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Syntheses of a Selective Peroxisome Proliferator Activated Receptor Modulator and Practical New Preparations of 2-(4-Alkoxyphenyl)ethylamines†

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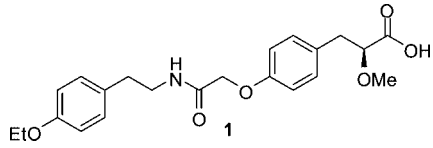
Abstract:

This article describes chemistry that was developed to give access to multigram quantities of the selective peroxisome proliferator activated receptor modulator (SPPARM), compound 1.[1] Fischer esterifications, phase transfer-catalyzed alkylations, amide couplings, crystallizations, and a new synthesis were developed to accomplish this task. In addition, an efficient method for preparing 2-(4-alkoxyphenyl)ethylamines 7a−d from tyramine 9 was developed that involves O-alkylation of intermediate Schiff base 11 and subsequent acid-catalyzed hydrolysis to afford the target molecules as crystalline hydrochloride salts.

Introduction

The selective peroxisome proliferator activated receptor modulator (SPPARM), compound **1**, was being developed at Lilly as an orally active compound for the treatment of type 2 diabetes with associated cardiovascular disease.[1] The goal for this SPPARM program was to develop a compound with an improved clinical profile compared to PPAR agonists currently on the market.



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Results and Discussion

The medicinal chemistry group at Lilly employed the synthesis depicted in Scheme 1 in order to make multigram quantities of compound **1** for biological evaluation. This synthesis had undesirable solvents, reagents, and chromatographic purifications, lacked a final crystallization to efficiently control the purity of compound **1**, and gave an overall yield of about 47% from the available carboxylate **2**.[1,2]

Due to the interesting biological properties of compound **1**, Lilly scientists required 300 g of this material, and the potential need for kilogram quantities was apparent. To fund a rapid 300 g delivery of compound **1**, modifications to the Scheme 1 chemistry were identified and made (Scheme 2): (1) The highly toxic MeI alkylation to prepare ester **3** was replaced with an acid-catalyzed Fischer esterification employing methanesulfonic acid (MSA) in MeOH. (2) To improve the productivity of the alkylation of the phenol moiety of **3** with alkyl bromide **4** and obviate the need for chromatography, the cesium carbonate was replaced with potassium carbonate, and a phase transfer catalyst (TBAI; tetrabutylammonium iodide) was added to greatly improve the yield of diester **5**. (3) To remove the undesirable chlorinated solvent from the ionization step in the conversion of *tert*-butyl ester **5** into carboxylic acid **6**, the dichloromethane was replaced with toluene. (4) To improve the productivity of the amide coupling of **6** to give **8**, remove the chlorinated solvent, and simplify the coupling agents and resultant byproducts, the imidazolide of **6** was generated with 1,1′-carbonyldiimidazole (CDI) in EtOAc, and 2-(4-ethoxyphenyl)ethylamine **7b**[3] introduced to the reaction mixture to give high yields of amide **8** with low levels of byproducts. The LiOH wet THF reaction conditions for the hydrolysis of ester **8** to give acid **1**, from the Scheme 1 synthesis, gave a high yield and did not epimerize the stereocenter, so there was no further development of this reaction for the Scheme 2 preparation. (5) Last, compound **1** had previously been isolated as an amorphous solid, so crystallization conditions from IPA were identified and developed to ensure control of the purity and potency of the active pharmaceutical ingredient (API). These process improve-

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† This paper is dedicated to the memory of our friend and former colleague Dr. Christopher R. Schmid.

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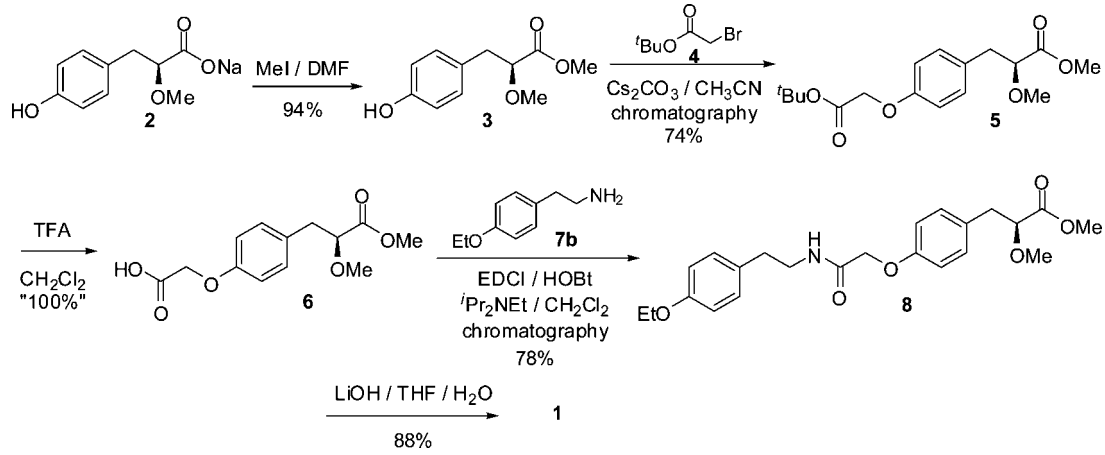
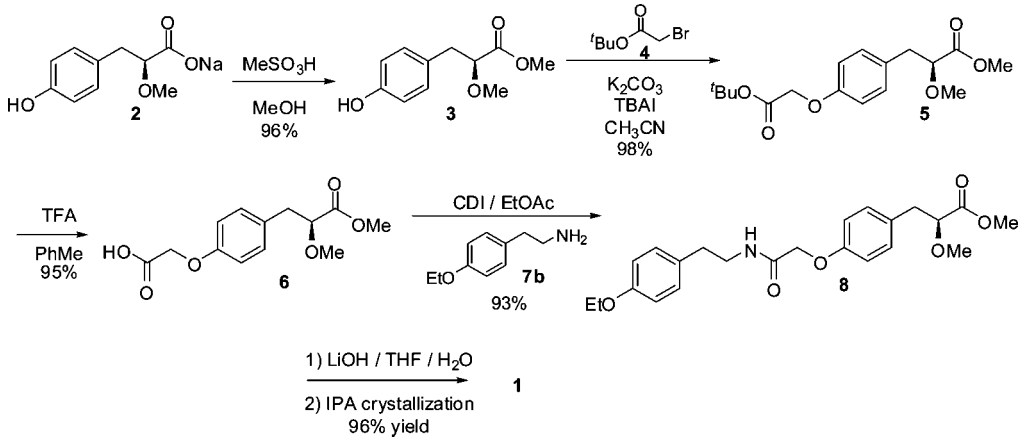
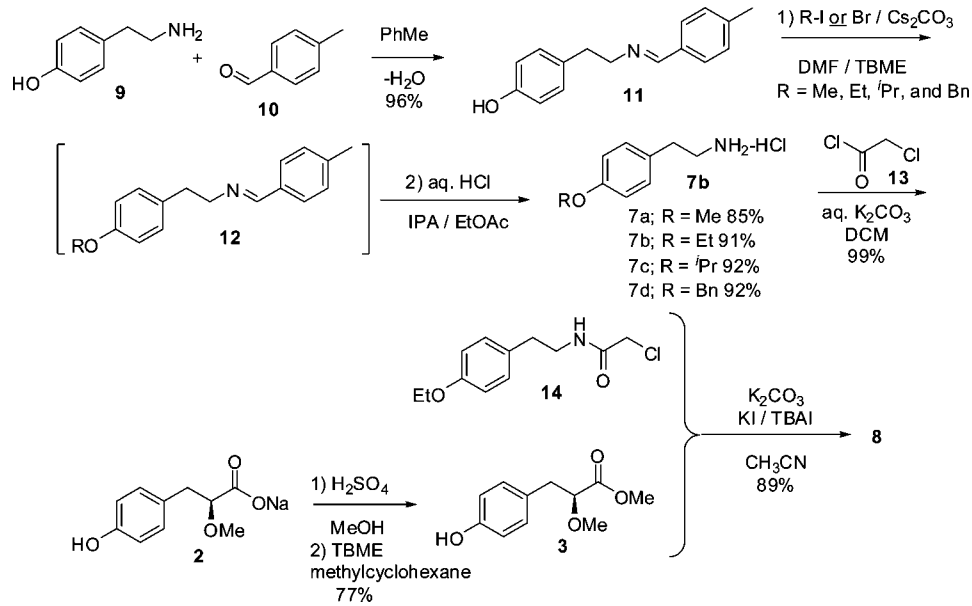
Scheme 1



Scheme 2



Scheme 3



ments gave an overall yield of 72%, removed the need for chromatography, and gave high-quality crystalline API, compound **1**.

In order to develop a process suitable for preparing kilogram quantities of compound **1** and meet the cost and efficiency objectives of a potential manufacturing process, the Scheme 3 synthesis was devised. During the course of investigating the Scheme 3 chemistry, the multigram (>100 g) supply of 2-(4-ethoxyphenyl)ethylamine **7b** ran out. Over the last century, there have been numerous accounts of a variety of syntheses of 2-(4-alkoxyphenyl)ethylamines.[4] After review and evaluation of the literature precedents for preparing 2-(4-alkoxyphenyl)ethyl-

amines, it was found that the new method of preparation illustrated in Scheme 3 was the most direct and practical. The synthesis of **7b** began by condensing tyramine **9**[5] with *p*-tolualdehyde **10** in refluxing toluene while removing water via distillation. After slowly cooling the reaction mixture, the resulting Schiff base **11** was isolated as a crystalline solid in 96% yield. The Schiff base **11** was subsequently dissolved in a 1 to 1 mixture of DMF and *tert*-butylmethyl ether (TBME) and reacted with cesium carbonate and ethyl iodide at 50 °C to form the corresponding Schiff base ethyl ether **12**. After an aqueous workup, **12** was dissolved in a mixture of IPA and EtOAc and treated with aqueous HCl to precipitate **7b** as a hydrochloride salt in 91% yield. This technique of preparing tyramine ether **7b** was applied to the preparation of methyl ether **7a** (85% yield), isopropyl ether **7c** (92% yield), and benzyl ether **7d** (92% yield) with good to excellent yields (Scheme 3).

The 2-(4-ethoxyphenyl)ethylamine **7b** was reacted in a Schotten−Baumann amide coupling with chloroacetyl chloride **13** in a dichloromethane lower phase and an aqueous K_2CO_3 upper phase to afford a 99% yield of amide **14** (Dichloromethane solvent was used for the preparation of amide **14** to avoid uncontrolled precipitation of the product.). In Scheme 3, the ester **3** was prepared as before via acid catalysis in MeOH with the switch made from methanesulfonic acid to the less expensive sulfuric acid. In addition, a crystallization of ester **3** from TBME and methylcyclohexane was utilized to afford a 77% yield. The amide **14** was reacted with ester **3** under phase transfer conditions in CH_3CN in the presence of K_2CO_3, KI, and TBAI to give ether adduct **8** in 89% yield after crystallization from IPA/water. The hydrolysis of ester **8** and final crystallization from IPA to afford **1** were not changed from the Scheme 2 synthesis. In the Scheme 3 chemistry, the expensive chiral carboxylate **2** underwent two transformations instead of the previous four (Schemes 1 and 2) to arrive at the ester **8**, which is an ester hydrolysis removed from the API, compound **1**.

Conclusion

In short, an efficient and "scalable" synthesis of the SP-PARM compound **1** was achieved. This involved developing Fischer esterifications, phase transfer-catalyzed alkylations, amide couplings, crystallizations, and the design and demonstration of a new synthesis. In addition, new efficient methods for preparing 2-(4-alkoxyphenyl)ethylamines were developed in order to accomplish this task.

Experimental Section

HPLC Methods. Column: Chromolith Performance RP-18 4.6 mm × 100 mm. Flow: 5 mL/min. Wavelength: 230 nm.

Solvent A: 0.05% trifluoroacetic acid in acetonitrile. Solvent B: 0.1% trifluoroacetic acid in water.

Gradient

time (min)	A%	B%
0	10	90
1	10	90
7	90	10
8	90	10
9	10	90
10	10	90

Retention times

compd	time (min)
1	3.6−3.8
2	1.0−1.1
3	2.2−2.3
7b	0.7−0.9
8	4.2−4.3
14	3.3−3.5

Chiral HPLC method (used for chiral separation of **1**). Column: Chiralpak AD, 0.46 cm × 25 cm. Flow: 1.0 mL/min. Wavelength: 270 nm. Eluent: heptane/isopropanol/trifluoroacetic acid, 80/20/0.1

Retention time

cmpd	time (min)
1	9.5−9.7

Experimental Procedures. *(S)-Methyl 3-(4-hydroxyphenyl)-2-methoxypropanoate (3).* Fischer esterification was done with sulfuric acid. Under a nitrogen atmosphere, carboxylate **2** (750.0 g, 3.44 mol, 99.9% ee) and MeOH (4050 mL) were combined at 23 °C, and sulfuric acid (269.7 g, 2.75 mol) was slowly added to the resulting mixture (an exotherm from 22 to 36 °C occurred during this addition). The reaction was heated to 40 °C, and held for 3 h. Analysis by HPLC indicated that 2.9% of **2** remained. The reaction mixture was cooled to 23 °C and slowly quenched into saturated sodium bicarbonate solution (4000 mL) while monitoring the pH to ensure basicity was maintained (the final pH was 7.8). TBME (4050 mL) and water (4000 mL) were added to the mixture and the layers separated. The resulting aqueous layer was extracted again with TBME (4000 mL). The TBME layers were combined and washed with saturated sodium chloride solution (4000 mL), followed by water (4000 mL). The organic phase was concentrated under vacuum at 32 °C to remove ∼2500 mL of distillate. Methylcyclohexane (3.5 L) was then added to the organic mixture at a rate comparable to the rate of distillate removal. With a final solvent ratio of methylcyclohexane (3500 mL) to TBME (1950 mL), the product had separated as an oil. Seed crystals were

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added at 43 °C, which caused nucleation to occur, and the resulting mixture was slowly cooled to 23 °C. The colorless crystalline product was collected by filtration, washed with methylcyclohexane (500 mL), and vaccuum-dried at 30 °C over 6 h to a constant weight. The product **3** was afforded in 77.3% yield (558.6 g). HPLC assay of the product **3** indicated 99.8 area %, and 100.0% ee. Mp 85.5−86.1 °C; $[\alpha]^{22.3}_{D}$ −13.6 (*c* = 5.0 MeOH); IR (KBr pellet) 3329, 3023, 3001, 2955, 2926, 2837, 1740, 1614, 1519, and 1517 cm^{-1}. ^1H NMR (DMSO-d_6, 400.0 MHz) δ 2.74−2.78 (2H, m) 3.18 (3H, s), 3.57 (3H, s), 3.92 (1H, dd, *J* = 5.7, 7.5 Hz), 6.60 (2H, d, *J* = 8.4 Hz), 6.92 (2H, d, *J* = 8.4 Hz), 9.15 (1H, s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 37.9, 51.9, 57.8, 81.4, 115.4, 127.2, 130.6, 156.4, 172.4. HRMS (AP+; accurate mass) calcd for $C_{11}H_{15}O_4$ 211.0963, found 211.0965. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 63.08; H, 6.75.

4-(2-(4-Methylbenzylideneamino)ethyl)phenol (11). Under a nitrogen atmosphere, tyramine **9** (470.0 g, 3.426 mol) and toluene (7.0 L) were combined, and the resulting slurry was heated to 82 °C. *p*-Tolualdehyde **10** (444.6 g, 3.700 mol) was added over 53 min. to the reaction mixture with continued heating to reflux. Over an additional 40 min., the temperature of the reaction mixture increased to 111 °C, while toluene and water were removed by atmospheric distillation. A total of 1570 mL of distillate was collected. The amount of water collected was 60 mL (Theory = 61.7 mL). The reaction mixture was cooled to 33 °C over 4.25 h, and an ice bath was used to further cool the slurry to 0−5 °C. After stirring at 0−5 °C for 1 h, the mixture was filtered, a toluene (1.5 L, 5 °C) wash was utilized, and drying was achieved under vacuum at 50 °C to afford **11** (789.0 g, 96.2% yield, GC assay 99.6 area %) as a white crystalline solid. Mp 178.4−180.5 °C; IR (KBr pellet) 3436, 2920, 2887, 2853, 1648, 1609, and 1514 cm^{-1}. ^1H NMR (DMSO-d_6, 400.0 MHz) δ 2.29 (3H, s), 2.74 (2H, t, *J* = 7.5 Hz), 3.67 (2H, t, *J* = 7.5 Hz), 6.61 (2H, d, *J* = 4.4 Hz), 6.98 (2H, d, *J* = 4.4 Hz), 7.19 (2H, d, *J* = 7.4 Hz), 7.55 (2H, d, *J* = 7.4 Hz), 8.45 (1H, s), 9.09 (1H, bs). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.5, 36.6, 63.0, 115.4, 128.2, 129.7, 130.1, 130.4, 134.0, 140.7, 155.9, 161.1. HRMS (AP+; accurate mass) calcd for $C_{16}H_{18}NO$ 240.1381, found 240.1383. Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.43; H, 7.25; N, 5.98.

2-(4-Ethoxyphenyl)ethanamine Hydrochloride (7b). Under a nitrogen atmosphere, **11** (100.0 g, 0.42 mol), cesium carbonate (204.2 g, 0.63 mol), DMF (350 mL), and TBME (350 mL) were combined. The resulting mixture was warmed to 40 °C, and iodoethane (69.8 g, 0.45 mol) was added over 15 min. The temperature was increased to 50−53 °C, and after 4 h, the reaction was determined to be complete by ^1H NMR. After cooling the reaction mixture to 20−30 °C, purified water (450 mL) was added slowly, keeping the temperature below 30 °C. TBME (225 mL) was added to the reaction mixture, and the layers were separated. The organic layer was washed with purified water (100 mL) and concentrated *in vacuo* to about one-third of its original volume. IPA (500 mL) was added to the mixture, followed by concentration *in vacuo* until 500 mL of distillate was collected. IPA (800 mL) was added to the mixture, followed again by concentration to a final volume of 500 mL. After cooling the mixture to 25 °C, a thick slurry formed, and 37% aqueous hydrochloric acid (40.96 g) and EtOAc (100 mL) were added. After 4 h, the reaction mixture was cooled to 0−5 °C, stirred at that temperature for 1 h, and filtered. The isolated solid was washed with cold IPA (500 mL) and TBME (300 mL) and then vaccuum dried at 40 °C to afford **7b** as a white crystalline solid (77.36 g, 91.8% yield). Mp 203.3−204.1 °C; IR (KBr pellet) 3447, 2979, 2937, 2890, 2781, 2723, 2050, 1609, 1581, and 1514 cm^{-1}. ^1H NMR (DMSO-d_6, 400.0 MHz) δ 1.26 (3H, t, *J* = 7.1 Hz), 2.76−2.80 (2H, m), 2.89−2.94 (2H, m), 3.95 (2H, q, *J* = 7.1 Hz), 6.82 (2H, d, *J* = 4.4 Hz), 7.11 (2H, d, *J* = 4.4 Hz), 8.10 (3H, bs). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 15.1, 32.5, 63.4, 114.9, 129.6, 130.1, 157.7. HRMS (AP+; accurate mass) calcd for $C_{10}H_{16}NO$ 166.1226, found 166.1226. Anal. Calcd for $C_{10}H_{15}NO$: C, 59.55; H, 8.00; N, 6.94. Found: C, 59.52; H, 7.81; N, 7.01.

2-Chloro-N-(4-ethoxyphenethyl)acetamide (14). Under a nitrogen atmosphere, 2-(4-ethoxyphenyl)ethanamine hydrochloride **7b** (275.0 g, 1.36 mol), potassium carbonate (305.3 g, 2.21 mol), DCM (1650 mL), and water (825 mL) were combined. The resulting mixture was cooled to about 5 °C, and a solution of choroacetyl chloride **13** (188.6 g, 1.64 mol) in DCM (290 mL) was slowly added to the reaction. During the addition, the temperature increased due to the exothermic nature of the reaction. When the reaction temperature exceeded 10 °C, gas evolution was observed, so that the addition rate was adjusted to maintain controllable off-gassing, which encompassed a total of 71 min. with a peak temperature of 12 °C. The clear, biphasic mixture was allowed to stir for nearly 2.5 h, and the temperature increased to 18 °C (HPLC analyses indicated no starting **7b** in the aqueous layer and 99.1 area % **14** in the organic layer). Water (100 mL) and DCM (250 mL) were used to aid the transfer of the reaction for phase separation. The organic layer was washed with water (1000 mL) and concentrated under vacuum at 40 °C. DCM (1000 mL) was added to the mixture for a subsequent concentration at 40 °C to azeotropically remove residual water. The amide **14** was isolated in 99.9% yield (329.1 g) with a purity of 99.1 area % by HPLC. Mp 97.9−99.0 °C; IR (KBr pellet) 3438, 3258, 3083, 2987, 2976, 2933, 2886, 2859, 1683, 1650, 1564, and 1513 cm^{-1}. ^1H NMR (DMSO-d_6, 400.0 MHz) δ 1.26 (3H, t, *J* = 7.1 Hz), 2.62 (2H, t, *J* = 7.3 Hz), 3.23 (2H, dt, *J* = 7.3, 5.7 Hz), 3.93 (2H, q, *J* = 7.1 Hz), 3.98 (2H, s), 6.79 (2H, d, *J* = 4.4 Hz), 7.10 (2H, d, *J* = 4.4 Hz), 8.21 (1H, t, *J* = 5.7 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 15.1, 34.4, 41.2, 43.1, 63.3, 114.7, 130.0, 131.3, 157.4, 166.2. HRMS (AP+; accurate mass) calcd for $C_{12}H_{17}NO_2$ 242.0941, found 242.0942. Anal. Calcd for $C_{12}H_{16}ClNO$: C, 59.63; H, 6.67; N, 5.79. Found: C, 59.61; H, 6.68; N, 5.90.

(S)-Methyl 2-Ethoxy-3-(4-(2-(4-ethoxyphenethylamino)-2-oxoethoxy)phenyl)propanoate (8). Under a nitrogen atmosphere, **14** (250.0 g, 1.03 mol), **3** (217.0 g, 1.03 mol), potassium carbonate 325 mesh (290.0 g, 2.10 mol), potassium iodide (86.0 g, 0.52 mol), tetrabutylammonium iodide (58.0 g, 0.16 mol), and CH_3CN (625 mL) were combined. The resulting mixture was heated to 55−60 °C for 24 h, and allowed to cool to 23 °C (HPLC analysis indicated 95.1 area % **8**, 1.6 area % **3**, and 1.0 area % **1**). The mixture was cooled to 10−15 °C, and 2 N

HCl (620 mL) added, while maintaining the temperature below 25 °C. EtOAc (1000 mL) was added, and a final pH adjustment to 7.2 with 2 N HCl (620 mL) was made. The layers were separated, and the aqueous layer was extracted with EtOAc (250 mL). The organic layers were combined and concentrated under vacuum at 45−50 °C to a weight of 525.5 g. EtOAc (625 mL) was added, followed by a second concentration to eliminate residual CH_3CN. The remaining residue was dissolved in EtOAc (2000 mL) and water (1250 mL) added. The layers were separated, and the organic layer was washed with water (1250 mL). The resulting organic layer was concentrated under vacuum at 45−50 °C to 497.8 g, which was then dissolved in IPA (625 mL) and concentrated again to displace residual EtOAc. The resulting residue was dissolved in IPA (1250 mL) and water (500 mL), and the mixture was seeded with **8** at 23 °C. Nucleation occurred, and additional water (750 mL) was added over 1 h, and the slurry stirred for another 3 h. After cooling to 0−5 °C and stirring for 2 h, the product **8** was collected by filtration. Three washes were applied to the filter cake (2 × 305 mL of 2:1 water/IPA and 1 × 610 mL water; all precooled to 0−10 °C). Vacuum drying at 45−50 °C to a constant weight resulted in an isolated yield for **8** of 386.4 g (89.9% yield) as a white crystalline solid. The HPLC purity of compound **8** was 99.7 area %. Mp 67.8−68.0 °C; $[\alpha]^{22.3}_D$ −7.60 (c = 5.0 MeOH); IR (KBr pellet) 3424, 3347, 3077, 3038, 2973, 2955, 2918, 2873, 1755, 1656, 1543, and 1513 cm^{-1}. ^1H NMR (DMSO-d_6, 400.0 MHz) δ 1.26 (3H, t, J = 7.1 Hz), 2.63 (2H, t, J = 7.3 Hz), 2.77−2.88 (2H, m), 3.18 (3H, s), 3.24−3.29 (2H, m), 3.58 (3H, s), 3.94 (2H, q, J = 7.1 Hz), 3.95−3.99 (1H, m), 4.36 (2H, s), 6.78 (4H, d, J = 6.6 Hz), 7.04 (2H, d, J = 8.8 Hz), 7.06 (2H, d, J = 8.8 Hz), 8.02 (1H, t, J = 5.7 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 15.1, 34.7, 37.8, 51.9, 57.8, 63.3, 67.4, 81.2, 114.7, 114.8, 129.9, 130.0, 130.6, 131.4, 156.8, 157.4, 168.0, 172.3. HRMS (AP+; accurate mass) calcd for $C_{23}H_{30}NO_6$ 416.2071, found 416.2068. Anal. Calcd for $C_{23}H_{29}NO_6$: C, 66.49; H, 7.03; N, 3.37. Found: C, 66.62; H, 7.03; N, 3.49.

(S)-3-(4-(2-(4-ethoxyphenethylamino)-2-oxoethoxy)phenyl)-2-methoxypropanoic Acid (1). Under a nitrogen atmosphere, **8** (1.0 kg, 2.41 mol), THF (8.0 L), and water (5.0 L) were combined, and an aqueous solution of lithium hydroxide (63.4 g, 2.65 mol in 3.0 L of water) was charged to the reaction mixture at 15−25 °C over 19 min. After 1 h, HPLC indicated 0.6% **8**. TBME (8.0 L) was added to the reaction mixture and the organic phase was separated. The resulting aqueous layer was washed two more times with TBME (2 × 4.0 L). The pH of the mixture was lowered to 6.4 by the addition of 5 N HCl (50 mL), while maintaining the temperature between 15−25 °C. EtOAc (8.0 L) was added to the mixture and the pH reduced to 2.1 with 5 N HCl (532 mL). The aqueous layer was separated and extracted with EtOAc (8.0 L). The combined organic layers were washed with water (2 × 2.0 L) and concentrated under vacuum at 35−40 °C. IPA (2.0 L) was added to the mixture, the temperature increased to 45−50 °C, and the reduced pressure concentration continued to give **1** as a crude solid. The crude solid **1** was suspended in IPA (3.5 L), and the resulting slurry heated to give a solution at 69 °C. The resulting mixture was cooled to 57−58 °C, seeded, and slowly cooled to 0−5 °C. After stirring for 1−2 h at 0−5 °C, the resulting slurry was filtered and washed with cold IPA (600 mL, 0−5 °C). The acid **1** was produced as a white crystalline solid that was dried under vacuum at 40−45 °C to a constant weight of 930.6 g (96% yield). HPLC: 99.8 area %; 99.8 wt %; ee > 99.9%. Mp 126.6−127.2 °C. $[\alpha]^{22.3}_D$ −13.21 (c = 5.0 MeOH); IR (KBr pellet) 3389, 3368, 3065, 3023, 2972, 2929, 2871, 2820, 1733, 1631, 1553, and 1511 cm^{-1}. ^1H NMR (DMSO-d_6, 400.0 MHz) δ 1.26 (3H, t, J = 7.1 Hz), 2.63 (2H, t, J = 7.5 Hz), 2.77 (1H, dd, J = 7.9, 14.1 Hz), 2.87 (1H, dd, J = 4.9, 14.1 Hz), 3.18 (3H, s), 3.25−3.30 (2H, m), 3.84 (1H, dd, J = 4.9, 7.9 Hz), 3.94 (2H, q, J = 7.1 Hz), 4.37 (2H, s), 6.78 (4H, d, J = 6.2 Hz), 7.04 (2H, d, J = 8.8 Hz), 7.09 (2H, d, J = 8.8 Hz), 8.02 (1H, t, J = 5.7 Hz), 12.66 (1H, s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 15.1, 34.7, 37.8, 57.7, 63.3, 67.4, 81.2, 114.7, 114.8, 130.0, 130.5, 130.6, 131.4, 156.8, 157.4, 168.0, 173.4. HRMS (AP+; accurate mass) calcd for $C_{22}H_{28}NO_6$ 402.1918, found 402.1911. Anal. Calcd for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.76; N, 3.49. Found: C, 65.90; H, 6.76; N, 3.63.

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Supporting Information Available

Experimental procedures and spectral data for compounds **3** (prepared with methanesulfonic acid in MeOH), **5**, **6**, **8** (prepared via CDI coupling of **6** and **7b**), **7a**, **7c**, and **7d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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