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Practical Asymmetric Synthesis of a Potent Cathepsin K Inhibitor. Efficient Palladium Removal Following Suzuki Coupling

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A large-scale, chromatography-free synthesis of a potent and selective Cathepsin K inhibitor **1** is reported. The key asymmetric center was installed by addition of (*R*)-pantolactone to the in situ-generated ketene **4a**. The final step of the convergent synthesis of **1** was completed via Suzuki coupling of aryl bromide **7a** with unprotected aryl piperazine boronic acid **13**. Residual palladium and iron generated in the Suzuki coupling were efficiently removed from crude **1** via a simple extractive workup using lactic acid.

Introduction

Bone is a dynamic living tissue that undergoes constant remodeling throughout adult life. This equilibrium process begins with resorption of old bone by osteoclasts followed by formation of new bone by osteoblasts. Osteoporosis is a disease caused by an imbalance in the bone remodeling process leading to bone loss due to excessive resorption. In the United States, 10 million people have the disease and an estimated 34 million are at risk due to low bone mass. Osteoporosis also accounts for more than 1.5 million fractures each year.[1] Cathepsin K is a cysteine protease and a member of the papain superfamily. It is highly expressed in osteoclasts, the cells responsible for bone resorption.[2,3] Cathepsin K has been implicated in the bone resorption process due to its localization[4] and because it is one of the few proteases that can efficiently hydrolyze native collagen, which makes up 90% of the protein in bone.[5] Selective inhibitors of Cathepsin K could therefore be potential therapeutic agents for the treatment of diseases characterized by excessive bone loss such as osteoporosis.

As part of an ongoing drug discovery program at our laboratories, substituted biphenyl **1** has been identified as a potent, selective, and reversible inhibitor of Cathepsin K.[6] To enable further study of the pharmacological properties of this compound, we sought an efficient, chromatography-free, large-scale synthesis suitable for the preparation of bulk quantities of **1**. We envisioned that the compound could be assembled in a highly convergent manner via Suzuki coupling of an aryl piperazine boronic acid **10** with an aromatic halide **7** to form the biaryl linkage. The key asymmetric center could be introduced by deracemization of acid **3** via addition of a chiral alcohol to the corresponding in situ-generated ketene **4** (Scheme 1).

Results and Discussion

Racemic 2-alkyl-arylacetic acids have been the subject of extensive research, and a number are commercially available as antiinflammatory and analgesic drugs.[7] The asymmetric synthesis of alkyl-arylacetic acids has also received considerable attention, and many elegant approaches have been developed.[8] Following an earlier discovery in our laboratories,[9] we envisioned that the asymmetric center of **1** could be installed via chiral protonation of the in situ-generated alkyl-aryl ketene **4a** with (*R*)-pantolactone (Scheme 2).

Thus, commercially available 3-bromophenyl acetic acid **2** was alkylated with 1-iodo-2-methylpropane in THF using LHMDS as a base to provide **3a**. The order of reagent addition proved to be crucial for achieving a high yield. For example, treatment of a THF solution of acid

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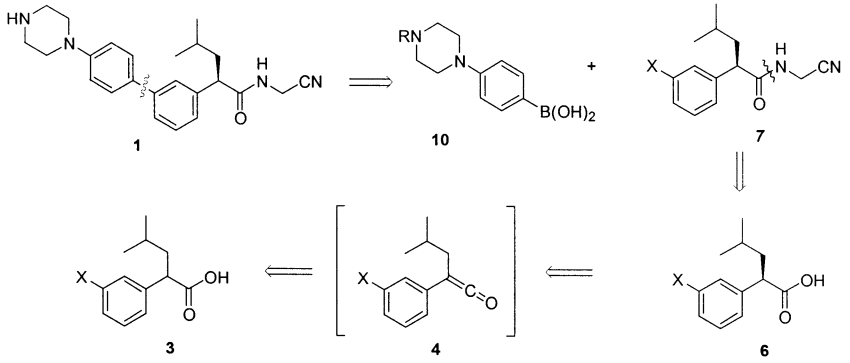
SCHEME 1



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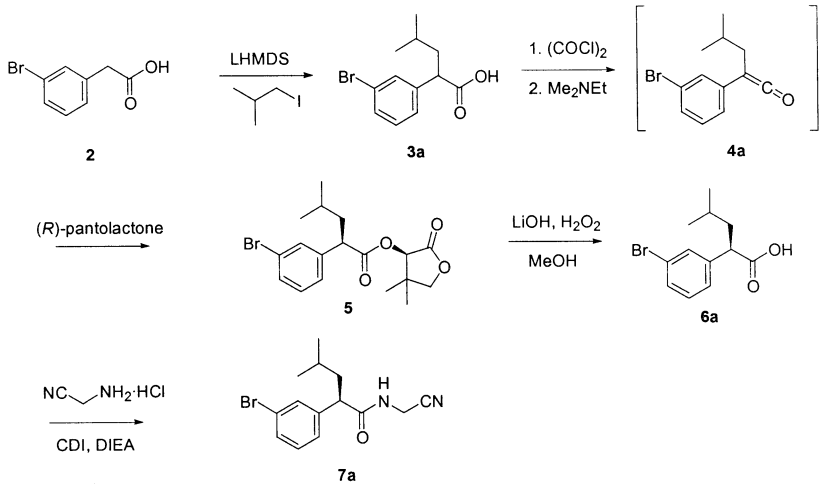

2 at −20 °C with LHMDS followed by addition of the iodide gave acid **3a** in ∼50% isolated yield. However, addition of LHMDS to a mixture of acid **2** and the iodide in THF improved the yield to 85%. Treatment of acid **3a** with oxalyl chloride and catalytic DMF in toluene at 25 °C generated the corresponding acid chloride. This mixture was cooled to 0 °C, and addition of *N*,*N*′-dimethylethylamine provided ketene **4a**. Addition of (*R*)-(−)-pantolactone to the ketene at <−65 °C gave the desired (*R*,*R*)-ester **5** in 96% yield and 87% diastereomeric excess as determined by chiral HPLC.

The overall success of this synthetic strategy was dependent on the development of reaction conditions for removal of the ester group and subsequent amide formation, without racemization. Initially we investigated acidic conditions (AcOH/HCl) for the hydrolysis of ester **5** to give (*R*)-acid **6a**. The reaction was sluggish and was not complete after 30 h at 85 °C. Increasing the temperature shortened the reaction time but led to ∼10% reduction in ee. Under alkaline conditions (LiOH/MeOH or THF/water), hydrolysis was complete in 24 h at 20 °C but led to significant racemization (25%). To our delight, the use of LiOH/H_2O_2[10] at 0 °C led to minimal racemization and the reaction was complete in less than 2 h, giving chiral acid **6a** in 93% yield. The optical purity was upgraded by crystallization of the acid as its (*R*)-(+)-α-methylbenzylammonium salt from 2-propanol/water. Thus, 83% ee acid was upgraded to 98.5% by a single crystallization of the α-methylbenzylammonium salt in 83.5% yield. The formation of amide **7a** without racemization was possible using *N*,*N*′-carbonyldiimidazole (CDI) or PyBOP. CDI provided a cleaner workup; thus, acid **6a** was treated with CDI at room temperature to generate the corresponding acyl imidazole. Addition of aminoacetonitrile hydrochloride and Hunig's base yielded amide **7a** in 98% yield and 98.1% ee as measured by chiral HPLC.

Our initial strategy for the formation of the biaryl moiety involved Suzuki coupling[11] of *N*-Boc-boronic acid **10a** with aryl bromide **7a** as outlined in Scheme 3. Thus, the amino moiety of bromophenylpiperazine **8** was protected using di-*tert*-butyl dicarbonate in acetonitrile to give *N*-Boc-piperazine **9** in 97% yield. Treatment of **9** with *n*-BuLi in 1:1 THF−toluene at −65 °C followed by addition of triisopropyl borate gave *N*-Boc-boronic acid **10a** after acidic workup. Suzuki coupling was completed in 3 h using 5 mol % $PdCl_2(dppf)\cdot CH_2Cl_2$ and aqueous Na_2CO_3 in DMF at 90 °C to yield *N*-Boc-biaryl **11**. Many conditions were screened for removal of the *N*-Boc group; however, in all cases, amide **12** was observed as a side product (Scheme 4). Amide formation was minimized using methanesulfonic acid; however, **12** was still formed in ∼5% yield. Amide **12** was not rejected by crystallization and could only be separated from **1** by column chromatography.

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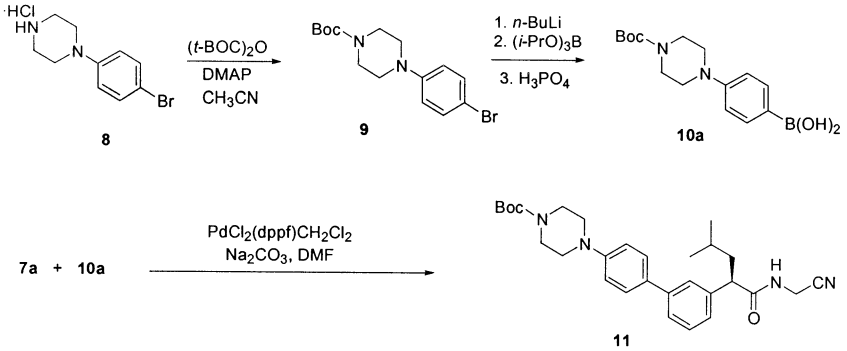
SCHEME 3



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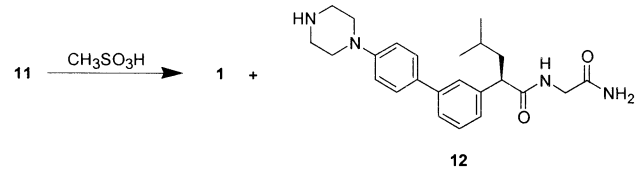
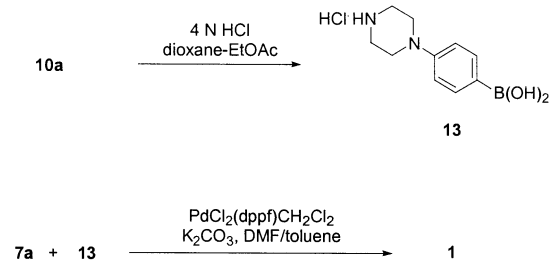


SCHEME 5



To avoid chromatography on a large scale, we turned our attention to a Suzuki coupling using unprotected boronic acid **13** (Scheme 5). The *N*-Boc group was effectively removed from piperazine **10a** using 4 N HCl in dioxane−ethyl acetate to give boronic acid **13**, isolated as a hydrochloride salt in 86% yield. Various reaction conditions were investigated for the Suzuki coupling of unprotected boronic acid **13** with aryl bromide **7a**. Limited success was achieved using $Pd_2(dba)_3$ or $Pd(OAc)_2$ with various solvent/phosphine/base combinations. Switching to 5 mol % $PdCl_2(dppf)\cdot CH_2Cl_2$ in DMF, the reaction was complete in 3 h at 80 °C. Upon optimization, the best conditions were found to be 3 mol % $PdCl_2(dppf)\cdot CH_2Cl_2$ as a catalyst with aqueous K_2CO_3 as a base in 10:1 toluene/DMF at 80 °C. Under these conditions, the reaction was complete within 2 h to afford **1** in 89% yield.

Despite the widespread use of palladium-mediated reactions on a research scale, their use on an industrial scale has had limited success. This is in part due to the high cost of palladium, and equally importantly, to the cost and difficulty of separating the palladium catalyst from the product. The removal of homogeneous palladium in an organic chemistry context is an issue that has been generally neglected in the literature.[12] Removal of even small amounts (parts per million levels) of catalyst can be very difficult, especially as standard workups or crystallizations often fail to reduce levels to the low parts per million range that is essential for the preparation of an active pharmaceutical ingredient (API). Therefore, it is generally undesirable to use a homogeneous transition metal catalyst in the final synthetic step of an API. Such reactions are often positioned early in the synthesis, thus allowing subsequent processing to help in reducing residual catalyst levels.

In an effort to address the cost of palladium and minimize the amount of palladium in solution, a number of reports have recently appeared describing heterogeneous recyclable catalysts. Thus, palladium catalysts on silica,[13] Pd/C,[14] and palladium on polymer supports[15] have been investigated in the Suzuki coupling reaction. Unfortunately, many of these heterogeneous catalysts suffer from lower catalyst activity than their homogeneous counterparts. In addition, the activity of the catalyst diminishes through recycling because palladium leaches from the solid support. Parrish and Buchwald have reported[16] polymer-supported dialkylphosphinobiphenyl ligands that upon treatment with a palladium source provide highly active recyclable catalysts for the Suzuki coupling reaction. However, for the Suzuki coupling of aryl bromide **7a** and boronic acid **13**, these ligands were unsuccessful when examined under homogeneous conditions.

We were therefore not surprised to find that as a consequence of our synthetic change, the levels of Pd and Fe in isolated crude **1** were ~8000 ppm. Neither chromatography nor treatment of crude **1** with n-Bu_3P[17] significantly reduced residual Pd/Fe levels. Consequently, an efficient workup procedure was required to remove the residual Pd and Fe from crude **1**. Due to the lability of the nitrile group of **1** under acidic conditions, aqueous solutions of strong acids could not be used to extract the product. Various organic acids were screened, and we were delighted to find that lactic acid formed a water-

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soluble salt of **1** and did not hydrolyze the nitrile group. Thus, crude **1** (~8000 ppm Pd/Fe) was dissolved in ethyl acetate and treated with 20 mol % *n*-Bu_3P. The mixture was extracted with aqueous lactic acid and the aqueous layer washed with ethyl acetate. The lactic acid salt was broken by addition of Na_2CO_3 and the product extracted into ethyl acetate. The ethyl acetate layer was concentrated and the product crystallized from toluene to give **1** with <50 ppm Pd and Fe. A final swish with acetonitrile gave **1** of excellent purity.

Summary

An efficient, large-scale, chromatography-free synthesis of cathepsin K inhibitor **1** has been developed. The key steps include deracemization of acid **3a** via in situ trapping of ketene **4a** with (*R*)-pantolactone and a Suzuki coupling of boronic acid **13** with bromide **7a** to generate the biaryl linkage and complete the convergent synthesis. A simple and efficient workup was developed using lactic acid to remove residual palladium and iron from **1** following the Suzuki coupling.

Experimental Section

General Procedures. All commercially available substrates, reagents, and solvents were used without further purification. ^{1}H NMR spectra were run at 500 MHz and ^{13}C NMR spectra at 125 MHz. Onedia Research Services, Inc., Whitesboro, NY, provided elemental analyses. High-resolution mass spectra (HRMS-FAB$^+$) were obtained at the Biomedical Mass Spectrometry Unit, McGill University, Montréal, Québec, Canada. The enantiomeric excess was determined by HPLC using chiral analytical columns. Melting points are uncorrected. Chiral assay of **1** was measured by SFC.

2-(3-Bromophenyl)-4-methylpentanoic Acid (3a). To a solution of 3-bromophenylacetic acid **2** (1.8 kg, 8.37 mol), DMPU (1.8 L, 14.88 mol), and 1-iodo-2-methylpropane (1.6 kg, 8.69 mol) in THF (9 L) at −20 °C was added LHMDS (1 M in THF, 17.6 L, 17.6 mol) over ~3 h maintaining a temperature between −19 and −22 °C. The mixture was aged for 4 h at a temperature between −15 and −20 °C and warmed to room temperature over 16 h. The batch was cooled to −5 °C, and HCl (6 N, 5.5 L) was added over 2 h maintaining the temperature at <20 °C. The lower aqueous layer was separated and the THF layer concentrated under vacuum to yield a viscous oil. The oil was dissolved in a premixed solution of methanol (7.2 L) and water (2.1 L). The temperature was adjusted to 20−22 °C, and water (0.5 L) was added, followed by seed (10 g). The batch was aged for 1 h during which time crystallization occurred. Water (8.1 L) was added over 3 h and the batch aged overnight at room temperature. The batch was filtered and the cake washed with 2/3 v/v methanol/water (2 × 3 L). The cake was dried under vacuum at 30 °C for 24 h to yield **3a** (1.92 kg, 85% yield). An analytically pure sample was obtained by recrystallization from heptane. HPLC: Zorbax SB C18 250 mm × 4.6 mm column. Eluents: A, 0.1% aqueous H_3PO_4; B, acetonitrile; 2 mL/min. Gradient: A:B from 95:5 to 20:80 in 16 min, held at 20:80 for 4 min. λ = 220 nm, temperature 35 °C. t_R: **2** = 10.1 min, **3a** = 14.3 min. Mp: 84−84.7 °C. ^{1}H NMR ($CDCl_3$): δ 7.48 (t, 1H, J = 1.6 Hz), 7.25 (app d, 1H), 7.40 (bd, 1H, J = 7.8 Hz), 7.19 (t, 1H, J = 7.8 Hz), 3.62 (t, 1H, J = 7.8 Hz), 1.94 (m, 1H), 1.66 (m, 1H), 1.48 (m, 1H), 0.91 (app d, 6H). ^{13}C NMR ($CDCl_3$): δ 179.9, 140.5, 131.0, 130.4, 130.0, 126.6, 122.5, 49.0, 41.7, 25.5, 22.3, 22.0. IR: 2957, 1702, 1571, 1212, 783, 690 cm^{-1}. Anal. Calcd for $C_{12}H_{15}BrO_2$: C, 53.16; H, 5.59 Found: C, 53.24; H 5.61.

(3*R*)-4,4-Dimethyl-2-oxotetrahydrofuran-3-yl-(2*R*)-(3-bromophenyl)-4-methyl Pentanoate (5). To a solution of **3a** (920 g, 3.39 mol) and DMF (5.1 mL, 0.066 mol) in toluene (13.8 L) was added oxalyl chloride (516 g, 4.06 mol). The mixture was aged at room temperature for 1.5 h. The solution was cooled to 8−10 °C and *N*,*N*′-dimethylethylamine (744 g, 10.17 mol) added over ~10 min. The temperature rose to 18 °C during the addition, and the batch was aged for 2 h at room temperature. The mixture was cooled to −69 °C, and a solution of (*R*)-(−)-pantolactone (529 g, 4.06 mol) in toluene (15.9 L) was added over 3 h while maintaining the temperature <−64 °C. The mixture was aged at <−40 °C for 16 h, warmed to room temperature, and quenched with water (9 L). The aqueous layer was separated, and the toluene layer was washed with saturated sodium bicarbonate (2 × 5 L) and water (5 L). The organic layer was concentrated under reduced pressure to give ester **5** (1.25 kg, 96% yield, 87% de). $[\alpha]_D^{25}$ = +7.9 (*c* 1.48, MeOH). HPLC: Zorbax SB C18 250 mm × 4.6 mm column. Eluents: A, 0.1% aqueous H_3PO_4; B, acetonitrile; 2 mL/min. Gradient: A:B from 95:5 to 20:80 in 16 min, held at 20:80 for 4 min. λ = 220 nm, temperature 35 °C. t_R: **3a** = 14.3 min, **5** = 17.6 min. Chiral HPLC: Chiralcel OD-R, 250 mm × 4.6 mm column. Eluents: A, 72% 0.5 M $NaClO_4$/$HClO_4$ pH = 2; B, 28% acetonitrile; 2.0 mL/min. λ = 220 nm, temperature 50 °C. t_R: (*R*,*R*)-**5** = 33.2 min, (*S*,*R*)-**5** = 36.2 min. ^{1}H NMR ($CDCl_3$): δ 7.52 (t, 1H, J = 1.6 Hz), 7.41 (bd, 1H, J = 7.8 Hz), 7.29 (bd, 1H, J = 7.8 Hz), 7.20 (t, 1H, J = 7.8 Hz), 5.32 (s, 1H), 4.02−3.97 (m, 2H), 3.78 (t, 1H, J = 7.8 Hz), 2.02 (m, 1H), 1.73 (m, 1H), 1.54 (m, 1H), 1.15 (s, 3H), 1.04 (s, 3H), 0.95 (d, 3H, J = 6.5 Hz), 0.94 (d, 3H, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$): δ 172.2, 171.6, 140.2, 130.9, 130.4, 129.9, 126.6, 122.4, 75.9, 75.1, 49.9, 41.1, 40.0, 25.7, 22.9, 22.2, 22.1, 19.6. IR: 2961, 1795, 1745, 1146, 995, 760 cm^{-1}. HRMS (FAB+) *m*/*z* 383.0857 [M + H$^+$, calcd for $C_{18}H_{23}BrO_4$, 383.0858].

(2*R*)-2-(3-Bromophenyl)-4-methylpentanoic Acid (6a). Pantolactone ester **5** (1.92 kg, 6.72 mol) was dissolved in methanol (22 L). The mixture was cooled to 0 °C, and hydrogen peroxide (30% in water, 1.9 L, 18.4 mol) was added. Aqueous lithium hydroxide (4 N, 1.85 L, 7.4 mol) was added over 45 min while maintaining the temperature at <5 °C. The mixture was aged for 2 h to complete the hydrolysis. The pH of the solution was adjusted to pH = 1 by addition of HCl (6 N, 1.4 L). Aqueous sodium sulfite (2 M, 8.74L, 17.5 mol) was added over 45 min, maintaining the temperature at <20 °C. The pH was adjusted to pH = 6 by addition of HCl (6 N, 4 L). Toluene (30 L) was added and the lower aqueous layer separated. The toluene layer was washed with water (2 × 5 L and 2 × 3 L) to give 1.7 kg of acid **6a** (93% yield, 83% ee) as assayed by HPLC. Chiral HPLC: Chiralcel OD-R, 250 mm × 4.6 mm. Eluent: A, 72% 0.5 M $NaClO_4$/$HClO_4$ pH = 2; B, 28% acetonitrile, 2.0 mL/min, λ = 220 nm, temperature 50 °C. t_R: (*R*)-**6** = 37.6 min, (*S*)-**6** = 40.6 min. The toluene solution of acid **6a** was concentrated under reduced pressure and the remaining oil dissolved in a mixture of 2-propanol (51 L) and water (2.5 L). (*R*)-(+)-α-Methylbenzylamine (760 g. 6.27mol) dissolved in 2-propanol (1 L) was added in one portion. A precipitate formed immediately, and the mixture was heated to 77 °C at which point all the precipitate dissolved. The mixture was cooled to 20−25 °C over 16 h during which time the salt precipitated. The salt was filtered, washed with 2-propanol (2 × 5 L), and dried under vacuum at 35 °C for 24 h to yield 2.05 kg (77.6% yield from **5**, 98.5% ee). Mp: 180−183 °C. Chiral HPLC: Chiralcel OD-R, 250 mm × 4.6 mm column. Eluents: A, 72% 0.5 M $NaClO_4$/$HClO_4$ pH = 2; B, 28% acetonitrile; 2.0 mL/min. λ = 220 nm, temperature 50 °C. t_R: (*R*)-**6a** = 37.6 min, (*S*)-**6a** = 40.6 min. ^{1}H NMR (methanol-d_4): δ 7.57 (t, 1H, J = 1.7 Hz), 7.43−7.36 (m, 5H), 7.31 (bt, 2H, J = 7.8 Hz), 7.16 (t, 1H, J = 7.8 Hz), 4.37 (q, 1H, J = 6.9 Hz), 3.51 (t, 1H, J = 6.8 Hz), 1.91 (m, 1H), 1.58 (d, 3H, J = 6.9 Hz), 1.54−1.46 (m, 2H), 0.91 (app d, 6H). ^{13}C NMR (methanol-d_4): δ 181.4, 146.8, 140.3, 132.0, 130.9, 130.2, 130.1, 130.0, 128.0, 127.6, 123.1, 54.3, 52.2, 44.5, 27.4, 23.1, 23.0, 21.0. Anal. Calcd for $C_{20}H_{26}BrNO_2$: C, 61.23; H, 6.68; N, 3.57. Found: C 61.48; H 6.42; N 3.85.

To a suspension of acid **6a** as its I-methylbenzylammonium salt (1.994 kg, 5.08 mol) in toluene (25 L) was added HCl (1 N, 12.7 L). The mixture was agitated until dissolution was

complete. The layers were separated, and the toluene layer was washed with HCl (1N, 5 L) and water (5 L). The mixture was solvent switched to THF to give 1.38 kg as assayed by HPLC (75.5% yield from **5**, 98.5% ee) of free acid **6a**. A pure sample of chiral acid **6a** was prepared by crystallization from hexanes, mp 68−70 °C, $[\alpha]_D^{25} = -41.1$ (*c* 1.19, MeOH). For ^{1}H and ^{13}C NMR data, see **3a** above.

(2*R*)-2-(3-Bromophenyl)-*N*-(cyanomethyl)-4-methylpentamide (7a). To a solution of acid **6a** (1.38 kg, 5.09 mol) in THF (20 L) was added *N*,*N*′-carbonyldiimidazole (988 g, 6.09 mol) portionwise over ∼5 min, maintaining the temperature ∼20 °C. After 30 min, aminoacetonitrile hydrochloride (938 g, 10.13 mol) was added over ∼5 min followed by addition of *N*,*N*-diisopropylethylamine (1.97 kg, 15.21 mol) over ∼5 min. The mixture became homogeneous after an additional 10 min. The batch was aged for 2.5 h at room temperature to complete the reaction. The reaction was quenched by addition of phosphoric acid (3 M, 6.8 L), followed by addition of toluene (18 L). The aqueous layer was separated, and the toluene layer was washed successively with aqueous phosphoric acid (1 M, 2 L), aqueous sodium bicarbonate (2 × 5 L), and water (3 L). The organic layer was concentrated under vacuum to yield amide **7a** as a pale yellow oil (1.53 kg, 97.5% yield, 98.1% ee). $[\alpha]_D^{25} = -47.7$ (*c* 1.49, MeOH). HPLC: Zorbax SB C18 250 mm × 4.6 mm column. Eluents: A, 0.1% aqueous H_3PO_4; B, acetonitrile; 2 mL/min. Gradient: A:B from 95:5 to 20:80 in 16 min, held at 20:80 for 4 min. $\lambda = 220$ nm, temperature 35 °C. t_R: **6a** = 14.3 min, **7a** = 13.8 min. Chiral HPLC: Chiralcel OD-R, 250 mm × 4.6 mm column. Eluents: A, 72% 0.5 M $NaClO_4$/$HClO_4$ pH = 2; B, 28% acetonitrile; 2.0 mL/min. $\lambda = 220$ nm, temperature 50 °C. t_R: (*R*)-**7a** = 56.9 min, (*S*)-**7a** = 65.2 min. ^{1}H NMR ($CDCl_3$): δ 7.45 (t, 1H, J = 1.6 Hz), 7.40 (bd, 1H, J = 7.8 Hz), 7.23 (bd, 1H, J = 7.8 Hz), 7.20 (t, 1H, J = 7.8 Hz), 6.76 (bt, 1H), 4.12 (dd, 1H, J = 17.5, 6.0 Hz), 3.97 (dd, 1H, J = 17.5, 5.6 Hz), 3.51 (t, 1H, J = 7.7 Hz), 1.96 (m, 1H), 1.70 (m, 1H), 1.44 (m, 1H), 0.90 (d, 3H, J = 6.5 Hz), 0.89 (d, 3H, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$): δ 173.4, 141.2, 131.0, 130.8, 130.5, 126.4, 122.7, 115.9, 50.0, 41.7, 27.5, 25.4, 22.6, 21.8. IR: 3304, 2957, 2262, 1656, 1529, 768, 690 cm^{-1}. HRMS (FAB+) *m*/*z* 309.0603 [M + H$^+$, calcd for $C_{14}H_{17}BrN_2O$, 309.0602].

***tert*-Butyl-4-(4-bromophenyl)piperazine-1-carboxylate (9).** To a slurry of 1-(4-bromophenyl)-piperazine hydrochloride (1.86 kg, 7.71 mol) in acetonitrile (16 L) were added triethylamine (2.03 kg, 20.06 mol), DMAP (81.8 g, 0.67 mol), and di-*tert*-butyl dicarbonate (1.75 kg, 8.01 mol). The resultant slurry was aged at 20−25 °C for 3 h. Water (40 L) was added over 20 min. The slurry was aged at 20−25 °C for 30 min and filtered. The wet cake was washed with water (10 L) and dried under vacuum/nitrogen at 55 °C for 12 h to give *N*-Boc piperazine **9**, 2.19 kg (95% yield). Mp: 146.3−147.5 °C. ^{1}H NMR (acetone-d_6): δ 7.38 (t, 2H, J = 9.1 Hz), 6.96 (d, 2H, J = 9.1 Hz), 3.56−3.54 (m, 4H), 3.18−3.15 (m, 4H), 1.48 (s, 9H). ^{13}C NMR (acetone-d_6): δ 155.0, 151.5, 132.6, 119.0, 112.1, 79.8, 49.7, 44.3, 28.6. IR: 2948, 1687, 1494, 1442, 1266, 733 cm^{-1}. HRMS (FAB+) *m*/*z* 341.0865 [M + H$^+$, Calcd for $C_{15}H_{21}BrN_2O_2$, 341.0865]. Anal. Calcd for $C_{15}H_{21}BrN_2O_2$: C, 52.77; H, 6.20, N, 8.21. Found: C, 52.85; H, 5.90; N, 8.17.

4-[4-(*tert*-Butoxycarbonyl)piperazin-1-yl]phenylboronic Acid (10a). To a mixture of THF (7 L) and toluene (7 L) was charged *N*-Boc piperazine **9** (1.14 kg, 3.34 mol). The solution was cooled to −70 °C, followed by dropwise addition of *n*-BuLi (1.6 M in hexanes, 2.3 L, 3.67 mol) while maintaining the temperature below −60 °C. The mixture was aged at −70 °C for 20 min followed by the addition of triisopropyl borate (752 g, 3.99 mol). The mixture was warmed to 0 °C, and the reaction was quenched with saturated aqueous NH_4Cl (4 L) and water (1 L). Phosphoric acid (85 wt %, 461 g, 4.0 mol) was added and the mixture agitated for 30 min. The organic layer was separated and concentrated under vacuum to give a dark blue slurry. The volume of the slurry was adjusted to ∼2 L with toluene. Heptane (8 L) was added dropwise over 2 h to the slurry. The slurry was filtered, and the wet cake was washed with heptane (2 L) and dried under vacuum/nitrogen for 12 h to give *N*-Boc boronic acid **10a** (940 g, 92%). Mp: 187−189 °C. ^{1}H NMR (DMSO-d_6, 3 drops of D_2O): δ 7.67 (d, 2H, J = 7.9 Hz), 6.88 (d, 2H, J = 8.0 Hz), 3.43 (s, 4H), 3.12 (s, 4H), 1.40 (s, 9H). ^{13}C NMR (DMSO-d_6, 3 drops of D_2O): δ 154.5, 152.6, 135.9, 123.6, 114.8, 79.7, 48.1, 43.8, 28.5. IR: 2976, 1695, 1602, 1366, 1227, 737 cm^{-1}. Anal. Calcd for $C_{15}H_{23}BN_2O_4$: C, 58.84; H, 7.57; N, 9.15. Found C, 58.94; H, 7.27; N, 9.08.

4-Piperazin-1-ylphenylboronic Acid Hydrochloride (13). To *N*-Boc boronic acid **10a** (930 g, 3.38 mol) in ethyl acetate (15 L) was added a solution of HCl in dioxane (4 N, 2.4 L, 9.6 mol). The resultant slurry was aged at ambient temperature for 6 h and filtered. The cake was washed with ethyl acetate (4 L) and dried under vacuum/nitrogen for 12 h to give phenylpiperazine boronic acid hydrochloride **13** (634 g, 86% yield). This material was used directly in the Suzuki coupling reaction. Mp: 161−162 °C. ^{1}H NMR (DMSO-d_6, 3 drops of D_2O): δ 7.69 (d, 2H, J = 8.5 Hz), 6.97 (d, 2H, J = 8.5 Hz), 3.46−3.42 (m, 4H), 3.23−3.19 (m, 4H). ^{13}C NMR (DMSO-d_6, 3 drops of D_2O): δ 151.2, 136.4, 122.8, 115.8, 46.2, 43.0. IR: 3343, 3285, 2405, 1397, 845, 741 cm^{-1}. An analytically pure sample of the boronic acid as a free base was prepared by treatment with NaOH followed by column chromatography. ^{1}H NMR (DMSO-d_6, 3 drops of D_2O): δ 7.63 (d, 2H, J = 8.7 Hz), 6.85 (d, 2H, J = 8.7 Hz), 3.11 (s, 4H), 2.83 (s, 4H). ^{13}C NMR (DMSO-d_6, 3 drops of D_2O): δ 153.6, 136.2, 123.4, 114.7, 48.8, 45.7. Anal. Calcd for $C_{10}H_{15}BN_2O_2$: C, 58.29; H, 7.34; N, 13.60. Found C, 58.06; H, 7.03; N, 13.53.

(2*R*)-*N*-Cyanomethyl-4-methyl-2-(4′-piperazin-1-yl-1,1′-biphenyl-3-yl)pentanamide (1). To a mixture of toluene (12 L), DMF (1.2 L), and H_2O (3.6 L) were added bromide **7a** (569 g, 1.84 mol), boronic acid **13** (669.3 g, 2.18 mol), K_2CO_3 (1.27 kg, 9.2 mol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (50 g, 0.0612 mol). The slurry was degassed by bubbling N_2 through for 30 min. The mixture was heated to 80−85 °C for 2 h. The mixture was cooled to 30 °C. EtOAc (12 L), H_2O (2 L), and tri-*n*-butylphosphine (75 g, 0.37 mol) were added. The layers were separated, and the organic layer was washed with H_2O (12 L). The organic layer was concentrated under reduced pressure to a volume of 1−2 L. The residue was washed with hexanes (5 L), and the solid that formed (crude **1**) was filtered and washed with hexanes (3 × 4 L).

To crude **1** (1010 g) in ethyl acetate (20 L) was added tri-*n*-butylphosphine (56 g, 0.277 mol) and the mixture aged for 1 h at room temperature. Water (15 L) and lactic acid (85%, 808 g, 7.6 mol) were added. The layers were separated, and the aqueous layer was washed with ethyl acetate (3 × 5 L). The combined organic layers were washed with water (5 L). The combined aqueous layers were added to a suspension of solid sodium carbonate (805 g, 7.6 mol) in ethyl acetate (15 L) and the mixture agitated for ∼15 min until the carbonate was dissolved. The aqueous layer was separated and the ethyl acetate layer washed with water (5 L). To the organic layer Darko KB® (200 g) and Solka Floc 40NF (200 g) were added. The mixture was aged overnight at room temperature, filtered through a bed of Solka Floc 40NF, and the cake washed with ethyl acetate (4 L). The batch was concentrated under reduced pressure and solvent switched to toluene. The volume was adjusted to bring the concentration to 10 mL/g. The batch was heated to 75 °C until completely dissolved, cooled to 65 °C and seeded. The slurry was cooled to room temperature over ∼8 h, filtered, and washed with toluene (2 L). The filter cake was dried under vacuum to yield **1** (640 g, 89% yield from amide **7**).

Compound **1** (590 g) was suspended in acetonitrile (5.9 L) and the mixture agitated for 16 h at room temperature. The slurry was filtered and washed with cold (0−5 °C) acetonitrile (2 L). The filter cake was dried under vacuum at 25 °C for 48 h to yield pure **1** (522 g, 88.5% recovery, 79% overall yield from amide **7a**, Fe/Pd <30 ppm, >99% ee). $[\alpha]_D^{25} = -47.9$ (*c* 2.14,

MeOH). Mp: 144−146 °C; HPLC: Zorbax SB C18 250 mm × 4.6 mm column. Eluents: A, 0.1% aqueous H_3PO_4; B, acetonitrile; 2 mL/min. Gradient: A:B from 95:5 to 20:80 in 16 min, held at 20:80 for 4 min. $\lambda = 220$ nm, temperature 35 °C. t_R: **1** = 8.5 min. Chiral SFC-HPLC Chiralpak AD 250 × 4.6 mm column, gradient 4−40% MeOH at 2%/min, held for 10 min, 1.5 mL/min, 300 bar, $\lambda = 215$ nm, 35 °C. Sample preparation: ∼1 mg of **1** was dissolved in 1 mL of acetonitrile, and 3−5 drops of acetic anhydride were added; assay. t_R: (*R*)-**1** = 20.4 min, (*S*)-**1** = 17.4 min. ^{1}H NMR (DMSO-d_6): δ 8.78 (t, 1H, J = 5.6 Hz), 7.53−7.48 (m, 3H), 7.45 (d, 1H, J = 7.7 Hz), 7.34 (t, 1H, J = 7.7 Hz), 7.20 (d, 1H, J = 7.6 Hz), 7.01 (d, 2H, J = 8.6 Hz), 4.12 (dd, 2H, J = 5.4, 3.3), 3.65 (t, 1H, J = 7.7 Hz), 3.11−3.08 (m, 4H), 2.86−2.84 (m, 4H), 1.96−1.90 (m, 1H), 1.59−1.52 (m, 1H), 1.44−1.38 (m, 1H), 0.90 (app d, 6H). ^{13}C NMR (DMSO-d_6): δ 174.3, 151.9, 141.7, 141.1, 130.9, 129.7, 128.0, 126.4, 126.1, 125.2, 118.5, 116.3, 50.0, 49.9, 46.5, 42.9, 28.0, 26.5, 23.3, 23.2. IR: 3296, 2957, 2262, 1679, 1521, 1239, 733 cm^{-1}. HRMS (FAB+) *m*/*z* 391.2497 [M + H$^+$, calcd for $C_{24}H_{31}N_4O$, 391.2498]. Anal. Calcd: C, 73.81; H, 7.74; N, 14.35. Found C, 73.87; H, 7.64; N, 14.28.

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