were separated, and the aqueous phase was extracted with 100 mL of methylene chloride. The combined organic phases were washed with 76 mL of brine. The organic phase was concentrated to an oil. Methanol (300 mL) was added, and the solution was again concentrated to an oil.

The oil (**5**), methanol (280 mL), and concd ammonium hydroxide (450 mL, 6.75 mol) were charged to a 1-L, one-neck Ace pressure flask equipped with a magnetic stirrer. The flask was sealed and heated to 40 °C for 3 h. The mixture was cooled, and 340 mL of methylene chloride was added. The aqueous phase was extracted with methylene chloride (2 × 150 mL). The organic phases were combined and distilled atmospherically to a final volume of 450 mL. Methylene chloride (250 mL) was added, and the organic phase was washed with 375 mL of water. HCl (375 mL, 0.5 M) was added. The phases were separated, and the aqueous phase was washed with 70 mL of methylene chloride. The pH of the aqueous was adjusted to greater than 12 with 50% aqueous NaOH. The mixture was extracted with methylene chloride (2 × 100 mL). The organic solution was distilled to an oil, and then 116 mL of EtOAc followed by 116 mL of heptane was added to the flask. The mixture was heated to dissolve the material and then cooled to rt to crystallize. Heptane (116 mL) was added and the slurry cooled to −15 °C. The solids were filtered and dried with rt nitrogen to yield 23.8 g, 60% overall from **4**; mp 98.8−100.5 °C (lit. mp 97−99 °C).[3] ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.49 (t, $J = 7.0$ Hz, 3H), 2.56 (dd, $J = 13.0$, 6.4 Hz, 1H), 2.66 (dd, $J = 13.0$, 3.5 Hz, 1H), 3.94 (m, 1H), 4.1 (t, $J = 7.0$ Hz, 2H), 4.75 (d, $J = 8$ Hz, 1H), 4.58 (d, $J = 8.2$ Hz, 1H), 6.60−6.93 (m, 4H), 7.31−7.39 (m, 5H); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 15.07, 43.42, 64.48, 76.92, 87.94, 113.17, 119.82, 121.07,123.53,127.50,128.55, 128.82, 138.98, 148.34, 150.27. LRMS-APCI *m/z* calcd for $C_{17}H_{21}NO_3$ $(M + H)^+$: 364. Found: $m/z = 364$ $[M + 1]^+$. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.94; H, 7.48; N, 4.80. $[\alpha]^{32.4}_{D}$ +41.0° (*c* 0.5 EtOH); (lit. $[\alpha]^{20}_{D}$ +34.4° (*c* 1, EtOH)).[3]

(2*S*,3*S*)-Reboxetine Succinate (9). Intermediate **6** (20.0 g, 0.069 mol) was slurried in 200 mL of toluene. A solution of sodium carbonate (14.7 g, 0.139 mol) in 74 mL of water was added, and the mixture was cooled to 5 °C. Chloroacetyl chloride (13.36 g, 0.118 mol, 9.4 mL) was dissolved in 66 mL of toluene, and this solution was added to the slurry over 1 h. The mixture was stirred at about 5 °C. When the reaction was complete, 200 mL of water was added, and the mixture was heated to 50 ° C. The phases were separated, and the organic phase was washed with water (200 mL) and brine (200 mL). The solution was distilled under vacuum until the KF was LT 0.20%. The total volume was adjusted to 150 mL with toluene.

Sodium *tert*-amylate (14.97 g, 0.135 mol) was dissolved in 247 mL of toluene and the solution cooled to −5 °C. The toluene solution of **7** was added, maintaining the temperature of the reaction at NMT −5 °C. When the reaction was complete, 309 mL of water was added and the mixture stirred 10 min. The phases were separated, and the organic phase washed with water (2 × 309 mL). The solution was dried by distillation. Toluene was added back during the distillation to maintain a volume of about 120 mL.

Vitride (65 wt %, 102 mL, 0.339 mol) was diluted with 100 mL of toluene and the solution cooled to −10 °C. The solution of **8** was added at a constant rate to the Vitride solution, keeping the temperature of the reaction mixture between 0 to +10 °C. When complete, the reaction was quenched with 22 mL of 50% NaOH in 184 mL of water. The mixture was allowed to exotherm to 45−55 °C. The phases were separated, and the organic phase was washed with 5% (w/v) Na_2CO_3 solution (3 × 274 mL). Water (335 mL) was added to the toluene solution, and 8% HCl was added to give a pH of 3. The phases were separated, and the aqueous phase was adjusted to pH 10−12 with 10% NaOH. Toluene (408 mL) was added, and the phases were separated. The organic phase was washed with 5% Na_2CO_3 solution (3 × 100 mL) and then with water (100 mL). The organic phase was concentrated to an oil (**9**) under vacuum at 65 °C bath temperature.

Intermediate **9** was dissolved in 474.6 mL of IPA. Succinic acid (9.9 g, 0.083 mol) was added to the solution, and the mixture was heated to about 75 °C and stirred until the solids dissolved. The solution was cooled to rt and stirred for 2 h. The solids were filtered, washed with 88.3 mL of IPA, and dried with rt nitrogen. Yield: 16.4g, 54.6%; mp 145.2−147.1 °C (lit. mp 148 °C).[8] ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.41 (t, $J = 7.0$ Hz, 3H), 2.4 (s, 4H), 2.9−3.06 (m, 2H), 3.15−3.22 (m, 2H), 3.81−3.86 (m, 1H), 4.02−4.09 (m, 3H), 4.17−4.24 (m, 1H), 5.13 (d, $J = 4.3$ Hz), 6.66−6.90 (m, 4H), 7.26−7.39 (m, 5H). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 15.08, 31.89, 43.24, 44.84, 64.72, 76.91, 82.91, 113.94, 118.27, 121.1, 127.38, 128.66, 136.94, 149.8, 178.73. LRMS-APCI m/z calcd for $C_{19}H_{23}NO_3$ $(M + H)^+$: 314. Found: $m/z = 314$ $[M + 1]^+$. Anal. Calcd for $C_{19}H_{23}NO_3{-}C_4H_6O_4$: C, 64.02; H, 6.77; N, 3.25. Found: C, 63.99; H, 6.77; N, 3.16. $[\alpha]^{32.4}_D$ +17.24° (c 0.5, EtOH).

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