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Suzuki−Miyaura Approach to JNJ-26076713, an Orally Active Tetrahydroquinoline-Containing $\alpha_V\beta_3/\alpha_V\beta_5$ Integrin Antagonist. Enantioselective Synthesis and Stereochemical Studies

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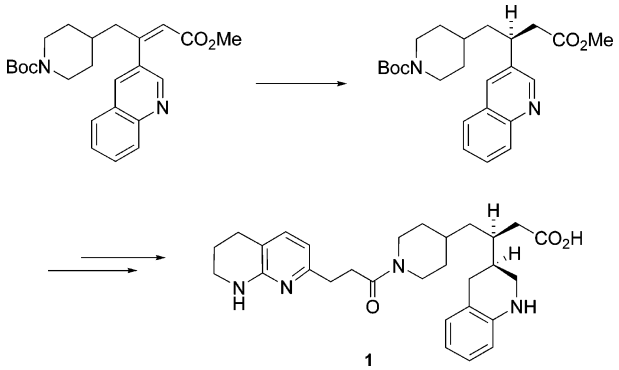

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An improved scale-up synthesis was required for the $\alpha_V\beta_3/\alpha_V\beta_5$ integrin antagonist **1**, which had demonstrated oral efficacy in eye disease models of angiogenesis and vascular permeability. A stereodefined, quinoline-substituted, unsaturated ester was conveniently prepared by a Suzuki−Miyaura coupling to facilitate exploration of multiple methods of asymmetric reduction. The catalytic chiral hydrogenation of the corresponding unsaturated acid (*Z*-**5b**) with a ruthenium-based metal precursor and the (*R*)-XylPhanePhos ligand proved particularly efficient and economical. The resulting (3*S*)-quinoline-containing intermediate was reduced to an equal mixture of tetrahydroquinoline diastereomers. The undesired diastereomer could be recycled to the desired one by an oxidation/reduction protocol. The absolute stereochemistry of **1** was established as 3*S*,3′*S* by a combination of X-ray diffraction and chemical means.

Introduction

Integrins are heterodimeric transmembrane receptors that are generally involved in migration, invasion, proliferation, and survival of cells. The $\alpha_V\beta_3$ integrin is expressed in several cell types, such as osteoclasts, endothelial cells, vascular smooth muscle cells, and certain tumor cells. Although the normal level of expression is typically low, expression is greatly enhanced in pathological conditions involving tissue remodeling and growth. The integrin $\alpha_V\beta_3$, which recognizes matrix proteins containing the cell-adhesion tripeptide motif arginine-glycine-aspartic acid (RGD), mediates various biological processes, including angiogenesis. Antagonists of $\alpha_V\beta_3$ have been described as potential treatments for osteoporosis, tumor growth/metastasis, diabetic retinopathy, and vascular restenosis.[1]

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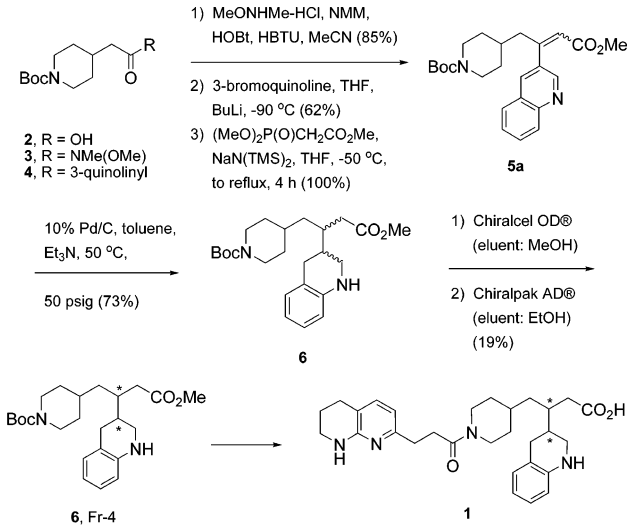
Recent human and animal efficacy data for established $\alpha_V\beta_3$/$\alpha_V\beta_5$ integrin antagonists have attracted renewed interest to this class of therapeutic agents. For example, the potent orally active $\alpha_V\beta_3$ selective integrin antagonist L-845704[2] was shown to be efficacious in increasing bone mineral density in postmenopausal women with osteoporosis.[3] In addition, this clinical agent was generally well tolerated for up to 12 months, which might otherwise have been a concern because of inhibition of angiogenesis. In this vein, the pan-α_V antibody CNTO-95 did not affect wound healing in cynomolgus macaques.[4] A cyclic RGD-containing peptide prevented angiogenesis in a mouse retinopathy (ROP) model[5] and a rat choroidal neovasularization study,[6] suggesting potential for the treatment of eye diseases, such as age-related macular degeneration (AMD) and diabetic retinopathy (DR). The nonpeptide dual $\alpha_V\beta_3/\alpha_V\beta_5$ antagonist SB-267268, which also demonstrated efficacy in the ROP model, is in phase I clinical studies for AMD.[7]

We have developed a series of piperidinyl-linked dual $\alpha_V\beta_3$/$\alpha_V\beta_5$ antagonists[8a] and identified one diastereomer of 1,2,3,4-tetrahydroquinoline (THQ), **1** (JNJ-26076713, Scheme 1), for evaluation based on its good potency, selectivity, oral bioavailability, and half-life.[8b] Recently, we reported that **1** exhibited oral efficacy in eye disease models of angiogenesis (ROP) and vascular permeability, a first for an $\alpha_V\beta_3$ integrin antagonist.[8c] To support further profiling of this promising candidate (**1**), process optimization and scale-up synthesis were initiated.

The original synthesis of **1** (Scheme 1)[8b] was not optimal for several reasons. First, the instability of the 3-lithioquinoline reagent necessitated the use of low temperature and an excess of reagents to afford a reasonable yield of **4**. This issue limited batch size and complicated purification of the product. Second, the unsaturated ester **5a** was generated as a mixture of *Z*- and *E*-isomers by the Horner−Wadsworth−Emmons reaction. These isomers would make an enantioselective reduction of the olefin challenging. Third, hydrogenation of **5a** generated an equal mixture of all four diastereomers **6**, which had to be separated by two sequential chromatographies on chiral columns. Although this process was scalable, it was inefficient in that only one diastereomer was needed (fraction-4, Fr-4, slowest eluting on Chiralpak AD-H), while the other three were discarded. A new synthetic route was designed to impart improved throughput and control of the olefin geometry within **5a**, thereby addressing two of the above issues and making possible the enantioselective reduction of the olefin in **5a**. Although effective enantioselective reductions of stereodefined unsaturated esters[9] and acids have been described in the literature,[10] our system presents a more structurally complex example.

SCHEME 1. Initial Synthesis of 1



Abbreviations: HBTU, *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; HOBt, 1-hydroxybenzotriazole; NMM, *N*-methylmorpholine.

Results and Discussion

Synthetic Studies. We envisaged a Suzuki−Miyaura[11] approach to a stereodefined, quinoline-containing, unsaturated ester **5a** by using vinyl triflate **8** and quinoline boronic acid **9** (Scheme 2). The approach taken by Romero and Romero in the preparation of an HIV-1 protease inhibitor gave us guidance.[10] The new synthesis started with the original starting material, carboxylic acid **2**, which was converted into the β-keto ester **7** by using a standard protocol. The β-keto ester was converted to the enol triflate with sodium hydride and Hünig's base to buffer the reaction medium. Without Hünig's base, the Boc-group was cleaved under the reaction conditions from a significant proportion of the material. Use of Hünig's base alone, without sodium hydride, afforded an (*E*,*Z*)-mixture of enol triflates, but the use of sodium hydride and Hünig's base together provided the *Z*-enol triflate with high selectively (<3% *E*-

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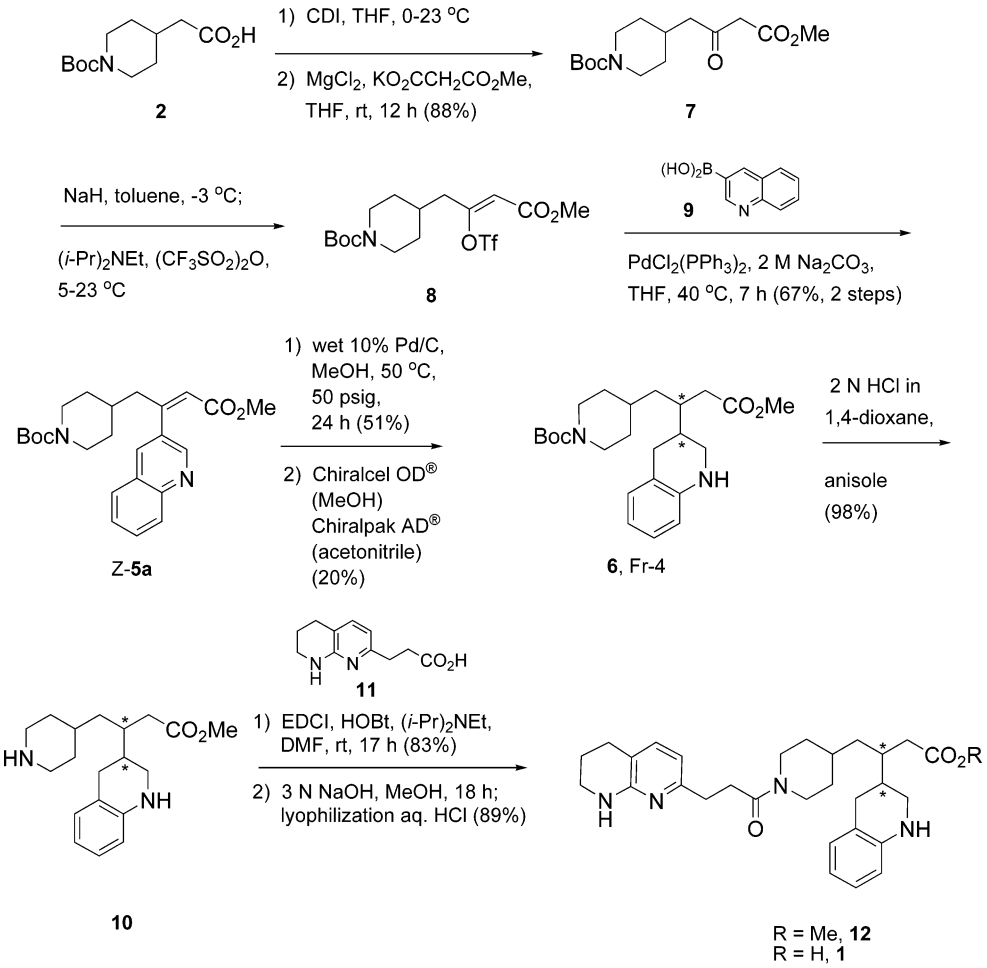
SCHEME 2. Stereoselective Synthesis of (*Z*)-5a and Conversion to 1



Abbreviations: CDI, 1,1'-carbonyldiimidazole; EDCI, *N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide

isomer). Enol triflate **8** was stable for weeks at 5 °C (^{1}H NMR), but it was typically made and used within a day or two. The Suzuki−Miyaura reaction gave a good yield of (*Z*)-**5a**, the stereochemistry of which was confirmed by NOE studies. There was a significant NOE between the vinylic proton and the methylene protons adjacent to the piperidine ring.

A sample of (*Z*)-**5a** was retained for examination of chiral reductions, but the remaining material was converted to **1** to supply our in vivo efficacy studies. The double bond and pyridine ring of (*Z*)-**5a** were reduced with hydrogen by using 10% Pd/C in wet methanol at elevated temperature. The modest yield (51%) was partly due to an unidentified impurity in the starting material, estimated to be 15% by ^{1}H NMR. The equal mixture of diastereomers **6** was purified by sequential chiral chromatography, yielding 20% of the desired diastereomer **6**, Fr-4, in excellent purity (96% desired diastereomer). Deprotection of the Boc-group with HCl afforded piperidine **10**, which was coupled with **11** by using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and Hünig's base. These conditions were devised to simplify the purification and prevent oxidation of the tetrahydroquinoline to the quinoline. The resulting ester **12** was purified by silica gel chromatography, as a final clean up before conversion to **1**. Saponification of the ester afforded acid **1**, which was extracted into dichloromethane as the zwitterion (pH 6.5). Conversion to the hydrochloride was done by adding 2 mol equiv of hydrochloric acid solution and then lyophilizing to an amorphous hygroscopic powder that was stored refrigerated under argon. This procedure afforded a 40-g batch of **1** for biological evaluation. For further scale-up campaigns, progress on a stereoselective synthesis was required.

Chiral copper-mediated hydrosilylations of (*Z*)-**5a** were evaluated (Scheme 3). Initially the Lipshutz[9b] asymmetric hydrosilylation was investigated (Method A) by using copper hydride ([(Ph$_3$P)CuH]$_6$, Stryker's reagent)[12] in the presence of the chiral di-*tert*-butyl ligand of the (*R*,*S*)-JOSIPHOS series.[13] A sample of (*Z*)-**5a** was reduced with 10% palladium on carbon at low pressure and the reaction was stopped when the double bond of the enoate was reduced to afford **13a** as a mixture of isomers.[8b] This racemate **13a** was used as a reference standard to develop a chiral HPLC assay. The enantiomers of **13a**, as well as the starting enoate (*Z*)-**5a**, all readily separated on Chiralpak AD or Chiralpak AD-H columns. Ester (*Z*)-**5a** (50 mg) was added to a toluene solution of the JOSIPHOS ligand (∼0.2 mol %), the Stryker reagent (2.4 mol %), polymethylhydrosiloxane (PMHS), and butanol at 0 °C. Since the reaction was only about 5% complete after 3−4 h, additional quantities of Stryker's reagent (3 mol %) and JOSIPHOS ligand (6 mol

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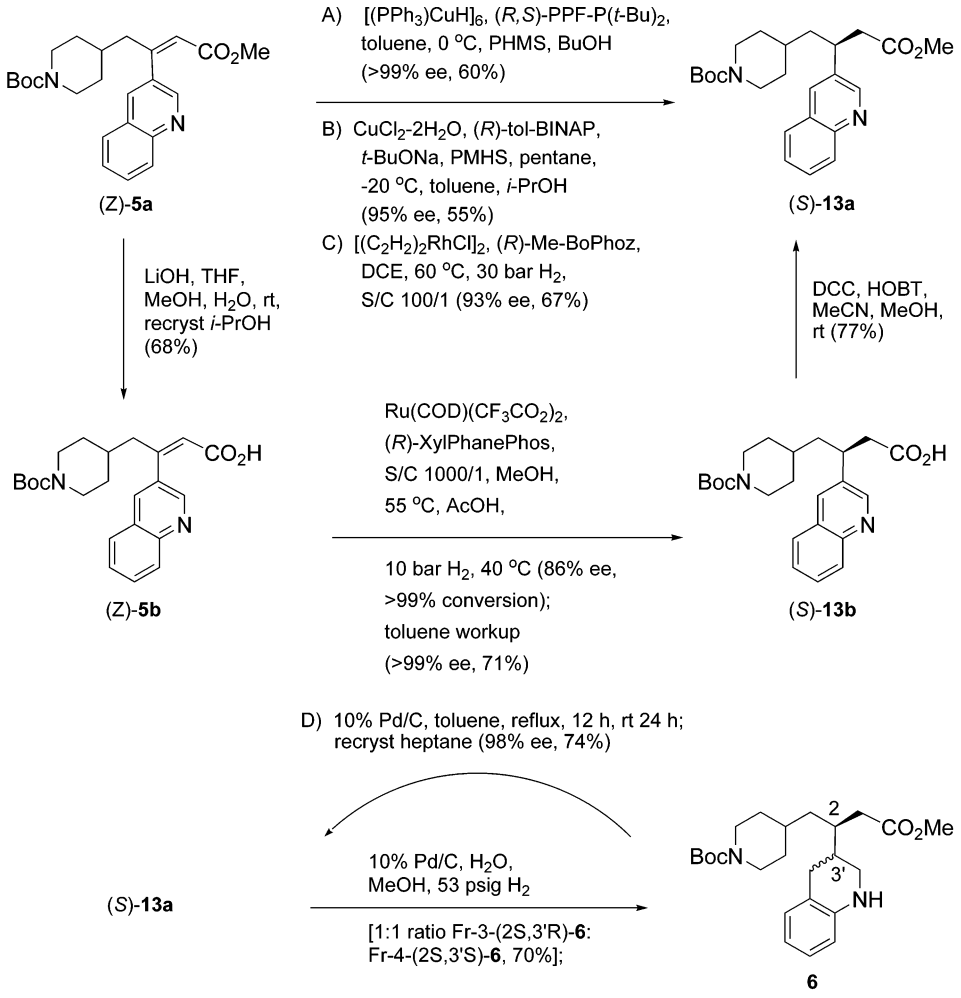
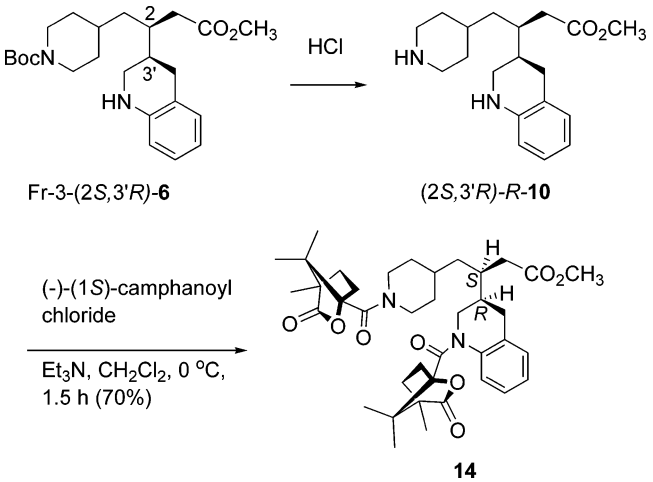
SCHEME 3. Stereoselective Hydrogenation of (*Z*)-5a or 5b



Abbreviations: BINAP, 2,2'-bis(phosphino)-1,1'-binaphthyl; COD, 1,5-cyclooctadiene; DCE, 1,2-dichloroethane; (*R*)-Me-BoPhoz, (*R*)-*N*-methyl-*N*-diphenylphosphino-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine; PHMS, polymethylhydrosiloxane; PPF, diphenylphosphinoferrocene; S/C, substrate-to-catalyst ratio; XylPhanePhos, 4,12-bis(di-3,5-xylylphosphino)-[2.2]-paracyclophane.

%) were added, and the reaction was placed in a cold room for several days. The reaction was ~50% complete in 72 h. After workup and purification, the hydrosilylated product was determined to have an enantiomeric purity of 84% ee, by means of the chiral HPLC assay. Efforts were made to drive this reaction to completion. Use of *tert*-butyl alcohol resulted in low conversion or no reaction. Increasing the amount of JOSIPHOS ligand to 3 mol % at the start, followed by subsequent additions of 3 mol %, along with additional Stryker reagent led to the best conversions. Under optimized conditions product (*S*)-**13a** was isolated in 60% yield along with starting material, which co-elutes as an 82:18 mixture (^{1}H NMR). Analysis of the mixture by chiral HPLC indicated >99% ee. However, any remaining (*Z*)-**5a** would result in generation of the 2-position isomers in equal amounts in the subsequent step. The Buchwald hydrosilylation procedure (Scheme 3, method B),[9a] using the (*R*)-tol-BINAP ligand, delivered (*S*)-**13a** in 55% isolated yield with more complete conversion (>95%) and excellent enantioselectivity (95% ee). Product **13a** was proven to have the (*S*)-absolute stereochemistry by hydrogenating **13a** to **6**, which was isolated primarily as a mixture of two THQ diastereomers, Fr-3 and Fr-4. The absolute configuration of **6**, Fr-3, was determined to be 2*S*,3′*R* by single-crystal X-ray analysis of its (1*S*)-(−)-camphanic acid derivative **14** (Scheme 4). Compound **6**, Fr-4, must have the (2*S*,3′*S*) orientation and the product **13a**, from which they were derived, must have the (*S*)-orientation. To determine the absolute configuration of **6**, Fr-4, we initially

SCHEME 4. Absolute Stereochemistry Assignment of Fr-3-6



explored vibrational circular dichroism (VCD) in conjunction with ^{1}H NMR. As the preferred conformations were not clear in such a flexible molecule, the prediction was not useful without prior knowledge of the X-ray conformation.

Attention was then directed toward homogeneous hydrogenation of the ester (*Z*)-**5a** and the acid (*Z*)-**5b** (Scheme 3). Asymmetric hydrogenation of substrate (*Z*)-**5a** in a parallel screen of ligands and catalysts determined[14a] that (*R*)-MeBoPhoz-rhodium (method C) produced the required transformation with high enantioselectivity (93% ee; (*S*)-**13a**) and full conversion (>97%). Because of the high catalyst loadings (substrate/catalyst, S/C = 100/1) and high pressure (30 bar) required for efficient conversion, substrate (*Z*)-**5b** was also examined. Saponification of (*Z*)-**5a** generated (*Z*)-**5b** with approximately 10% of the (*E*)-isomer, which was removed by recrystallization along with the unknown impurity in (*Z*)-**5a**. Catalyst screening and optimization of asymmetric homogeneous conditions was performed on substrate (*Z*)-**5b** with a better outcome.[14b] A ruthenium-based catalyst prepared from Ru(COD)$(CF_3CO_2)_2$, (R)-XylPhanePhos ligand, and acetic acid gave excellent conversions (>99%) at low catalyst loadings (S/C 1000/1) and reasonable pressure (10 bar) in methanol at elevated temperature (40 °C). The initial 86% ee of (*S*)-**13b** could be upgraded by precipitating the undesired enantiomer from toluene during the workup (>99% ee, 72% yield). Prior to chiral HPLC analysis of the acids (*Z*)-**5b** and **13b**, the aliquot was treated with TMS−CH=N_2 to form the esters. The (*S*)-**13b** was easily converted back to methyl ester (*S*)-**13a** to connect back into the original synthetic route. Methyl ester (*S*)-**13a** was converted to the mixture of diastereomers (2*S*,3′*S*)-**6** and (2*S*,3′*R*)-**6**, which could be separated by chiral HPLC. The undesired diastereomer (2*S*,3′*R*)-**6** was recycled to the quinoline (*S*)-**13a** by controlled oxidation with 10% Pd/C and air (refluxing toluene). Then, the diastereomeric mixture **6** can be regenerated again, yielding additional (2*S*,3′*S*)-**6**. With optimization of the yields and procedures, this recycling procedure could offer a practical means of obtaining (2*S*,3′*S*)-**6**.

In summary, we have described a convenient scale-up synthesis of lead compound **1**. The Suzuki−Miyaura coupling provided stereodefined quinoline-substituted olefins (*Z*)-**5a** and (*Z*)-**5b**, which allowed us to explore multiple methods of chiral reduction to obtain (*S*)-**13a** and (*S*)-**13b**. The chiral hydrogenation of (*Z*)-**5b** with a ruthenium-(*R*)-XylPhanePhos-based catalyst proved to be particularly efficient (>99% conversion, >99% ee after workup). The quinoline was reduced to an equal mixture of tetrahydroquinoline diastereomers by using 10% Pd/C and the undesired diastereomer could be recycled to the desired one, (2*S*,3′*S*)-**6**.

Experimental Procedures

4-(3-Methoxycarbonyl-2-oxo-propyl)piperidine-1-carboxylic Acid *tert*-Butyl Ester (7). To a 4-necked, 5-L flask, equipped with a Teflon-coated thermocouple, reflux condenser, mechanical stirrer, and a nitrogen inlet, was charged the potassium salt of methyl malonate (320.9 g, 2.056 mol), $MgCl_2$ (92.9 g, 0.976 mol), and THF (1.25 L). The suspension was heated at 50 °C for 5 h, and then cooled to rt. To a separate 3-necked, 1-L flask, equipped with a mechanical stirrer, nitrogen inlet, Teflon covered thermocouple, and septum, was added carbonyl diimidazole (CDI, 333.4 g, 2.056 mol) portionwise over 10 min to a cooled solution of **2** (250.0 g, 1.028 mol) in THF (1.25 L) at 0 °C. The mixture was allowed to warm to rt and stirred for 1.5 h. The solution of the acylimidazole was transferred into the ambient temperature suspension of methyl malonate and $MgCl_2$ and the resulting mixture was stirred for 12 h at rt. The thick white suspension was diluted with EtOAc (1 L), transferred to a separatory funnel, and washed twice with saturated $NaHSO_4$ (2 L). The aqueous phases were combined and extracted with EtOAc (1 L). The combined organic extracts were washed twice with saturated $NaHCO_3$ (500 mL). The combined bicarbonate extracts were back extracted with EtOAc (2 L) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure affording 290 g of crude product as a yellow oil that crystallized upon standing over 5 h. Purification by chromatography on silica gel (200−400 mesh, 1.25 kg, gradient elution with 4 L of hexanes, 4 L of 20% EtOAc/hexanes, and 8 L of 40% EtOAc/hexanes) afforded the β-ketoester **7** (272.1 g, 88%) of as a pale yellow oil that crystallized on standing. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (br s, 2 H), 3.74 (s, 3 H), 3.43 (s, 2 H), 2.79−2.65 (t, J = 12.4 Hz, 2 H), 2.47 (d, J = 6.7 Hz, 2 H), 2.10−1.95 (m, 1 H), 1.7−1.6 (d, J = 12.7 Hz, 2 H), 1.44 (s, 9H), 1.18−1.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 167.7, 154.9, 90.4, 79.6, 52.6, 49.8, 49.6, 43.8, 42.3, 31.9, 31.7, 28.7; LC/MS (ES+) m/z 300.2 (M + 1). Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 60.32; H, 8.15; N, 4.59.

4-(3-Methoxycarbonyl-2-trifluoromethanesulfonyloxyallyl)-piperidine-1-carboxylic Acid *tert*-Butyl Ester (8). To a 4-necked, 5-L flask, equipped with a mechanical stirrer, Teflon-coated thermocouple, addition funnel, and nitrogen inlet, was charged sodium hydride (60% in mineral oil, 30.0 g, 0.752 mol) and toluene (450 mL). The suspension was cooled to an internal temperature of −5 °C and a solution of the β-ketoester **7** (150.0 g, 0.501 mol) in toluene (1200 mL) was added dropwise at such a rate as to maintain the internal temperature below −3 °C during the addition. Once addition was complete the mixture was aged for 40 min at 0 °C, followed by sequential dropwise addition of diisopropylethylamine (436.3 mL, 2.505 mol), followed by trifluoromethanesulfonic anhydride (118.7 mL, 0.706 mol), maintaining the internal temperature below 5 °C during the addition. After the addition was complete, the mixture was allowed to warm to rt and stirred for 1 h. The mixture was cooled to 0 °C, quenched with saturated brine (1.5 L), and diluted with EtOAc (1 L), then the two phases were separated. The organic extract was washed with water (1 L) followed by re-extraction of the combined aqueous phases with EtOAc (1 L). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated affording the vinyl triflate **8** (287 g) as a red-brown oily solid. The material was judged satisfactory for use in the next reaction step by ^{1}H NMR analysis. The signal for the vinyl proton appears at ~6.0 ppm in the *E*-isomer and at 5.75 ppm in the *Z*-isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (s, 1H), 4.1 (br s, 2H), 3.78 (s, 3H), 2.61−2.78 (t, J = 12.6 Hz, 2H), 2.31 (m, 2H), 1.78 (m, 1H), 1.65−1.77 (d, J = 12.8 Hz, 2H), 1.45 (s, 9H), 1.20 (m, 2H), 0.80−1.30 (residual diisopropylethylamine); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.8, 157.0, 154.8, 113.2, 79.8, 52.3, 41.9, 33.7, 31.7, 29.9, 28.6. HPLC Method A (Phenomenex Jupiter: 5 μm, C-18, 300 Å, 4.6 × 250 mm, 29 °C) H_2O:MeCN 90:10 to 10:90 in 15 min, hold at 90:10 for 2 min; flow rate: 1.5 mL min^{-1}; UV detection: 220 nm; H_2O buffered with 0.025% TFA; retention time: 15.39 min.

(2,3-*Z*)-4-(3-Methoxycarbonyl-2-quinolin-3-yl-allyl)piperidine-1-carboxylic Acid *tert*-Butyl Ester ((*Z*)-5a). To a suspension of quinoline-3-boronic acid (**9**, 130.0 g, 0.752 mol), vinyl triflate **8** (216.1 g, 0.501 mol), and bistriphenylphosphine palladium dichloride (17.5 g, 0.025 mol) in THF (1.2 L) was added 2 M Na_2CO_3 (160 mL, 0.32 mol). The mixture was heated to 40 °C and monitored for completion by HPLC analysis. After 7 h the reaction was judged complete (>97% conversion by HPLC) and the mixture was filtered and diluted with EtOAc (1 L). The mixture was washed

(14) (a) Zanotti-Gerosa, A.; Kinney, W. A.; Grasa, G. A.; Medlock, J.; Seger, A.; Ghosh, S.; Teleha, C. A.; Maryanoff, B. E. *Tetrahedron*: *Asymmetry*. Manuscript in preparation. (b) Grasa, G. A.; Zanotti-Gerosa, A.; Ghosh, S.; Teleha, C. A.; Kinney, W. A.; Maryanoff, B. E. *Org. Lett*. Manuscript in preparation.

with $NaHCO_3$ (2 × 2 L) and 0.5 M NaOH (2 × 2 L). The combined aqueous phases were extracted with EtOAc (1 L) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure affording crude **5a** (200 g) as a brown oil. Purification by chromatography on silica gel (1 kg, 70−230 mesh, gradient elution with 4 L of hexanes, 4 L of 10% EtOAc/hexanes, 2 L of 40% EtOAc/hexanes, and 100% EtOAc) afforded a dark brown oily solid. The oily solid was triturated with hexanes (150 mL) and collected by filtration affording α,*β*-unsaturated ester **5a**, which was 96% pure by HPLC analysis (139.1 g, 67%, mp 119−124 °C). NMR analysis indicated lower purity in the aromatic region (15% impurity). The olefin **5a** was the *Z*-isomer as determined by NOE studies (*Z*-isomer vinyl proton resonance at 6.05 ppm, *E*-isomer at 6.28 ppm). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, J = 2.2 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 2.2 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.72 (td, J = 7.0, 1.3 Hz, 1H), 7.56 (td, J = 7.0, 1.3 Hz, 1H), 6.05 (s, 1H), 4.01 (br s, 2H), 3.47 (s, 3H), 2.59 (br s, 2H), 2.51 (d, J = 7.0 Hz, 2H), 1.70−1.60 (m, 2H), 1.42 (s, 10 H), 1.20−1.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.9, 154.9, 154.2, 150.0, 147.7, 133.8, 132.7, 130.0, 129.6, 128.2, 127.6, 127.1, 120.3, 79.6, 51.5, 47.7, 44.0 (br), 34.0, 32.1, 28.6. HPLC Method A: retention time: 11.21 min; LC/MS (ES+) *m*/*z* 411.2 (M + 1). Anal. Calcd for $C_{24}H_{30}N_2O_4$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.87; H, 7.56; N, 6.58. Palladium: 170 ppm by ICP.

4-[3-Methoxycarbonyl-2-(1,2,3,4-tetrahydroquinolin-3-yl)propyl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (6). To a 5-L, 6-necked pressure vessel equipped with a pressure relief valve, pressure gauge, large stirring bar, blast shield, and quick connect gas inlet was charged 10% Pd/C (112.5 g, Degussa type-50% water wet), which was vacuum/N_2 degassed, followed by addition of a solution of (*Z*)-**5a** (150 g, 0.365 mol) in methanol (3.4 L). The mixture was pressurized with H_2 at 50 psig and stirred at ambient temperature for 24 h. The hydrogen pressure was adjusted back up to 50 psig as needed. The reaction was judged complete by TLC (30% EtOAc in hexanes) by disappearance of (*Z*)-**5a**. The reaction mixture was filtered through 150 g of Celite in a glass-fritted filter, and rinsed with additional methanol (6 L). The methanol filtrate was then concentrated under reduced pressure, affording an orange-red gum. The gum was purified by chromatography on silica gel (3.0 kg, 230−400 mesh, gradient elution with 20 L hexanes, 20 L of 10% EtOAc/hexanes, 20 L of 20% EtOAc/hexanes, and then 20 L of 30% EtOAc/hexanes). This afforded racemic **6** (76.0 g, 51%) as an orange gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (m, 2H), 6.61 (t, J = 7.2 Hz, 1H), 6.46 (d, J = 8.4 Hz, 1H), 4.05 (m, 2H), 3.84 (br s, 1H), 3.66 (s, 3H), 3.24 (d, J = 10.5 Hz, 1H), 2.99 (td, J = 10.5, 3.0 Hz, 1H), 2.78−2.55 (m, 5H), 2.46−2.21 (m, 2H), 2.20−1.90 (m, 2H), 1.66 (m, 2H), 1.45 (s, 9H), 1.40−1.00 (m, 4H). HPLC Method A with UV detection at 254 nm: retention time: 11.57 min; purity: 85%; LC/MS (ES+) *m*/*z* 417.4 (M + 1).

Isolation of Fr-4, (2-*S*,3′-*S*)-4-[3-Methoxycarbonyl-2-(1′,2′,3′,4′-tetrahydroquinolin-3′-yl)propyl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (6). Racemic **6** (323 g, 0.775 mol) was purified by sequential chiral chromatography. In this paper, the isomer numbering is based on Chiralpak AD elution order (Fr-4, last eluting). Previously, the Chiralcel OD column was used for numbering, thereby reversing the order of Fr-2 (c) and Fr-3 (b).[8b] Crude **6** was a 1/1/1/1 ratio of Fr-1, -2, -3, and -4. Compound **6**, Fr-1 and Fr-3 were separated from **6**, Fr-2 and Fr-4 by using a Chiralcel OD column [110 mm i.d. dynamic axial compression (DAC) column filled with 2000 g of 20 μm Chiralcel OD (Daicel); temperature of eluent: 28 °C; column wall temperature: 30 °C; eluent: methanol; flow rate: 750 mL/min]. The sample was prepared by dissolving 5.8 g of **6** in 200 mL of the eluent (29 mg/mL) and injected at a rate of 3.6 runs per hour (20.9 g of **6**/h). The purification was complete after 15 h of continuous chromatography (56 injections). Compound **6**, Fr-2 was separated from **6**, Fr-4 by using a Chiralpak AD column [110 mm i.d. DAC filled with 2000 g of Chiralpak AD; temperature of eluent: 38 °C; temperature of column wall: 40 °C; eluent: acetonitrile (750 mL/min), ethanol (rinsing plug); injection amount: 4 g/ 250 mL of eluent; capacity: 3.5 runs/h (14 g/h)]. Compound **6**, Fr-4 (65 g; 20% yield; 96.1% pure by chiral HPLC; 0.68, 1.87, 1.35% of Fr-1, -2, and -3, respectively) was isolated. Samples of the other fractions were also obtained in similar purity,[8b] but no attempt was made to maximize the quantity of them in this purification. Chiral HPLC Method A: Chiralpak AD (5 μm, 150 mm × 4.6 mm); isocratic ethanol; ambient; flow rate: 1.0 mL/min; UV detection: 254 nm; retention times: **6**, Fr-1, 5.5 min; **6**, Fr-2, 6.0 min; **6**, Fr-3, 7.5 min; **6**, Fr-4, 8.5 min.

(3*S*,3′*S*)-4-Piperidin-4-yl-3-(1,2,3,4-tetrahydroquinolin-3-yl)-butyric Acid Methyl Ester (10). A 3-L, 3-necked, round-bottomed flask, equipped with magnetic stirrer and argon inlet, was charged with compound Fr-4-(2*S*,3′*S*)-**6** (55.22 g, 133 mmol), methoxybenzene (1.44 mL, 13.3 mmol), and 1,4-dioxane (880 mL). This solution was treated with 4 M HCl gas in dioxane (883 mL, 3.53 mol) to give a clear solution that became hazy and deposited a thick red oil that was difficult to stir. A spatula was used to loosen the red oil. After 4 h, additional 4 M HCl/dioxane (90 mL, 0.36 mol) was added and the reaction was stirred for an additional 7 h until complete by LC/MS. The solvent was removed in vacuo at 45 °C to afford a solid that was triturated with ethyl ether (1 L), collected by filtration, and washed with ethyl ether (0.5−1 L). The isolated light pink solid was dried in a vacuum oven (55−60 °C) for 6 h to give **10** as the bis-hydrochloride salt (50.87 g, 98%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.2−6.8 (m, 4H), 3.58 (s, 3H), 3.33−3.21 (m, 3H), 3.0−2.4 (m, 6H), 2.33−2.26 (m, 1H), 2.04 (m, 2H), 1.82−1.76 (m, 2H), 1.59 (m, 1H), 1.4−1.1 (m, 4H). HPLC Method B: >99% area; retention time: 4.85 min; Thermo Betabasic-C-18, 4.6 × 150 mm^2; ambient; H_2O:MeCN 95:5 to 5:95 in 12 min, H_2O and acetonitrile buffered with 0.1% TFA; flow rate: 1.5 mL min^{-1}; UV detection: 210 nm, 254 nm; LC/MS (ES+) *m*/*z* 317.3 (M + 1). Anal. Calcd for $C_{19}H_{28}N_2O_2\cdot 2HCl\cdot 0.35H_2O\cdot 0.60C_4H_{10}O$: C, 57.30; H, 7.98; N, 6.24; Cl, 15.81. Found: C, 56.94; H, 8.13; N, 6.70; Cl, 15.77. Karl Fisher Titration Calcd: 1.41%. Found: 1.39% (w/w).

(3-*S*,3′-*S*)-4-[1-(3−5,6,7,8-Tetrahydro[1,8]naphthyridin-2-yl-propionyl)piperidin-4-yl]-3-(1,2,3,4-tetrahydroquinolin-3-yl)butyric Acid Methyl Ester (12). A 2000-mL, round-bottomed flask, equipped with magnetic stirrer and argon inlet, was charged with a slurry/solution of piperidine (3*S*,3′*S*)-**10** (29.5 g, 75.8 mmol), acid **11** (20.23 g, 83.3 mmol, Adesis Inc., New Castle, DE), 1-hydroxybenzotriazole hydrate (5.89 g, 37.9 mmol), and dimethylformamide (295 mL). This solution was purged with an argon stream (15−20 min) and chilled in an ice bath. To the reaction was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 15.98 g, 83.3 mmol) in one portion and diisopropylethylamine (39.64 mL, 227 mmol) in a dropwise fashion. The reaction was stirred for 60 min, removed from the ice/water bath, and stirred at rt for 17 h. The reaction was complete by LC/MS and was poured into saturated sodium bicarbonate (3 L). The reaction mixture was extracted with ethyl acetate (4 × 750 mL) and the combined organic phases were washed with saturated ammonium chloride (2 × 500 mL) and brine (3 × 500 mL), dried ($MgSO_4$ and Na_2SO_4), and concentrated to give crude amide product (35.4 g). This was dissolved in dichloromethane and loaded onto an Analogix column (2 runs; SiO_2, 220 g) and eluted (linear gradient, dichloromethane to 1:6:3:90 NH_4OH/*i*-PrOH/EtOH/dichloromethane) to give crude **12** (4.1 g), followed by pure **12** (31.7 g). The mixed fractions were dissolved in dichloromethane and loaded onto an Isco column (SiO_2; 120 g) and eluted (linear gradient, dichloromethane to 1.5:6:3:89.5 NH_4OH/*i*-PrOH/EtOH/dichloromethane) to give additional product (2.7 g). After combining and concentrating from chloroform, the total yield of **12** was 34.4 g (83%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.00 (m, 1H), 6.84−6.80 (m, 2H), 6.42−6.38 (m, 2H), 6.28−6.23 (m, 2H), 5.60 (br s, 1H), 4.35 (br d, J = 13 Hz, 1H), 3.82 (br d, J = 13 Hz, 1H), 3.59 (s, 3H), 3.3−3.1 (m, 3H), 3.0−2.8 (m, 2H), 2.7−2.4 (m, 10H), 2.29−2.27 (m, 1H), 1.98 (m, 1H), 1.8−1.4 (m, 6H), 1.30 (m, 1H), 1.14 (m, 1H), 0.88 (m, 2H). HPLC

Method C: >99% area; retention time: 21.3 min; Agilent Eclipse XDB-C18, 3.0 × 150 mm^2; 45 °C; A:B 85:15 to 15:85 in 27 min, (A) 10 mM ammonium acetate/H_2O, (B) 10 mM ammonium acetate/(H_2O:acetonitrile, 1:9); flow rate: 0.6 mL min^{-1}; UV detection: 220−400 nm; LC/MS (ES+) *m/z* 505.4 (M + 1). Anal. Calcd for $C_{30}H_{40}N_4O_3 \cdot 0.4CHCl_3 \cdot 0.25H_2O$: C, 65.56; H, 7.40; N, 10.06; Cl, 7.64. Found: C, 65.70; H, 7.42; N, 10.09; Cl, 7.89. Residue after ignition: <0.10%. Karl Fisher Titration Calcd: 0.81%. Found: 0.87% (w/w).

(3-*S*,3′-*S*)-4-[1-(3−5,6,7,8-Tetrahydro[1,8]naphthyridin-2-yl-propionyl)piperidin-4-yl]-3-(1,2,3,4-tetrahydroquinolin-3-yl)butyric Acid (1). A 1-L, round-bottomed flask, equipped with magnetic stirrer and argon inlet, was charged with (3*S*,3′*S*)-**12** (34.44 g, 62.8 mmol), methanol (138 mL, 3.40 mol), and 3 M sodium hydroxide solution (62.8 mL, 188 mmol) to give a solution. Argon was bubbled through the solution to remove oxygen (30 min) and the reaction mixture was stirred at rt (18 h) and then concentrated to remove methanol. The oily aqueous residue was diluted with water (700 mL) and the pH was adjusted to 6.5 with 2 N HCl (~100 mL) and NaOH (1 N) to give a white slurry. This slurry was extracted with dichloromethane (3 × 300 mL). The turbid solution of combined organics was diluted with THF, dried (Na_2SO_4), and concentrated to give **1** as a free base (34.7 g, 97%) mixed with THF (~0.75 equiv). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.05 (d, J = 7 Hz, 1H), 6.84−6.80 (m, 2H), 6.43−6.37 (m, 2H), 6.29 (d, J = 7 Hz, 1H), 5.63 (br s, 1H), 4.35 (br d, J = 13 Hz, 1H), 3.82 (br d, J = 13 Hz, 1H), 3.2−3.1 (m, 3H), 3.0−2.8 (m, 2H), 2.7−2.4 (m, 9H), 2.34−2.13 (m, 2H), 1.97 (m, 1H), 1.8−1.4 (m, 6H), 1.19 (m, 1H), 1.14 (m, 1H), 0.87 (m, 2H). HPLC Method C: >98% area; retention time: 11.9 min; LC/MS (ES+) *m/z* 491.2 (M + 1). Anal. Calcd for $C_{29}H_{38}N_4O_3 \cdot 0.75 \cdot THF \cdot 0.05CH_2Cl_2 \cdot 0.45H_2O$: C, 69.10; H, 8.14; N, 10.06; Cl, 0.64. Found: C, 68.73; H, 7.68; N, 9.85; Cl, 0.65. Residue after ignition: <0.10%. Karl Fisher Titration Calcd: 1.46%. Found: 1.28% (w/w).

Compound **1**-freebase (41.15 g, 74.85 mmol) was dissolved in water (617 mL), 1 M aqueous hydrogen chloride (150 mL, 150 mmol), and acetonitrile (93 mL). The resulting solution was syringe filtered (0.45 μm, Nylon) into six 600-mL lyophilization bottles and frozen. These bottles were lyophilized for 5 days to give **1**·HCl (40.5 g, 92%, mp 146−148 °C dec). HPLC Method D: >98% area; retention time: 15.9 min; Agilent Eclipse XDB-C18, 3.0 × 150 mm^2; 45 °C; A:B 95:5 to 25:75 in 27 min, (A) 10 mM ammonium acetate/H_2O, (B) 10 mM ammonium acetate/(H_2O:acetonitrile, 1:9); flow rate: 0.6 mL min^{-1}; UV detection: 220−400 nm; LC/MS (ES+) *m/z* 491.2 (M + 1). Anal. Calcd for $C_{29}H_{38}N_4O_3 \cdot 2.2HCl \cdot H_2O$: C, 59.15; H, 7.22; N, 9.51; Cl, 13.25. Found: C, 59.55; H, 7.47; N, 9.55; Cl, 13.75. Residue after ignition: <0.10%. Karl Fisher Titration Calcd: 3.06%. Found: 3.36% (w/w).

Enantioselective Reduction of (*Z*)-5a to (*S*)-4-(3-Methoxycarbonyl-2-quinolin-3-ylpropyl)piperidine-1-carboxylic Acid *tert*-Butyl Ester (*S*-13a). Method A (Lipshutz Method).[9b] To a 15-mL, 2-necked flask equipped with a Teflon coated thermocouple, stirbar, and nitrogen inlet was charged $[(PPh_3)CuH]_6$ (5 mg, 0.016 mmol), (*R*,*S*) PPF(*t*-Bu)$_2$ (2 mg, 0.004 mmol), and toluene (0.4 mL). The mixture was cooled to an internal temperature of 0 °C, and PMHS (18 μL, 0.273 mmol) was added followed by BuOH (125 μL, 1.27 mmol) and a solution of (*Z*)-**5a** (56 mg, 0.137 mmol) in toluene (0.5 mL). After being stirred for 2 h, the solution was allowed to stand for 12 h at 0 °C. Only a trace of reaction was observed as judged by LC-MS analysis. Additional $[(PPh_3)CuH]_6$ (5 mg, 0.016 mmol), (*R*,*S*)-PPF(*t*-Bu)$_2$ (2 mg, 0.004 mmol), PMHS (18 μL, 0.273 mmol), and BuOH (125 μL, 1.27 mmol) were added sequentially, and the mixture was stirred for 4 h at 0 °C then allowed to stand for an additional 12 h at 0 °C without stirring. The reaction was again judged incomplete by LC-MS analysis. Additional $(PPh_3)CuH$ (5 mg, 0.016 mmol) and (*R*,*S*)-PPF(*t*-Bu)$_2$ (2 mg, 0.004 mmol) were added and the mixture was allowed to stand for 12 h at 0 °C. The reaction was quenched by addition of saturated $NaHCO_3$ (1 mL), and the mixture was stirred for 2 h at rt. The mixture was extracted with EtOAc (20 mL) and washed with additional saturated $NaHCO_3$ (10 mL) followed by water (10 mL), then the organic extract was dried over Na_2SO_4, filtered, and concentrated, affording a yellow semisolid as a 82:18 mixture of saturated to unsaturated ester by ^{1}H NMR analysis. The mixture was purified by chromatography on silica gel (15 g, 70−230 mesh), eluting first with hexanes (100 mL) and then 50% EtOAc/hexanes (300 mL). This afforded (*S*)-**13a** (41 mg, 60%) of the product (along with starting material which co-elute, as an 82:18 mixture by ^{1}H NMR). Analysis of the mixture by chiral HPLC indicates >99% ee. Chiral HPLC Method B: Chiralpak AD-H (4.6 × 250 mm^2); isocratic hexane:*i*-PrOH 80:20; 23 °C; flow rate: 1.0 mL min^{-1}; UV detection: 254 nm; retention time: 16.5 min for (*S*)-**13a** and 26.6 min for (*R*)-**13a**.

Method B (Buchwald Method).[9a] To a flask was added copper-(II) chloride dihydrate (2 mg, 0.012 mmol), (*R*)-tol-BINAP (8 mg, 0.012 mmol), sodium *tert*-butoxide (5 mg, 0.052 mmol), and polymethylhydrosiloxane (PMHS, 65 μL) under nitrogen. Pentane (0.8 mL) was added and the reaction mixture was stirred for 2 h and cooled to −20 °C. Compound (*Z*)-**5a** (100 mg, 0.24 mmol) in toluene (0.5 mL) was added followed by isopropanol (74 μL). After 16 h the reaction mixture was treated with saturated sodium bicarbonate solution, extracted with methyl *tert*-butyl ether (2 × 30 mL), dried (Na_2SO_4), and concentrated. The crude material was purified by flash chromatography (9 g, gradient elution with 0 to 50% ethyl acetate in hexane) affording pure (*S*)-**13a** (55 mg, 55% yield). Analysis of the mixture by Chiral HPLC Method B indicates 95% ee and >95% conversion; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.10 (m, 1H), 7.90 (m, 1H), 7.80 (m, 1H), 7.70 (m, 1H), 7.50 (m, 1 H), 4.00 (m, 2 H), 3.55 (s, 3H), 3.45 (m, 2H), 2.70 (m, 1H), 2.50 (m, 2H), 1.80 (m, 2H), 1.60 (m, 1H), 1.40 (s, 9H), 1.3−1.0 (m, 4H); LC/MS (ES+) *m/z* 413.25 (M + 1). Anal. Calcd for $C_{24}H_{32}N_2O_4 \cdot 0.2H_2O$: C, 69.27; H, 7.85, N, 6.73. Found: C, 69.08; H, 7.72; N, 6.35. $[\alpha]^{23}_D$ −23.2 (*c* 0.48, MeOH).

Method C ([Ir(COD)Cl]$_2$/(*R*)-Me-BoPhoz-Catalyzed Hydrogenation). (*R*)-Me-BoPhoz ligand (6.7 mg, 0.011 mmol) and the rhodium precursor $[(C_2H_4)_2RhCl]_2$ (1.9 mg, 0.005 mmol) were loaded in a glass liner. The glass liner was placed in the Argonaut hydrogenator, then the Argonaut was sealed and purged with nitrogen. Dichloroethane (DCE, 1 mL, anhydrous, degassed) was injected via the injection port and the mixture was stirred under nitrogen for 30 min at rt to form in situ the (*R*)-Me-BoPhoz-rhodium catalyst (0.01 mmol, S/C 100/1). After 30 min, (*Z*)-**5a** (410 mg, 1 mmol) in DCE (4 mL) was injected via the injection port. The substrate stock solution was prepared under nitrogen, using anhydrous, degassed DCE. The resulting mixture was purged five times with hydrogen without stirring and five times with hydrogen while stirring. The reaction mixture was stirred at 60 °C, 30 bar H_2, for 16 h. The crude reaction mixture was analyzed for conversion and ee by chiral HPLC Method B and it showed 97% conversion and 93% ee in (*S*)-**13a**. Chiral HPLC Method B: Chiralpak AD-H (4.6 × 250 mm^2); isocratic hexane:*i*-PrOH 80:20; 35 °C; flow rate: 1.0 mL min^{-1}; UV detection: 210 and 254 nm; retention times: 13.2 min for (*S*)-**13a**, 25.9 min for (*R*)-**13a**, 9.6 min for (*Z*)-**5a**. Flash chromatography (2-cm diameter, 30−35% ethyl acetate in heptane) afforded pure (*S*)-**13a** (276 mg, 67%) by NMR and LC/MS.

Method D (Recycling of 6). A solution of (3*S*,3′*R*)-**6**, Fr-3 (21.6 g, 51.9 mmol) was dissolved in dry toluene (420 mL) and 10% Pd/C (11.3 g) was carefully added. The reaction was brought to a gentle reflux under air. The reaction was refluxed for 6 h and left overnight at room temperature. After another 5 h of reflux, additional 10% Pd/C (2.0 g) was added as a slurry in toluene (20 mL). The reaction mixture was refluxed for an additional hour, left at rt overnight, filtered through Celite, washed several times with toluene, and evaporated to give a yellow oil. This material solidified on evaporation over the weekend to give an off-white solid (19.4 g) that was 85−90% pure by NMR and LC. The solid

was recrystallized once from heptane (100 mL) to give (*S*)-**13a** (15.8 g, 74%, mp 90−102 °C) as an off-white solid. Chiral HPLC Method C results: 99% (*S*)-**13a**, 0.56% (*R*)-**13a**; Chiralpak AD-H (4.6 × 150 mm^2); isocratic hexane:*i*-PrOH 80:20; 35 °C; flow rate: 1.0 mL min^{-1}; UV detection: 210 and 254 nm; retention times: 7 min for (*S*)-**13a**, 10 min for (*R*)-**13a**. Anal. Calcd for $C_{24}H_{32}N_2O_4$: C, 69.88; H, 7.82, N, 6.79. Found: C, 69.87; H, 7.98; N, 6.79. Palladium: 169 ppm by ICP.

Achiral Hydrogenation of (*S*)-13a to 4-[3-Methoxycarbonyl-2-(1′,2′,3′,4′-tetrahydroquinolin-3′-yl)propyl]piperidine-1-carboxylic Acid *tert*-Butyl Ester [6, Fr-3 (2-*S*,3′-*R*) and 6, Fr-4 (2-*S*,3′-*S*)]. A sample of (*S*)-**13a** (48 mg, 0.12 mmol), water (90 mg), and 10% palladium on carbon (50 mg) in methanol was hydrogenated in a Parr apparatus at 53 psig for 28 h. After filtration through Celite and evaporation, the residue was purified on silica gel [elution with 30% ethyl acetate (0.1% triethylamine) in heptane] to yield tetrahydroquinoline **6** (35 mg, 70%), as a mixture of Fr-3 (2-*S*,3′-*R*) and Fr-4 (2-*S*,3′-*S*). HPLC Analysis was performed by using Chiral HPLC Method A showing 45% of **6**, Fr-3 and 45% of **6**, Fr-4. Proton NMR and LC/MS was consistent with other batches of **6**.

X-ray Study on 6a, Fr. 3. (−)-(S)-Camphanic Acid Amide of (2*S*,3′*R*)-4-Piperidin-4-yl-3-(1′,2′,3′,4′-tetrahydroquinolin-3′-yl)-butyric Acid Methyl Ester (10, Fr-3). Compound **6**, Fr-3 (2*S*,3′*R*, 4.50 g, 10.8 mmol) was dissolved in 1,4-dioxane (45 mL) and treated with anisole (few drops) and 4 N HCl in 1,4-dioxane (45 mL). After 2 h the reaction mixture was evaporated to give a crude solid (4.5 g). A portion of the solid (2.9 g) was partitioned between saturated sodium carbonate solution (25 mL) and ethyl acetate (25 mL). The organic layer was dried (Na_2SO_4) and evaporated to yield **10**, Fr-3, as a yellow oil (2.06 g, 93%, LC/MS: consistent). Compound **10**, Fr-3 (162 mg, 0.51 mmol) was dissolved in dichloromethane (10 mL) under nitrogen and treated with triethylamine (0.21 mL, 1.5 mmol) and (−)-(*S*)-camphanic acid chloride (277 mg, 1.28 mmol) at 0 °C and stirred for 1.5 h. The reaction mixture was poured into saturated sodium bicarbonate solution (25 mL), extracted with dichloromethane (3 × 25 mL), washed with brine (25 mL), dried ($MgSO_4$), and evaporated. The residue was dissolved in dichloromethane and applied to a flash column (2 cm diameter, gradient elution with 30−35% ethyl acetate in heptane) affording the diamide **14** as a colorless oil, which later turned to a solid (234 mg, 68%). LC/MS (ES+) *m*/*z* 677.0 (M + 1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2−7.1 (m, 4 H), 4.6−4.2 (m, 3H), 3.67 (s, 3H), 3.2−2.8 (m, 3H), 2.6−1.6 (m, 14H), 1.22 (s, 3H), 1.18 (s, 3H), 1.10 (s, 6H), 1.00 (s, 6H), 1.5−0.8 (m, 5H), 0.88 (t, J = 7 Hz, 2H). Anal. Calcd for $C_{39}H_{52}N_2O_8$: C, 69.21; H, 7.74; N, 4.14. Found: C, 69.44; H, 7.94; N, 4.02. A small sample of **14** (23 mg) was dissolved in methanol (3 mL) and water was added dropwise until just cloudy. A small amount of methanol was added to clarify and the sample was left to slowly evaporate with a slightly vented aluminum foil cap. When the first solid came out after 1 day, methanol was added to dissolve again and the evaporation was repeated. This time crystals formed after 5 days (mp 122−132 °C) and were examined by single-crystal X-ray diffraction.

(*Z*)-4-(3-Carboxy-2-quinolin-3-ylallyl)piperidine-1-carboxylic Acid *tert*-Butyl Ester ((*Z*)-5b). Methyl ester (*Z*)-**5a** (16.67 g, 40.6 mmol, >99% *Z*-isomer by NMR estimation) was dissolved in THF (48 mL) and methanol (64 mL). To this solution was added LiOH (8.2 g, 200 mmol) dissolved in water (64 mL). The mixture was stirred at room temperature for 1.5 h. The progress of the reaction was monitored by HPLC. The reaction was quenched with 1 N HCl (95% of theory, 190 mL) to pH 7 on litmus paper, and concentrated on a rotovap at 27 °C. A final amount of 1 M HCl was added (10 mL) with stirring and the solid was collected by filtration then washed with water (2 × 50 mL) to afford acid, which was air-dried and vacuum-dried (60 °C) overnite. The brown solid (15 g) was an Z/E mixture of ∼90:10 by HPLC. This material was recrystallized from *i*-PrOH (200 mL) by heating to reflux to dissolve the material and then allowing it to cool to ambient temperature and aging for 1−2 h. The white solid was isolated by filtration and washed with ice cold *i*-PrOH to afford (*Z*)-**5b** (10.96 g, 68%, mp 216−217 °C). The compound was 98.3% pure *Z*-isomer by HPLC (R_t 6.868 min). The only impurity was the *E*-isomer (1.62% at R_t 6.654 min). HPLC conditions: MeCN:H_2O, 0.1% TFA gradient elution from 10:90 to 90:10 in 12 min, hold 90:10 for 2 min, flow 1.3 mL/min, UV at 254 nm, eclipse column (5 μm, C-8, 4.6 × 150 mm^2); LC/MS (ES+) *m*/*z* 397 (M + 1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (d, J = 2.1 Hz, 1H), 8.02 (m, 2H), 7.82 (d, J = 8.1 Hz, 1H), 7.67 (t, J = 7.2 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 6.35 (br s, 1H), 6.09 (s, 1H), 4.00 (br m, 2H), 2.51 (m, 4H), 1.61 (d, J = 12.6 Hz, 2H), 1.43 (m, 10H), 1.13 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 154.7, 152.1, 149.7, 146.0, 134.4, 132.7, 130.1, 128.0, 127.9, 127.5, 127.1, 121.5, 79.4, 47.1, 43.5, 33.9, 31.8, 28.4. Anal. Calcd for $C_{23}H_{28}N_2O_4$: C, 69.67; H, 7.12, N, 7.07. Found: C, 69.63; H, 7.19; N, 7.06. Palladium: 74 ppm by ICP; ash <0.1%.

4-(3-Carboxy-2-quinolin-3-ylpropyl)piperidine-1-carboxylic Acid *tert*-Butyl Ester (*S*-13b). The ruthenium precursor Ru(COD)-$(CF_3COO)_2$ (0.004 mmol, 1.74 mg) and (*R*)-XylPhanePhos (0.0044 mmol, 3.1 mg) (S/C 1000/1) were loaded in a 5 mL Schlenk tube. The tube was evacuated by performing three vacuum/nitrogen refill cycles and 2 mL of anhydrous, degassed MeOH was injected. The resulting mixture was stirred at 55 °C for 2 h. After 2 h the tube was taken out of the heating bath and glacial HOAc (undegassed, 1.2 equiv, 4.8 mmol, 0.275 mL) was injected. The resulting solution was stirred while cooling (approximately 10 min). The solid substrate (*Z*)-**5b** (4.0 mmol, 1.58 g) was loaded in a 25 mL Parr container and the vessel was sealed, then purged ten times with hydrogen. The pressure was released and the catalyst solution was injected via the injection port. The Schlenk tube was rinsed with 2 mL of MeOH (degassed, anhydrous, 4 × 0.5 mL portions) and injected quickly via the injection port. The resulting mixture was purged 5 times without stirring and 10 times with stirring. The reaction mixture was stirred at 10 bar H_2 and 40 °C. The reaction was sampled after 17 h and analyzed by HPLC, after in situ conversion to the methyl ester: >99% conversion and 86% ee. The crude reaction mixture was treated with Et_3N (4.8 mmol, 0.5 mL), solvent was evaporated, and the product was extracted with CH_2Cl_2/satd NH_4Cl (aq). The CH_2Cl_2 extracts were dried over Na_2SO_4 and filtered, then solvent was evaporated yielding an off-white solid (1.52 g). To this solid was added toluene (30 mL). Upon stirring, a little fine solid formed immediately after addition of toluene. The mixture was left stirring at rt over the weekend. Sampling of the mother liquor showed enhanced ee (>99%). The reaction mixture was filtered and the filtrate was evaporated yielding (*S*)-**13b** as a beige solid (1.13 g, 71%, mp 60−70 °C). The reaction mixtures, generated from the hydrogenation of substrate (*Z*)-**5b**, were analyzed by the chiral HPLC Method C, after in situ derivatization to the corresponding methyl ester. For 0.1 M reactions, a 50 μL reaction sample (2 mg substrate/product, 0.005 mmol) was treated in an HPLC vial with 50 μL of 2 M TMSCH═N_2 in Et_2O (0.1 mmol) and MeOH (1.5 mL). This solution was analyzed by Chiral HPLC Method C: >99% ee; LC/MS (ES+) *m*/*z* 399.3 (M + 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.4 (br m, 1H), 8.86 (s, 1H), 8.07 (m, 2H), 7.82 (m, 1H), 7.66 (m, 1H), 7.55 (m, 1 H), 4.04 (m, 2 H), 3.55 (m, 1H), 2.9−2.4 (m, 4H), 1.9−1.5 (m, 3H), 1.45 (s, 9H), 1.3−1.0 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 154.8, 150.1, 145.8, 137.2, 135.0, 129.5, 128.1, 127.7, 127.1, 79.4, 43.70 (br), 42.6, 42.3, 36.7, 33.3, 32.6, 31.4, 28.4. Anal. Calcd for $C_{23}H_{30}N_2O_4$: C, 69.32; H, 7.59, N, 7.03. Found: C, 69.58; H, 7.92; N, 6.68.

Conversion of Acid (*S*)-13b to Ester (*S*)-13a. Compound (*S*)-**13b** (0.10 g, 0.25 mmol) was dissolved in acetonitrile (9 mL) and treated with 1-hydroxybenzotriazole (0.034 g, 0.25 mmol), dicyclohexylcarbodiimide (0.11 g, 0.53 mmol), and methanol (200 μL, 4.9 mmol) at rt. The reaction mixture was stirred for 4 h, filtered thru 0.45 μm filter, washed with acetonitrile (3 × 3 mL), concentrated in vacuo, and dissolved in dichloromethane. This

solution was washed with saturated sodium bicarbonate solution (2 × 25 mL), water (2 × 25 mL), and brine (2 × 25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The resulting solid was dissolved in boiling heptane. When the suspension was reduced in volume (~1 mL), it was filtered and allowed to crystallize, yielding (*S*)-**13a** as a white solid (0.080 g, 77%), which was pure by LC/MS and ^{1}H NMR.

Supporting Information Available: Information on the X-ray diffraction study of **14** and the NMR spectra of all intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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