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Development of an Enantioselective Hydrogenation Based Synthesis of a Glucokinase Activator

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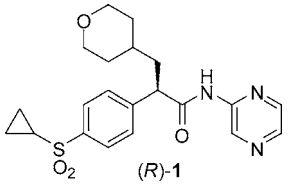
Supporting Information

ABSTRACT: This article describes the development and optimization of chemical reactions and subsequent multikilogram preparation of the glucokinase activator (*R*)-**1** to fund clinical evaluation as a potential therapeutic for type II diabetes. The major process developments presented here are a Wittig olefination isomerization based synthesis of an *E*-acrylic acid, an optimized enantioselective hydrogenation of the *E*-acrylic acid, and a challenging final amide coupling.

INTRODUCTION

The glucokinase activator (GKA) (R)-1 was developed as a potential therapeutic for the treatment of type 2 diabetes. Type



(*R*)-**1**

2 diabetes, a disease characterized by elevated blood glucose concentrations, i.e., hyperglycemia, is becoming ever more prevalent as a result of the recent dramatic rise in obesity levels.[1a] The glucose-phosphorylating enzyme glucokinase (GK) represents an attractive target for type 2 diabetes therapies[1b] because it plays a critical role in whole-body glucose control through its actions in multiple organs.[1c−f] In particular, in the cells of the pancreas, GK acts as the glucose sensor that determines the threshold for insulin secretion, while, in the liver, this enzyme is rate-determining for glucose metabolism. These GK activators have been shown to engender potent antihyperglycemic actions in rodents, both by increasing pancreatic insulin secretion and by augmenting hepatic glucose metabolism.[1g,h] In effect, these dual pancreatic and hepatic actions represent a "double whammy" on the hyperglycemia associated with type 2 diabetes, and it may be that GK activators could provide enhanced glycemic control by combining, in a single molecule, the glucose-lowering effects of insulin secretagogues, e.g., sulfonylureas, with hepatic antidiabetic actions reminiscent of the biguanide metformin.

Due to the clinical trial requirements to evaluate GKA (R)-1, we needed to develop a process capable of delivering ton quantities of the API. Prior to our involvement with the project, kilogram quantities of (R)-1 had been prepared via a synthesis devised by Prosidion, the originator of (R)-1 (Scheme 1).[2] The Prosidion synthesis illustrated in Scheme 1 begins with a Friedel−Crafts acylation which involves reacting cyclopropylphenylsulfide[3] (**2**) with ethyl 2-chloro-2-oxoacetate activated by aluminum chloride ($AlCl_3$) in CH_2Cl_2 (CH_2Cl_2 was necessary for compatibility with the $AlCl_3$ promoted chemistry) to afford sulfide-α-ketoester (**3**) as a yellow oil with excellent regiocontrol and good yield. For the following oxidation of sulfide to sulfone, *m*-chloroperbenzoic acid (*m*-CPBA) was found to be one of the most productive oxidants for producing sulfone-α-ketoester **4**. However, *m*-CPBA is relatively expensive, is potentially explosive,[4] can be contaminated with H_2SO_4, which promotes Baeyer−Villiger rearrangement to give anhydride **5**, and was shown to operate most effectively in CH_2Cl_2 (toxicity of chlorinated solvents is undesirable) to transform **3** into **4**. Sulfone-α-ketoester **4** is transformed to the *E*-acrylic acid (**8**) via Wittig olefination followed by double bond isomerization and ester hydrolysis in poor overall yield. For the Wittig olefination, phosphonium iodide (**6**)[2b] was deprotonated with lithium hexamethyldisilazide in THF to generate the corresponding ylide as a thin slurry and the sulfone-α-ketoester **4** was added to it. This mode of addition appeared problematic, as the initial low concentrations of electrophile **4** bearing acidic protons in the basic ylide media give rise to potential side reactions. *E*-Acrylic acid (**8**) was converted to (*R*)-**9** via enantioselective hydrogenation mediated by the catalyst system formed from the precatalysts (*R*)-(*S*)-MOD-Mandyphos and bis-(norbornadiene)-rhodium(I)-tetrafluoroborate ($[Rh(NBD)_2]BF_4$).[2b,5] The hydrogenation required 750 psig of hydrogen and a substrate to catalyst ratio (s/c) of 2000 to 1 to afford chiral acid (*R*)-**9** with 86% ee. The catalyst formed and the reaction ran best in MeOH, and about 16% toluene by volume was added to aid the dissolution of the *E*-acrylic acid (**8**). The hydrogenation afforded an 86% ee of (*R*)-**9** at a reaction temperature of 30 °C, which took about 18 h to reach completion (higher temperatures caused a decline in ee). In addition, a charcoal adsorbent treatment was required to remove residual rhodium, and a recrystallization to elevate the ee of isolated (*R*)-**9** to >99%. The final step is an amide coupling with activated (*R*)-**9** and poorly nucleophilic 2-aminopyrazine **10**. (*R*)-**9** is activated via reaction with stoichiometric Vilsmier reagent in CH_2Cl_2 and the resulting mixture cooled to −45 °C before adding pyridine and **10** to the reaction mixture to give (*R*)-**1** (Note: CH_2Cl_2 was required for

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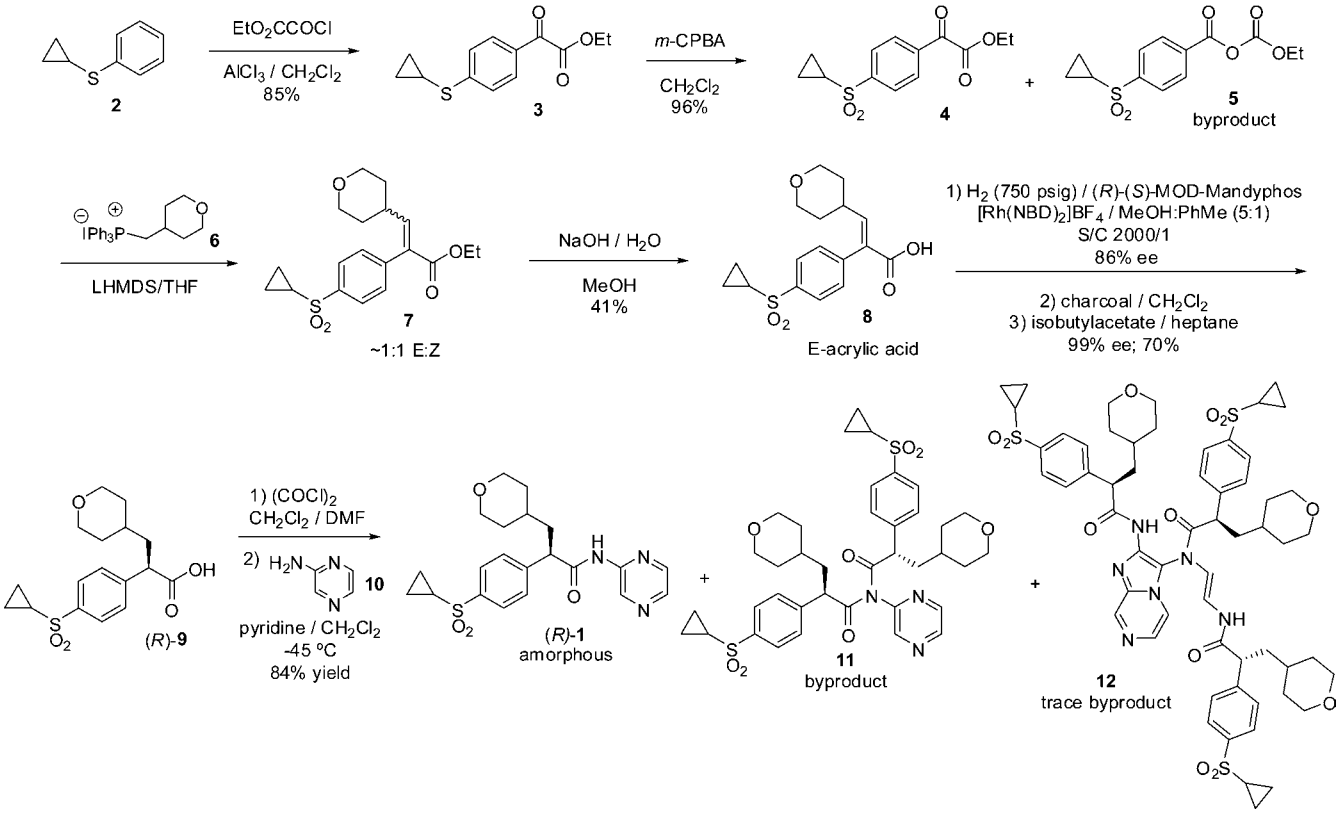
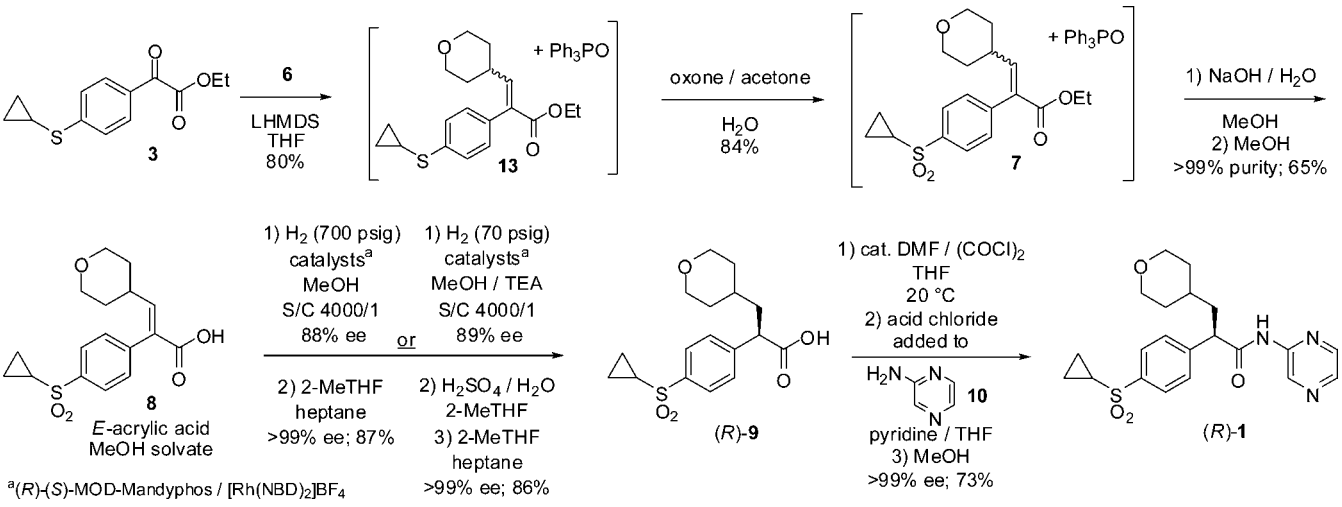
Scheme 1. Prosidion's Synthesis of (*R*)-1



Scheme 2. Lilly's Optimized Synthesis of (*R*)-1



solubility, and higher temperatures and bases stronger than pyridine caused stereochemical erosion). When repeating this reaction, we observed the imide **11** to form as a byproduct by MS, as well as the trace byproduct **12** (see Supporting Information for structural proof), and we concluded that adding **10** to activated (*R*)-**9** created a situation of an initial low concentration of **10** which caused per-acylated byproducts to form. Perhaps most problematic was the lack of a crystal form and therefore purity control of (*R*)-**1**.

RESULTS AND DISCUSSION

To develop the Scheme 1 chemistry to prepare multi-kilogram amounts of high purity (*R*)-**1**, the order of the steps and chemicals were changed and the reaction conditions were optimized. A reliable and sustainable oxidation to convert sulfide-α-ketoester **3** to sulfone-α-ketoester **4** was not identified by Prosidion, so we decided to examine running the Wittig olefination first followed by oxidation of sulfide to sulfone to avoid the Baeyer–Villiger degradation issues. Wittig olefination of **3** was conducted by generating the ylide of **6** as before, but reversing the addition order to add the thin slurry of ylide to the sulfide-α-ketoester **3**. This afforded solution yields of *E*/*Z*-sulfide-acrylates **13** of 80% (the opposite addition order gave solutions yields of about 10% lower). We investigated the isomerization of the mixture of *E*/*Z*-sulfide-acrylates **13** to the *E*-isomer and determined that the sulfone functional group was

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essential for a productive isomerization (see Supporting Information for an illustration of an isomerization study). The isomerization to the *E*-isomer was imperative to maximize the yield of **8**, since crystallization of acrylic acid **8** from MeOH affords the *E*-isomer preferentially as a MeOH solvate, leaving proportionately more *Z*-isomer than *E*-isomer in the liquor. These observations dictated the Scheme 2 telescoped sequence of Wittig olefination, sulfide to sulfone oxidation, olefin isomerization, and ester hydrolysis. This telescoped process from **3** to **8** without intermediate purifications was also necessary, since triphenylphosphine oxide (Ph_3PO), which was generated in the first step Wittig chemistry, could not be efficiently removed until production of acrylic acid **8**, which afforded Ph_3PO removal via selective extraction. Therefore, crude *E*/*Z*-sulfide-acrylates **13** contaminated with Ph_3PO was reacted with oxone in aqueous acetone to afford *E*/*Z*-**7** in 84% yield. Crude *E*/*Z*-**7** contaminated with Ph_3PO was reacted with aqueous NaOH in MeOH to affect olefin isomerization to the *E*-isomer and hydrolysis to *E*-acrylic acid (**8**), which was worked up with a selective base extraction to remove Ph_3PO and crystallized from MeOH to give **8** as a MeOH solvate in 65% yield with >99% purity.

Chiral acid (*R*)-**9** has about 20 times greater solubility in MeOH than *E*-acrylic acid (**8**); therefore, it appeared practical that the hydrogenation conversion could start as a suspension and homogenize during the process. Indeed, this is the case, and conversion of **8** into **9** transpires in just 3 h at 700 psig in a neat MeOH system. The highly pure *E*-acrylic acid (**8**), produced from the Scheme 2 synthesis, allowed the catalyst load to be lowered to a s/c of 4000 to 1, obviating the need for a workup and adsorbent treatment to remove rhodium. The chiral acid (*R*)-**9** was crystallized from a mixture of 2-MeTHF and heptane to afford an 87% yield with >99% ee.

In our attempts to find a solvent system for the hydrogenation that would improve the solubility of *E*-acrylic acid (**8**), we found that the triethylammonium carboxylate salt of **8** showed excellent solubility in MeOH (>1 g/mL). In addition, TEA gave the benefit of dramatically increasing reduction rates, to the point that the hydrogen pressure could be reduced to 70 psig, with complete reductions transpiring in less than 4 h (this procedure required a workup involving an acid wash to remove the TEA).[6,7] Interestingly, reduction rates began to decrease when greater than 1 equiv of TEA was used. The (*R*)-(*S*)-MOD-Mandyphos ligand contains basic amine functionality; hence, we speculate that the triethylamine may either be assisting with dissociation of **9** from the catalyst complex or relieving ligand protonation, leading to improved reduction efficiency. Triethylamine did not impact the enantioselectivity of the reduction, and (*R*)-**9** was produced with 89% ee and was isolated via the aforementioned crystallization in 86% yield with >99% ee.

For the final step, amide coupling, the order of addition was reversed from the Prosidion procedure so that the activated chiral acid (*R*)-**9** was added to the 2-aminopyrazine (**10**). This addition order did mitigate per-acylated byproducts, and as an added bonus, the stereocenter became stable toward epimerization under ambient conditions. This equated to a 65 °C increase in reaction temperature (from −45 to 20 °C) and made it possible to switch the solvent system from CH_2Cl_2 to THF due to increased solubility. The final procedure was to dissolve (*R*)-**9** in THF at 20 °C, and add catalytic DMF, followed by slow addition of oxylyl chloride to produce the corresponding acid chloride. The acid chloride was then added to a second reactor containing 2-aminopyrazine (**10**) in THF with 10 equiv of pyridine present to minimize formation and precipitation of the hydrochloride salt of **10**. This procedure resulted in solution yields of 89−94% of (*R*)-**1** with the stereocenter maintained with >99% ee. After reaction completion, pyridine hydrochloride was filtered off, EtOAc was added to improve phase separations, and residual **10**, pyridine, and 4−5% of unreacted (*R*)-**9** were washed away with acid and base, respectively. The resulting solvents in the solution of crude (*R*)-**1** in THF/EtOAc were replaced with MeOH via azeotropic distillation and seeding employed to crystallize a form of (*R*)-**1** that was discovered at Lilly in 73% yield.[8] Attempts to improve the yield by reducing the solubility of (*R*)-**1** in the crystallization system led to production of crude solids with darker color and poor physical properties.

■ CONCLUSION

To avoid Baeyer−Villiger degradation issues, permit use of more benign reagents and solvents, and improve control, yield, and purity, the steps for the preparation of *E*-acrylic acid (**8**) were developed and the sequence changed. The high quality *E*-acrylic acid (**8**) produced by the new process led to improved productivity in the subsequent high pressure enantioselective hydrogenation to produce chiral acid (*R*)-**9**. In addition, low pressure conditions for the hydrogenation involving in situ formation of an ammonium carboxylate of *E*-acrylic acid (**8**) were identified. Lastly, development of the final amide coupling and crystallization resulted in a six step synthesis starting from cyclopropylphenyl sulfide **2** to produce the GKA, (*R*)-**1** in 23% overall yield.

■ EXPERIMENTAL SECTION

General. ^1H and ^{13}C NMR spectra were obtained on a Varian spectrometer at 400 and 101 MHz, respectively. Processes for the preparation of cyclopropylphenyl sulfide (**2**) and triphenyl((tetrahydro-2H-pyran-4-yl)methyl)phosphonium iodide (**6**) have not been investigated or developed at Lilly. Cyclopropylphenyl sulfide (**2**) and triphenyl((tetrahydro-2H-pyran-4-yl)methyl)phosphonium iodide (**6**) are known compounds, and the respective preparations have been documented.[2,3] Spectroscopic data for **6**: ^1H NMR (DMSO-d_6, 400 MHz) 7.83−7.89 (m, 9H), 7.72−7.77 (m, 6H), 3.62−3.67 (m, 4H), 3.12 (dt, 2H, J = 2.8, 11.6 Hz), 1.90−1.99 (m, 1H), 1.30−1.42 (m, 4H). ^{13}C NMR (DMSO-d_6, 101 MHz) 135.39, 135.36, 134.1, 134.0, 130.7, 130.6, 119.8, 119.0, 66.7, 34.0, 33.9, 30.2, 30.1, 26.9, 26.4. IR (film) 2927, 2834, 1432 cm^{-1}. HRMS (ESI^+) caldc for $C_{24}H_{26}IOP$ 488.07659, found 488.07643.

Analytical methods: GC: Column: DB-5 MS; 30 m × 0.25 mm, 0.25 μm; Carrier gas: helium; Flow rate: 2.3 mL/min; Temp: 50 °C, hold for 2.0 min, then ramp at 20 °C/min to 260 °C; Run time: 22.5 min. HPLC for enantiomeric excess determination of chiral acid (*R*)-**9**: Column: ChiralPak AD-RH, (0.46 cm × 15 cm, 5 μm), Flow rate: Isocratic flow, 0.6 mL/min, 30 °C, UV detection: 230 nm. Eluent: 68% H_2O/32% CH_3CN/0.1% TFA. Run time: 15 min, (*R*)-**9** rt = 7.8, (*S*)-**9** rt = 10.9. HPLC for enantiomeric excess determination of chiral amide (*R*)-**1**: Column: Diacel OJ-RH (0.46 cm × 15 cm, 5 μm), Flow rate: Isocratic flow, 0.5 mL/min., 23 °C, UV detection: 235 nm. Eluent: 65% H_2O/35% CH_3CN. Run time: 30 min, (*R*)-**1** rt = 9.1, (*S*)-**1** rt = 12.7. HPLC for reaction monitoring: Colunm: Agilent Ecilipse XDB-C8 (0.46 cm × 15 cm, 3.5 μm). Flow rate: 2 mL/min, A = 0.1% H_3PO_4, B =

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CH_3CN, Gradient: 95% A to 5% A over 10 min; change to 95% A over 1 min and hold for 4 min, 30 °C, UV detection: 220 nm.

Ethyl 2-(4-(Cyclopropylthio)phenyl)-2-oxoacetate (3). A reactor was charged with CH_2Cl_2 (702.0 kg) and cooled to 0−5 °C, and $AlCl_3$ (109.5 kg, 820.2 mol) was added to the mixture in five portions while maintaining the temperature at 0−5 °C. After the addition was complete, the mixture was stirred for 0.25 h, and ethyl 2-chloro-2-oxoacetate (90.0 kg, 659.3 mol) was added to the mixture at a rate of 18−22 kg/h at 0−5 °C. After the addition, the temperature was maintained at 0−5 °C for 1.5−2.0 h. Maintaining the temperature at 0−5 °C, cyclopropylphenyl sulfide **2** (90.0 kg, 599.2 mol) was added to the mixture at a rate of 18−22 kg/h. After 2.0 h, a sample of the reaction mixture was analyzed by GC, which indicated that the cyclopropylphenyl sulfide **2** was <3.0%. The reaction mixture was transferred to a second reactor at a rate of 200−250 kg/h in five portions into crushed ice (900.0 kg) and water (270.0 kg) while maintaining the temperature at 0−10 °C. After quenching the reaction, the mixture was held for 0.5 h at 5−10 °C. The aqueous phase was separated and extracted with CH_2Cl_2 (282.0 kg). The organic phases were combined and washed with a 6.3% aqueous solution of $NaHCO_3$ (302.4 kg), followed by saturated brine (162.4 kg) until the KF measurement of the organic layer was <0.3%. The organic phase was concentrated under atmospheric pressure at 39−45 °C until no further distillate could be collected, and then the mixture was concentrated under vacuum (140 mmHg) below 35 °C until the CH_2Cl_2 content was <1.0%. The product sulfide-α-ketoester **3** was a yellow liquid which had a weight of 139.0 kg with a 92.3% potency (yield 85.5%). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.90 (d, 2H, J = 8.8 Hz), 7.43 (d, 2H, J = 8.8 Hz), 4.42 (q, 2H, J = 7.2 Hz), 2.18 (tt, 1H, J = 4.4, 7.6 Hz), 1.40 (t, 3H, J = 7.2 Hz), 1.13−1.18 (m, 2H), 0.69−0.73 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) 185.5, 163.8, 149.7, 130.0, 128.5, 125.1, 62.1, 14.0, 10.8, 8.5. IR (film) 1729, 1670, 1584, 1283, 1205, 1175 cm^{-1}. HRMS (ESI$^+$) calcd for $C_{13}H_{14}O_3S$ 250.06637, found 250.06613.

(*E*/*Z*)-Ethyl 2-(4-(Cyclopropylthio)phenyl)-3-(tetrahydro-2H-pyran-4-yl)acrylate (13). A reactor was charged with THF (355.0 kg) followed by hexamethyldisilazane (135.4 kg, 838.9 mol). The mixture was cooled to −10 to 0 °C, and *n*-butyllithium (246.1 kg, 881.5 mol) was added at a rate of 25−30 kg/h while maintaining the temperature between −10 and 0 °C. After the addition was complete, the temperature was maintained at −10 to 0 °C for 2.0−3.0 h. To a second reactor was charged THF (533.0 kg) followed by phosphonium iodide (**6**; 389.5 kg, 798.2 mol) in four portions. The lithium hexamethyldisilazide/THF mixture was added to the phosphonium iodide (**6**)/THF mixture at a rate of 80−110 kg/h at 0−10 °C, and after the addition, the temperature was maintained at 0−10 °C for 0.5 h. The temperature was raised to 15−20 °C, and after 2.5 h the mixture was cooled to 0−5 °C, and in a third reactor was charged THF (355.0 kg) followed by the addition of sulfide-α-ketoester **3** (200.6 kg, 801.4 mol). The mixture was cooled to 0−10 °C, and the ylide mixture was added to the sulfide-α-ketoester **3** mixture within 8.0−10.0 h while maintaining the temperature at 0−10 °C. After the addition was complete, the reaction mixture was maintained at 15−20 °C, and after 2.0 h a sample of the mixture was analyzed by HPLC, which indicated that the sulfide-α-ketoester **3** was <2.0%. The resulting mixture was transferred to a reactor that contained an aqueous 1 M solution of citric acid (1006.0 kg) (final pH = 2.0−3.0) while maintaining the temperature at 0−15 °C. The mixture was filtered, and the filter cake (Ph_3PO) was rinsed with THF (10.0 kg). The aqueous phase was separated, and the organic phase was concentrated under atmospheric pressure at 65−70 °C until no further distillate could be removed. The concentrated organic phase was cooled to 20−25 °C, and the aqueous phase was extracted with MTBE (295.0 kg) and separated. The separated organic phase was added to the concentrated organic phase, and the resulting mixture was concentrated at atmospheric pressure at 56−60 °C until no further distillate could be removed. The organic phase was further concentrated under vacuum (140 mmHg) at 40−45 °C until no further distillate could be removed, and the organic phase was left under vacuum for a further 6.0−8.0 h until the THF and MTBE contents were <10.0%. The organic phase was cooled to 20−25 °C, and acetone (100.0 kg) was added followed by stirring for 0.5 h. The acetone solution weighed 213.2 kg and contained Ph_3PO and a ∼1:1 mixture of *E*:*Z*-sulfide acrylic ester product **13**, with 41.5% potency (yield 80.0%), which was taken directly into the next step.

Ethyl 2-(4-(Cyclopropylsulfonyl)phenyl)-3-(tetrahydro-2H-pyran-4-yl)acrylate (7). A reactor was charged with a solution of sulfide **13** in acetone (213.2 kg; 41.5 wt %; 641.2 mol), from the prior step, followed by the addition of water (213.2 kg) at 5−15 °C. Oxone (K_2SO_4, $KHSO_4$, $2KHSO_5$) (650.2 kg, 2116.1 mol) was added to the mixture in 23 portions over 11.5 h at 5−15 °C. The mixture was analyzed by HPLC, the peak area of **13** (*E*+*Z*) was <0.1%, and intermediate content (*E*+*Z*-sulfoxide) was <0.3%. While maintaining the reaction temperature between 0 and 15 °C, saturated aqueous $NaHSO_3$ solution (336.8 kg) was added to the mixture at a rate of 50.0−60.0 kg/h until potassium iodide-starch paper did not turn blue. The mixture was transferred to a centrifuge for filtration, and the filter cake (Ph_3PO) was washed with acetone (2 × 341.0 kg) until the product content in the filter cake was <0.5%. The filtrate was transferred to a reactor, and 2 M NaOH solution (1302.0 kg) was added to the mixture at a rate of 140−160 kg/h until the pH was 6−7. The mixture was concentrated under vacuum (140 mmHg) at 40−47 °C until no more acetone distilled out. The mixture was cooled to 25−30 °C and extracted with MTBE (471.2 kg), and the aqueous phase was separated. The aqueous phase was extracted with MTBE (471.2 kg), and the product content in the aqueous phase was <0.5%. The organic phases were combined and washed with water (2 × 213.2 kg). The organic phase was concentrated under atmospheric pressure at 55−62 °C until no further distillate could be removed. The organic phase was concentrated under vacuum (140 mmHg) at 30−40 °C until no further distillate could be removed, and the residue continued to concentrate under vacuum for 9.0 h until the MTBE and acetone content was <10.0%. The residue was cooled to 20−25 °C, and MeOH (336.8 kg) was added to the mixture (*E*/*Z*-**7** and Ph_3PO) for the following step. The MeOH solution of *E*/*Z*-**7** had a weight of 197.0 kg, had a potency of 26.8% (yield 84.3%), appeared as a yellow liquid, and was taken directly into the next step.

(*E*)-2-(4-(Cyclopropylsulfonyl)phenyl)-3-(tetrahydro-2H-pyran-4-yl)acrylic Acid (8). The solution of *E*/*Z*-**7** (197.0 kg, 541.2 mol) in MeOH (624.0 kg), from the prior step, was charged to a reactor. To the solution was added a 7.4% aqueous solution of NaOH (779.5 kg) while maintaining the temperature between 10 and 30 °C. The mixture was heated to 65−70 °C for 2.0 h, and a sample of the reaction mixture was analyzed by HPLC, which indicated that **7** (*E*+*Z*) was <0.3%. The mixture was cooled to 40−45 °C and concentrated under

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vacuum (140 mmHg) at 43−50 °C until no further distillate was observed (content of methanol in the aqueous phase was <3.0%). The resulting mixture was cooled to 10−15 °C, and water (1383.0 kg) was added. After the addition was complete, the temperature was maintained at 10−15 °C for 2.0−3.0 h, the reaction mixture was filtered by centrifuge, and the filter cake (Ph_3PO) was washed with a 3.7% aqueous solution of NaOH (296.4 kg), and water (296.0 kg), respectively. All of the filtrates were combined and extracted with MTBE (449.0 kg + 298.0 kg). The organic phases were combined and washed with water (198.0 kg). All of the aqueous phases were combined, and MTBE (449.0 kg) was added while maintaining the temperature at 13−18 °C. The pH of the mixture was adjusted to 1−2 with 1 M sulfuric acid (1183.0 kg) at 13−18 °C. After the addition was complete, the temperature was maintained at 13−18 °C for 5.0−6.0 h. The mixture was filtered by centrifuge, and the filter cake was washed with water (2 × 84.0 kg). The filter cake was dried at 35−40 °C until the KF measurement was <3.0%, and crude *E*-acrylic acid (**8**; 132.0 kg) was obtained. The aqueous phase of the filtrate was separated and extracted with MTBE (2 × 449.0 kg). The organic phases were combined, and active carbon (9.9 kg) was added, which was rinsed with MTBE (25.0 kg) in advance. The mixture was heated to 40−50 °C and the temperature maintained at 40−50 °C for 1.0 h. The mixture was filtered at 20−40 °C and concentrated under vacuum (140 mmHg) at 35−45 °C until there was 150−200 L remaining. MTBE (126.0 kg) was added to the mixture, stirred for 1.0 h, and cooled to 0−5 °C for 3.0−4.0 h. The mixture was filtered by centrifuge, and product was reclaimed from the mother liquor again to give crude **8** (15.2 kg). The crude **8** (132.0 kg +15.2 kg) was recrystallized from MeOH (927.4 kg). The mixture was heated to 63−68 °C and stirred until the solids were completely dissolved. The mixture was cooled to 10−15 °C within 6.0 h and the temperature maintained at 10−15 °C for 1.0 h. The mixture was cooled to 0−5 °C within 2.0 h and the temperature was maintained at 0−5 °C until the wt % of **8** was <2.0% in the filtrate. The mixture was filtered by centrifuge, and the filter cake was washed with cold (0−5 °C) MeOH (58.9 kg). The cake was dried at 35−40 °C until the KF measurement was <0.5% and the LOD measurement was <3.0%. *E*-Acrylic acid (**8**) was isolated as a MeOH solvate and appeared as an off-white solid with a weight of 132.9 kg, a potency of 88.9%, and a purity of 99.9% (yield 64.9%). Mp 152.5−153.6 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) 12.72 (s, 1H), 7.87 (d, 2H, J = 8.4 Hz), 7.43 (d, 2H, J = 8.4 Hz), 6.81 (d, 1H, J = 10.3 Hz), 3.70−3.80 (m, 2H), 3.12−3.18 (m, 2H), 2.88−2.91 (m, 1H), 2.12−2.26 (m, 1H), 1.38−1.55 (m, 4H), 1.04−1.18 (m, 4H). ^{13}C NMR (DMSO-d_6, 101 MHz) 167.7, 148.4, 141.4, 139.9, 132.3, 131.0, 127.4, 66.3, 35.7, 32.4, 31.4, 5.9. IR (neat) 3497, 2940, 2910, 2612, 1689, 1629, 1414, 1391. HRMS (ESI$^+$) calcd for $C_{17}H_{21}O_5S$ 337.1104, found 337.1099.

(*R*)-2-(4-(Cyclopropylsulfonyl)phenyl)-3-(tetrahydro-2H-pyran-4-yl)propanoic Acid ((*R*)-9). To prepare the catalyst, degassed MeOH (900 mL), under N_2, was combined with (*R*)-(*S*)-MOD-Mandyphos (SL-M004-1) (9.68 g, 9.17 mmol) and $[Rh(NBD)_2]BF_4$ (3.25 g, 8.69 mmol), and the resulting mixture was stirred under ambient conditions (~23 °C) for 14.0 h. In a separate reactor, *E*-acrylic acid (**8**; MeOH solvate) (13.3 kg with 88.94% potency = 11.83 kg, 35.17 mol) was suspended in MeOH (52 L) and charged to an autoclave using vacuum for the transfer. The autoclave was pressurized with N_2 to 700 psig for >1 min and vented to 1−20 psig (this process was repeated 4 times). A transfer line to add the catalyst solution to the autoclave was purged with N_2, and then the catalyst mixture was transferred to the autoclave by utilizing pressure. The autoclave was pressurized to 700 psig with H_2, and the reaction mixture was heated to 30 °C for 3.0 h (the reaction starts as a slurry and becomes homogeneous). The autoclave was cooled to 20 °C, vented to 5−20 psig, and sampled and assayed for reaction completion by HPLC, which indicated 0.11% of **8** remaining. The reaction mixture was transferred to a reactor with MeOH (5 L) used to rinse the autoclave, which was added to the reactor. The resulting mixture was distilled at 23 °C under vacuum to a final volume of approximately 24 L. 2-MeTHF (84 L) was added to the mixture and distillation continued to a final volume of 60 L. Additional 2-MeTHF (24 L) was added to the mixture during distillation at the same rate as distillate removal while maintaining the reactor volume at 60 L. The mixture was heated to 50 °C, and heptane (24 L) was added over 0.5 h. Seeds of (*R*)-**9** (10 g) were suspended in heptane (200 mL) and added to the reaction mixture, followed by a heptane (36 L) addition over 1.0 h. The resulting slurry was cooled to 20 °C over 2.0 h, stirred for 3.0 h, and filtered. The filter cake of (*R*)-**9** was washed with a mixture of 2-MeTHF (10 L) and heptane (23 L), and the cake was dried with a stream of N_2 for 1.0 h and further dried *via* roto-vap under vacuum at 50−60 °C. The chiral acid (*R*)-**9** was isolated as an off white solid with a weight of 10.43 kg, potency of 99.8%, purity of 99.9%, and chiral purity of 99.72% ee with 29 ppm of Rh (yield 87.5%). Mp 153.9−154.4. ^{1}H NMR (DMSO-d_6, 400 MHz) 0.99−1.05 (m, 2H), 1.06−1.19 (m, 4H), 1.26−1.33 (m, 1H), 1.50−1.60 (m, 2H), 1.63 (ddd, 1H, J = 7.2, 7.2, 14.0 Hz), 1.92 (ddd, 1H, J = 7.6, 7.6, 13.6 Hz), 2.82 (dddd app tt, 1H, J = 4.8, 8.0 Hz), 3.11−3.18 (m, 2H), 3.73−3.80 (m, 3H), 7.57 (d, 2H, J = 8.4 Hz), 7.83 (d, 2H, J = 8.4 Hz), 12.54−12.60 (br s, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz) 5.8, 32.4, 32.6, 32.8, 33.0, 48.0, 67.3, 127.9, 129.4, 139.6, 146.0, 174.6. IR (film) 3000−2600 (br s), 2916, 1718, 1316, 1294, 1272, 1223 cm^{-1}. HRMS (ESI$^+$) calcd for $C_{17}H_{22}O_5S$ 338.1187, found 338.1183. $[\alpha]_D^{24}$ −53.8 (MeOH, c = 2.8).

Preparation of (*R*)-2-(4-(Cyclopropylsulfonyl)phenyl)-3-(tetrahydro-2H-pyran-4-yl)propanoic Acid ((*R*)-9) in the Presence of Triethylamine. To prepare the catalyst, degassed MeOH (3.8 mL), under N_2, was combined with (*R*)-(*S*)-MOD-Mandyphos (SL-M004-1) (11.1 mg, 0.0105 mmol) and $[Rh(NBD)_2]BF_4$ (3.7 mg, 0.01 mmol), and the resulting mixture was stirred under ambient conditions (~23 °C) for 14.0 h. In a separate reactor, *E*-acrylic acid (**8**; 13.35 g, 39.65 mmol) was combined with triethylamine (4.01 g, 39.65 mmol) and MeOH (62.8 mL) to provide a colorless solution. The solution was purged of O_2 by pressure cycling with N_2 to 50 psig (repeated 3 times). While maintaining an inert environment, the catalyst solution was transferred to the reactor and the system was pressurized to 70 psig with H_2 with a reactor temperature of 20 °C. After 4.0 h, the reaction was sampled and assayed for completion by HPLC, which indicated <1% of **8** remaining. The system was purged of H_2, and then a portion of the MeOH was removed by distillation under reduced pressure (300 Torr, 42 °C) to give approximately 40 mL of reactor volume. Water (18 mL) was added, and the remaining MeOH was removed by distillation under reduced pressure (250 Torr, 55 °C), resulting in an approximately 25−28 mL reactor volume. The condensate was diluted with 2-MeTHF (100 mL) and then extracted with 1 M H_2SO_4 (20 mL). The organic

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phase was concentrated (at atmospheric pressure, 71 °C) to a reactor volume of 42 mL. To the hot solution was charged 20 mL of 2-MeTHF followed by 25 mL of heptane. After cooling, the product was collected by filtration and then dried under vacuum to give an 86% yield (11.55 g, 99.8% ee) of (*R*)-**9** identical to that described above.

(*R*)-2-(4-(Cyclopropylsulfonyl)phenyl)-*N*-(pyrazin-2-yl)-3-(tetrahydro-2H-pyran-4-yl)propanamide ((*R*)-1). At 20−25 °C, a reactor was charged with THF (100 L) followed by chiral acid (*R*)-**9** (23.10 kg, 55.59 mol) which was rinsed into the reactor with THF (5 L). DMF (0.275 kg, 3.76 mol) was charged to the reactor followed by the addition of oxalyl chloride (9.125 kg, 71.89 mol) over 0.25 h, maintaining the temperature below 30 °C. The resulting mixture was held for 1.0 h, and a sample was quenched into MeOH for HPLC analysis, which indicated >99% conversion to the acid chloride via analysis of the methyl ester derivative. THF (116 L) was charged to a second reactor followed by 2-aminopyrazine (**10**; 7.15 kg, 75.23 mol), which was rinsed into the reactor with THF (6 L). Pyridine (54 kg, 682.7 mol) was charged to the second reactor, and the temperature was maintained at 20−25 °C. The acid chloride mixture was transferred to the mixture of **10** in THF over 0.75 h while maintaining the temperature below 30 °C. THF (24 L) was used to rinse the acid chloride reactor into the second reactor. The resulting mixture was held for 1.0 h, and a sample was quenched into MeOH for HPLC analysis, which indicated <1% of the methyl ester derivative and production of (*R*)-**1**. Solids (pyridinium hydrochloride) were removed via filtration, and the resulting waste cake was washed with EtOAc (230 L), which was combined with the reaction mixture. Aqueous HCl (81.8 kg of 37% HCl in 61 L water) was added to the reaction mixture over 10 min while maintaining the temperature below 30 °C. At 20−25 °C, the aqueous layer was separated and aqueous $NaHCO_3$ (4.88 kg in 64.2 kg water) was added to the reaction mixture over 8 min followed by removal of the aqueous layer. The resulting mixture was heated to 30−45 °C under vacuum (190−210 mmHg) to remove distillate to a final volume of 90−95 L. EtOAc (230 L) was added to the mixture followed by distillation at 30−45 °C under vacuum (190−220 mmHg) to a final volume of 90−95 L (this operation was repeated two more times to give 0.02% water by KF and <1.0% THF by GC). MeOH (230 L) was added to the reactor followed by distillation at 30−45 °C under vacuum (170−220 mmHg) to a final volume of 115 L (this operation was repeated two more times to a final volume of 95 L to give 0.14% water by KF and <1.0% EtOAc by GC). The mixture was maintained at 38−42 °C while seed crystals of (*R*)-**1** (0.23 kg, 0.55 mol) were added. The resulting mixture was held at 40 °C for 2.0 h, cooled to −10 °C over 8.0 h, and held at −10 °C for 1.0 h. The solids were filtered on a filter dryer and washed with cold (−10 °C) MeOH (92 L). The filter dryer was maintained at 25 °C while N_2 was blown through the product cake for 2.0 h; then a switch to pulling vacuum through the bottom of the cake was made until constant weight was achieved. The chiral amide (*R*)-**1** was isolated as an off white solid with a weight of 21.06 kg, potency of 100.0%, and chiral purity of >99% ee (yield 73.6%). Mp 156.8−157.9 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) 0.96−1.01 (m, 2H), 1.03−1.08 (m, 2H), 1.11−1.24 (m, 2H), 1.31−1.38 (m, 1H), 1.51−1.55 (m, 1H), 1.60−1.67 (m, 2H), 2.03−2.11 (m, 1H), 2.79 (tt, 1H, J = 4.8, 8.0 Hz), 3.13−3.20 (m, 2H), 3.76 (ddd, 2H, J = 2.0, 2.0, 11.6 Hz), 4.21 (dd, 1H, J = 6.0, 8.4 Hz), 7.65 (d, 2H, J = 8.8 Hz), 7.84 (d, 2H, J = 8.4 Hz), 8.32 (d, 1H, J = 2.4 Hz), 8.35 (dd, 1H, J = 1.2, 2.4 Hz), 9.30 (d, 1H, J = 1.2 Hz), 11.1 (s, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz) 5.8, 32.4, 32.9, 33.0, 48.4, 67.2, 128.0, 129.3, 136.6, 139.7, 140.5, 143.1, 146.1, 149.0, 172.3. IR (film) 3239, 2841, 1670, 1532, 1405 cm^{-1}. HRMS (ESI$^+$) calcd for $C_{21}H_{25}N_3O_4S$ 415.15658, found 415.1562. $[\alpha]_D^{24}$ −49.5 (MeOH, c = 3.2).

■ ASSOCIATED CONTENT

Supporting Information

Structure proof for compound **12** and HPLC trace of **8**'s transformation in 2 M methanolic NaOH. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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