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Multi-Kiloscale Enantioselective Synthesis of a Vitronectin Receptor Antagonist

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Abstract:

The development of a novel, cost-effective synthesis of the vitronectin receptor antagonist SB-273005 became necessary as the compound proceeded to Phase 1. A practical synthesis of the compound presented challenges to the process chemist. Chief among the challenges was developing an enantioselective route to the compound. Second was either developing a scalable Mitsunobu coupling of the side chain to the main body or finding alternate chemistry. In this paper we will describe the chemistry we developed which allowed us to make over a hundred kilograms of SB-273005 by a process that we believe is suitable for even larger scale manufacturing.

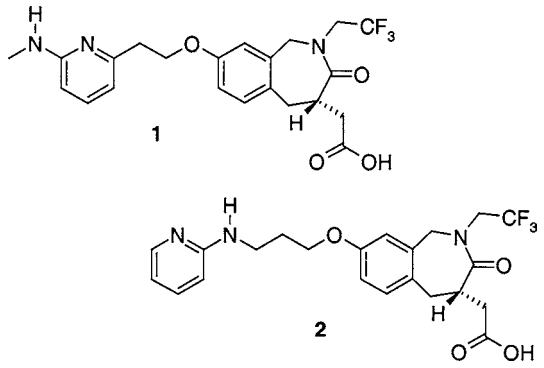

Figure 1. **Active benzazepine compounds.**

The integrin family of transmembrane glycoproteins that acts as cell adhesion receptors and signal transducers include the victronectin receptor, $\alpha v\beta 3$.[1] The vitronectin receptor, $\alpha v\beta 3$, is known to assist a wide variety of biological processes, and as a consequence of this broad activity, it was anticipated that suitably designed antagonists would be useful in the treatment of inflammation,[2] cardiovascular disorders,[3] cancer,[4] and osteoporosis.[5] Two potent second generation $\alpha v\beta 3$ receptor antagonists intended for the treatment of osteoporosis have been reported[6] (Figure 1).

Compound **1** (SB-273005), a 2,4,9-trisubstituted-2-benzazepine-3-one, was discovered by our colleagues in the Medicinal Chemistry group at SmithKline Beecham, and their original synthesis was disclosed with the synthesis of compound **2**.[6] Simultaneous with the Medicinal Chemistry work, new routes were being investigated by members of the Process Chemistry team, and as SB-273005 approached the clinic, a more practical route was deemed a necessity. The topic of this report is to describe the final synthetic route to SB-273005 which is notable for its novelty, brevity, ease to scale, and cost-effectiveness.

Synthetic methods for 2-benzazepin-3-ones are not extensive, but there are examples and probably the most common method for construction is the lactamization of appropriate ortho substituted benzylamines.[7] Indeed, that was the selected method described above by the Medicinal Chemistry group and was blueprinted as the foundation of our plan as well. More recently, that same lactam bond connection strategy was employed by Van Rompaey in the preparation of 2,4-disubstituted 2-benzazepin-3-ones[8] (eq 1, Scheme 1). A different method to generate the C−N bond was employed by Busacca, whereby a dehydrative cyclization between an amide and ketone yielded an acylimine which was successfully hydrogenated to generate the desired benzazepinone structure[9] (eq 2, Scheme 1). In a method that did not construct the benzazepinone ring system through C−N bond formation, researchers at Merck modified the Pictet−Spengler reaction (usually reserved for isoquinoline synthesis) and cyclized onto an acylimine[10] (eq 3, Scheme 1). Other researchers as well have used subtle variations on Pictet−Spengler chemistry to afford the desired benzazepinone skeleton.[11,12] The Schmidt, and Beckman, rearrangements of β-tetralones may also be used to prepare 2-benzazepin-3-ones.[13]

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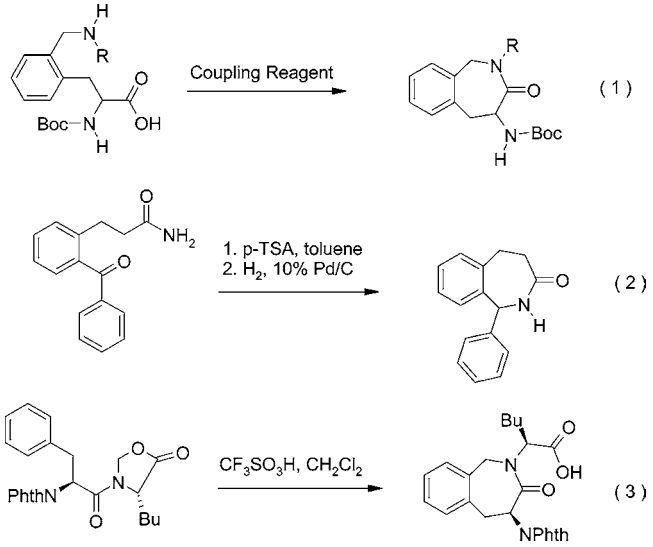
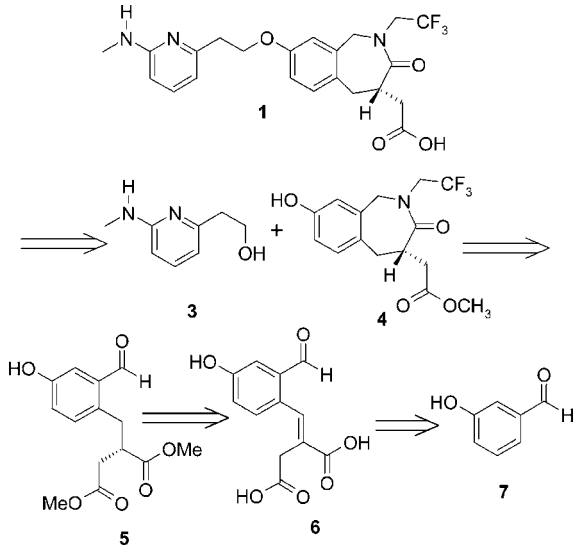
Scheme 1. **Alternate Methods of Benzazepinone Synthesis**

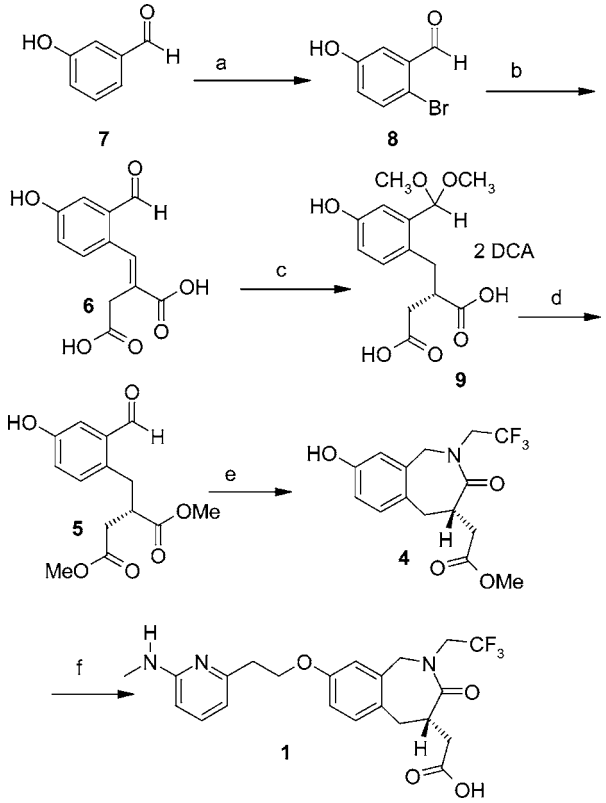


Scheme 2. **Retrosynthetic Analysis of SB-273005**



As mentioned above, our synthetic design of SB-273005 hinged upon the construction of an asymmetric synthesis of an appropriate ortho substituted benzylamine intermediate (which would come about via reductive amination) but additionally relied upon Mitsunobu coupling (if not some other classical means) of the newly prepared chiral 2,4,9-trisubstituted benzazepinone to a 2,6-disubstituted pyridyl alcohol (Scheme 2). Retrosynthetically, SB-273005 was targeted as coming from a routine phenol alkylation of benzazepinone **4** with the previously reported disubstituted pyridine **3**.[14] The alkylation would be brought about via Mitsunobu in the worst case or more likely with compound

Scheme 3. **Synthesis of SB-273005**[a]



[a] (a) Br_2, CH_2Cl_2, reflux, 65%. (b) (1) MeOH, HCl, rt; (2) itaconic acid, Et_3N, $Pd(OAc)_2$, P(o-tolyl)$_3$, Bu_4NBr, CH_3CN, 80%. (c) DCA, $[RuCl_2(R\text{-BINAP})]_2$-$Et_3N$, 60 psi of H_2, 60 °C, MeOH/H_2O, 84%. (d) H_2SO_4, MeOH, reflux, 86%. (e) (1) trifluoroethylamine-HCl, $ZnCl_2$, CH_3CN, reflux; (2) $NaBH(OAc)_3$, DMA; (3) TFA, toluene, reflux, 72%. (f) (1) PPh_3, DIAD, 6-methylamino-2-pyridineethanol (compound **3**), TBME; (2) LiOH H_2O, THF/H_2O, 50 °C, 66%.

3 derivatized as a suitable leaving group (vide infra). Benzazepinone **4** would be synthesized from the chiral diester aldehyde **5** after reductive amination with commercially available trifluoroethylamine. Diester aldehyde **5** was figured to arise from diesterification after asymmetric hydrogenation of unsaturated diacid **6**, which was reasoned as a Heck product from coupling to itaconic acid after bromination of the readily available 3-hydroxy benzaldehyde **7**.

The bromination of inexpensive 3-hydroxybenzaldehyde **7** on a 100 kg scale using Br_2 in CH_2Cl_2 to afford the known bromoaldehyde **8**[15] (Scheme 3) proceeded in reproducible isolated yields of 63−68%. As expected the main problem with this chemistry was formation of the regioisomeric 4-bromo-3-hydroxy benzaldehyde. Fortunately, the desired product crystallized from the reaction mixture without contamination from the regioisomer. Additionally, this simple procedure increased the throughput and minimized the waste. In an effort to address the modest yield, investigations after the plant campaign revealed an improved 75−78% yield when the starting substrate was treated with bromine in glacial acetic acid. Recent articles using both sets of conditions report yields consistent with ours.[16,17]

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(14) Compound **3** was synthesized in 47% yield over seven steps (including two steps for purification). Beginning with commercially available 2-amino picoline, the amine was protected with $(Boc)_2O$, followed by *N*-methylation. The C6 methyl was homologated with diethyl carbonate, followed by $LiBH_4$ reduction of the ester. The amine was deprotected, and purification was carried out by conversion of the crude product to the aqueous soluble formate salt, followed by liberation back to the free base after the impurities were extracted. See ref 6 for details.

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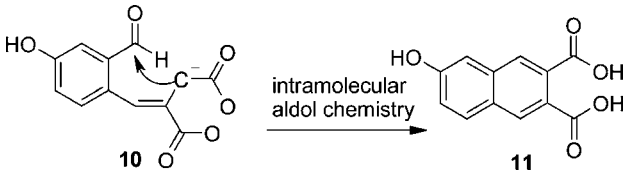


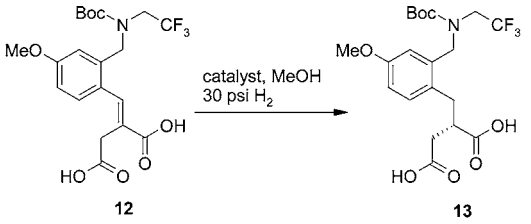
Figure 2. **Intramolecular aldol side reaction.**

The Heck reaction between bromoaldehyde **8** and itaconic acid was carried out by first converting the aldehyde into the dimethylacetal. Simple stirring in methanol with catalytic HCl effected this transformation, and the reaction progress was easily monitored by ^{1}H NMR (the transformation could also be monitored by ReactIR). Treatment of the dimethylacetal with itaconic acid, excess Et_3N, tetrabutylammonium bromide (TBAB), and 1.0% $Pd(OAc)_2$ in a 1:3 molar ratio with respect to tri-*o*-tolylphosphine generated the desired product in 80% yield. In general, the *E* diastereoisomer was the only product observed by ^{1}H NMR. The workup and isolation procedure was tedious and wasteful (mutilple extractions, mutiple solvents, etc.), but it allowed for purification of the product by extraction into aqueous base and residual palladium levels were always less than the heavy metal specification.[18] Additionally, the disposal concerns and decreased throughput were justified by the novelty of the chemical process. Other researchers have coupled itaconate esters to bromoanisoles,[19,20] but our report is the first to address direct coupling of itaconic acid to such a structurally complex aryl bromide.

When the Heck chemistry was carried out directly on bromoaldehyde **8**, intramolecular aldol condensation chemistry of the product occurred as a side reaction (Figure 2). The intramolecular aldol chemistry was presumably base catalyzed given the excess triethylamine and the lower pK_a of the methylene protons of the Heck product. Given the ease with which the acetal of bromoaldehyde **8** was formed and reversed (the aldehyde was easily regenerated upon exposure to aqueous acid), this simple additional transformation permitted us to sidestep the above aldol problem.

With unsaturated diacid **6** in hand, the asymmetric hydrogenation was next examined. Putting this chemistry into practice was more straightforward than we had anticipated. For example, it was known that certain 2(*E*)-alkylidene itaconic acid derivatives had been successfully hydrogenated in the presence of chiral rhodium,[21] and ruthenium,[22] sources. In addition, the application of $Ru_2Cl_4[(+)\text{-BINAP}]_2(Et_3N)$ on 2-acylaminoacrylic acids,[23] and itaconic acid itself,[24] has

Scheme 4. **Catalyst Screen**



Catalyst	% Enantiomeric excess[a]
1. [Ru((S)-BINAP)(Cl)(p-cymene)Cl	8.7%
2. $[Rh(COD)Cl]_2$-(S,S)-DIOP	13.5%
3. $[Rh(NBD)_2]ClO_4$-JOSIPHOS	39.8%
4. [(R,R)-DIPAMP)Rh(COD)]BF_4	52.7%
5. $Ru_2Cl_4[(+)\text{-BINAP}]_2(Et_3N)$	84.2%
6. [(S,S)-DiethylDUPHOS)Rh]CF_3SO_3	89.9%

a. Enantiomeric excess was determined by chiral HPLC – Chiralcel OD-H,

produced high yields of the hydrogenated products in good enantiomeric excesses. Therefore, several commercially available catalysts, including the ruthenium based example above, were screened for their ability to hydrogenate an intermediate diacid (or its corresponding diester) from one of our earlier syntheses (Scheme 4).

Entries 5 and 6 provided the most promising results; however, the results from the rhodium DUPHOS catalyst (entry 6) were not always reproducible. Additionally, the ruthenium catalyst was less expensive,[25] more easily handled (air stable, easier to prepare, etc.), and routinely provided reproducible results. Therefore, it was selected for further development, and when it was applied to unsaturated diacid **6** in methanol (i.e., the dimethylacetal of compound **6**) in the presence of H_2 at 60 psi and 60 °C, consistent yields and ee's were generated (80−85% chemical yield and 90−95% ee). Although the results were encouraging, the hydrogenated diacid would not easily crystallize, and thus a brief crystallization study was undertaken.

Various dicarboxylate salts were examined (Na, K, Et_3N, etc.), but recrystallization of the dicylohexylamine (DCA) salt proved to be the most consistent method. Recrystallization of the DCA salt improved the chemical purity from 95% to >99% and the ee from 94% to >99%. From these results, it was envisaged that DCA could be directly added to the hydrogenation reaction mixture. Fortunately this turned out to be the case, and the crude DCA salt isolated from precipitation of the reaction mixture was generally >98% chemically pure and 98% enantiomerically pure. The general conditions that were developed for this transformation were 2.1 equiv of DCA, 0.2 mol % catalyst, in aqueous methanol at 60 psi of H_2 and 60 °C. A simple solvent swap into acetonitrile effected product precipitation in 84% chemical yield with purity and ee as described above. The catalyst was never recycled. The product was assigned an absolute

(18) Interestingly, the palladium level was of no consequence as it was observed that Heck product contaminated with 1000 ppm of residual palladium underwent asymmetric hydrogenation with ee comparable to the standard case. This result was somewhat surprising to us because we thought that bound palladium might competitively catalyze racemic hydrogenation.
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(25) The cost of $Ru_2Cl_4[(+)\text{-BINAP}]_2(Et_3N)$ was considerably cheaper due to the fact that it was prepared in house (see ref 23 above for preparation).

configuration of (*S*) on the basis of X-ray analysis. In general, material of this quality was then elaborated to API without deterioration of chirality.

The diesterification of diacid acetal **9** to afford diester aldehyde **5** was carried out uneventfully. Refluxing concentrated H_2SO_4 in MeOH served the purpose. The byproduct DCA sulfate salts were easily removed by filtration after a solvent swap into EtOAc, but the filtrate had to be tediously washed with H_2O, 10% H_2SO_4, and $NaHCO_3$ before another solvent swap and isolation in CH_3CN. Typical yields were 85−90%, and the purity was sufficient for direct exposure to the subsequent set of conditions.

The conversion of diester aldehyde **5** to the desired benzazepinone **4** was carried out by a reductive amination−cyclization sequence. First, the Shiff base was formed with trifluoroethylamine-HCl, and catalytic $ZnCl_2$, in refluxing CH_3CN with azeotropic removal of water. The Schiff base intermediate was then reduced to the 2°-amine with $NaBH(OAc)_3$ in DMA. Typically, the Schiff base chemistry was monitored by ^1H NMR. The desired chemistry was always complicated by incomplete consumption of the aldehyde, and after reduction the desired amine product was usually contaminated with 10−15% of the benzyl alcohol product even after workup.[26] After $NaHCO_3$ quench, extraction into EtOAc, and solvent swap into toluene, the crude amine was directly cyclized.

Cyclization of amine diester was conducted with TFA in refluxing toluene. Lactam formation was generally complete within 3−4 h and was unaccompanied by competitive lactone formation from the benzyl alcohol contaminant in the starting material. In addition, as reported earlier,[27] none of the regioisomeric eight-membered ring lactam product was observed. Presumably, the transannular and Pitzer strains are reduced in the transition state leading to the seven-membered ring. After workup (aqueous H_2SO_4, aqueous $NaHCO_3$, and H_2O), the 2,4,9-trisubstituted-2-benzazepin-3-one compound **4** was precipitated from toluene in 72% yield, with >97% chemical purity and >98% ee.

Finally, benzazepinone **4** was coupled to the aforementioned 2-methylamino-6-ethanol pyridine **3** via Mitsunobu chemistry. In the planning stages, the Mitsunobu was thought to be the last method by which we would choose to construct the desired product. Mitsunobu chemistry is environmentally unfriendly, atom uneconomical, and complicated to purify due to the phosphine oxide and hydrazide byproducts. Therefore, the simple Williamson etherification (i.e., phenoxide alkylation with an appropriate leaving group at the ethyl terminus of the 2,6-disubstituted pyridyl alcohol) was considered first.

What was perceived to be a routine phenoxide alkylation was terminally complicated by variable amounts of elimination to vinyl pyridine **16** (Figure 3). Simple modification of the terminal hydroxy of disubstituted pyridine **3** as a tosylate or mesylate (using potassium as the phenoxide counterion) did not increase the amount of alkylation. At that point,

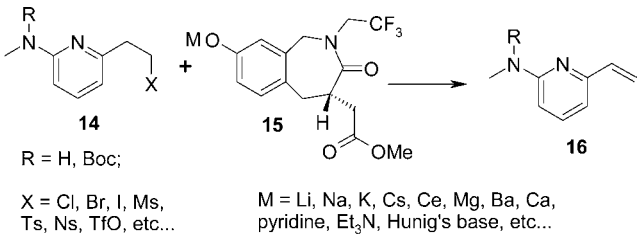

Figure 3. **Elimination problem.**

statistical arrays of experiments[28] were designed using all of the above listed leaving groups and counterions (solvent changes, and concentrations, were also examined). Unfortunately, alkylation was never the major product under any set of conditions, and many times vinyl pyridine **16** was the exclusive product.[29]

Ironically, the chemistry that we had least desired to optimize turned out to be our last hope. The Mitsunobu chemistry was unique in that it was the only method that afforded the desired product in a reasonable yield (80%). This fact necessitated its development. In general, the most reproducible results were achieved using PPh_3 and DIAD as activating agents and TBME as reaction solvent. Typically, the product was contaminated by 10% of starting material benzazepinone **4** and 10% vinyl pyridine **16** in addition to the triphenylphosphine oxide and DIAD hydrazide. Starting material was easily removed with a 1 N NaOH wash. Removal of triphenylphosphine oxide was not quantitative, but approximately 75−80% of it could be removed by precipitation from TBME. The DIAD hydrazide, the vinyl pyridine, and the residual 20% phosphine oxide were not easily removed. Initially, large scale chromatography was considered, but most eluent mixtures did not provide efficient resolutions.

Fortunately, we were able to take advantage of the fact that the subsequent step was a saponification. After the phosphine oxide was filtered off, and the organic layer was washed with 1 N NaOH, the crude mixture in TBME was diluted with an aqueous solution of $LiOH\cdot H_2O$ and the bilayered mixture was refluxed. The desired product was sufficiently aqueous soluble as a carboxylate salt and the organic side products were easily removed by extraction into the organic layer. SB-273005 then precipitated from the aqueous solution after dilution with methanol and acidification with HCl. The crude product was directly recrystallized from MeOH to afford 99% pure SB-273005 in 66% yield over two steps. This streamlined process permitted an otherwise undesirable reaction to be scaled and dramatically reduced any cost that would have been associated with a bulk chromatography.

The overall cost to produce SB-273005 on scale was $2100.00/kg which we believe was a very competitive price given the originality of the overall synthesis. The synthesis included a novel Heck reaction, a new asymmetric hydro-

(26) Unfortunately, ReactIR could not detect the iminium ion, but presumably the rate of consumption of the iminum ion was faster than the aldehyde reduction.

(27) See ref 7.

(28) The equipment used for the numerous experiments was the Anachem SK233 coupled to an Agilent 1100 HPLC.

(29) The chronic failure of this O-alkylation chemistry was thought to be inherent in the electrophile. A preferred anti conformation of the leaving group and pyridine ring would force the nucleophile in an S_N2 type mechanism syn periplanar to the pyridine ring thereby generating unfavorable steric interactions.

genation, and a unique application of the Mitsunobu etherification. The yield for the brief seven-step synthesis was 15% (76% average yield for each step). Finally, the synthetic route was scaled to 100 kg quantities and could be easily scaled to manufacture much greater amounts.

Experimental Section

Reagents from commercial sources were used as is. Tetramethylsilane was used as the internal standard for NMR work.

2-[(2-Formyl-4-hydroxyphenyl)methylidene]succinic Acid (6). 6-Bromo-3-hydroxybenzaldehyde (62 kg, 310 mol, 1.0 equiv) was dissolved in 253 L of MeOH. The resulting solution was filtered. To the solution was added concentrated HCl (1.5 kg, 41.6 mol, 0.13 equiv). The mixture was stirred at room temperature for 2 h. After confirmation by ^{1}H NMR that the dimethyl acetal was completely formed, Et_3N (159 kg, 1571 mol, 5.0 equiv) was added, followed by 615 L of CH_3CN. The reaction mixture was purged with N_2. To the mixture was added itaconic acid (41 kg, 315 mol, 1.0 equiv), $Pd(OAc)_2$ (0.70 kg, 3.1 mol, 0.01 equiv), P(*o*-tolyl)$_3$ (2.9 kg, 9.3 mol, 0.03 equiv), and Bu_4NBr (10 kg, 31 mol, 0.1 equiv). The resulting reaction mixture was heated at reflux for 10 h at which point the reaction was deemed complete by HPLC. After cooling to room temperature, about half of the reaction solvent was removed by distillation. Aqueous KOH solution (235 L at 15% w/w) was added at room temperature. The aqueous solution was washed with 250 L of TBME. The aqueous solution was acidified to pH 1 using 282 L of 3 N HCl solution. The acidic aqueous solution was extracted with 4 × 250 L of TBME. The combined TBME extracts were filtered. About half of the reaction solvent was removed by distillation. To the mixture was added 250 L of acetonitrile. The distillation/dilution process was then repeated 3 times. The heterogeneous solution was cooled to −10 °C for 2 h, and the resulting precipitate was collected. The cream-colored solid product was dried under vacuum (50 °C, 20 in. Hg) to afford 61.3 kg of **6**, 79% yield, 98% pure by HPLC: Ultrasphere ODS 5 μ, 150 mm × 4.6 mm i.d.; conditions, isocratic 20% A/80% B[A = 90% H_2O/10% CH_3CN/0.1% TFA, B = 90% CH_3CN/10% H_2O/0.1% TFA], run time = 30 min, flow rate = 1.0 mL/min, λ = 220 nm. ^{1}H NMR (400 MHz, d_6-DMSO): δ 3.17 (s, 2 H), 7.10 (dd, 1 H), 7.22 (d, 1 H), 7.30 (d, 1 H), 8.11 (s, 1 H), 10.01 (s, 1 H), 10.23 (s, 1 H), 12.51 (bs, 2 H). ^{13}C NMR (75 MHz, d_6-DMSO) δ 192.8, 172.6, 168.6, 158.6, 138.9, 135.5, 131.4, 128.6, 128.0, 121.4, 117.8, 34.0 ppm. MS (Ion Mode: ESI) m/z = 251 $[M + H]^+$, 273 $[M + Na]^+$.

(*S*)-2-Carboxyl-4-[(2-formyldimethylacetal-4-hydroxyphenyl)]butyric Acid, Bis(dicyclohexylamine) Salt (9). 2-[(2-Formyl-4-hydroxyphenyl)methylidene]succinic acid 6 (50 kg, 200 mol, 1.0 equiv) was dissolved in 455 L of refluxing MeOH. After 4 h at reflux, the solution was cooled to ambient temperature and filtered. After the filtrate had been transferred to an appropriate hydrogenation vessel, DCA (77 kg, 425 mol, 2.1 equiv) was added, followed by 50 L of water. After purging and venting with nitrogen, $[RuCl_2$(R-BINAP)$]_2$-TEA (0.125 kg, 0.25 wt %) was added. After purging and venting with hydrogen 3 times, the reaction vessel was maintained at 60 psi of pressure and the contents were heated at 60 °C. The mixture was stirred for 30 h before ^{1}H NMR confirmed the consumption of starting material. The contents were cooled to ambient temperature and filtered. Approximately half of the filtrate was removed by distillation. To the residual mixture was added 400 L of CH_3CN, and the mixture was distilled to approximately half volume. The dilution/distillation process was repeated twice. The residual mixture was cooled to 20−25 °C, and it was held at that temperature for 6 h. The solid was then collected, rinsed with cold CH_3CN, and dried in vacuo (40° C, 20 in. Hg) to afford 111 kg of **9**, 84% yield, 98% pure by HPLC: Hypersil HyPurity Elite C18, 150 mm × 4.6 mm i.d., 5 μ; conditions, isocratic 90% A/10% B [A = 100% H_2O/0.1% TFA, B = 100% CH_3CN/0.1% TFA], run time = 12 min, flow rate = 2.0 mL/min, λ = 223 nm. >98.0% ee by chiral HPLC: Chiralcel OD-H, 250 mm × 4.6 mm i.d., 5 μ; conditions, isocratic 93% hexane/7.0% IPA/0.1% TFA, run time = 30 min, flow rate = 1.0 mL/min, sample concentration = 1.0 mg/mL, λ = 223 nm, desired product (*S*) = 25 min. ^{1}H NMR (400 MHz, d_6-DMSO): δ 1.06−1.88 (overlapping multiplets, 40 H), 2.51 (m, 4H), 2.13 (dd, 1 H), 2.22 (dd, 1 H), 2.43 (dd, 1 H), 3.03 (dd, 1 H), 2.50 (m, 1 H), 3.22−3.23 (2 s, 6 H), 5.40 (s, 1 H), 6.63 (dd, 1 H), 6.87 (d, 1 H), 6.95 (d, 1 H), 9.20 (bs, 1 H). ^{13}C NMR (75 MHz, d_6-DMSO) 177.6, 175.0, 155.6, 137.5, 131.6, 129.1, 115.4, 113.7, 101.4, 53.5, 53.5, 52.7, 44.7, 38.0, 33.1, 31.6, 25.8, 24.7 ppm. MS (Ion Mode: ESI) m/z = 275 $[M + Na]^+$.

Dimethyl (2*S*)-2-[(2-Formyl-4-hydroxyphenyl)methyl]-butanedioate (5). (*S*)-2-Carboxyl-4-[(2-formyldimethylacetal-4-hydroxyphenyl)butyric acid, bis(dicycyclohexylamine) salt **9** (99 kg, 150 mol, 1.0 equiv) was dissolved in 620 L of MeOH. To the solution was added concentrated H_2SO_4 (49 kg, 500 mol, 3.3 equiv). The mixture was heated at reflux for 19 h at which point the reaction was deemed complete by HPLC. The mixture was cooled to 20−25 °C. Approximately 75% of the MeOH was removed by distillation. To the residual mixture was added 485 L of EtOAc. Approximately 70% of the volume was removed by distillation. The dilution/distillation process was repeated 3 times. The solvent was adjusted to approximately 500 L. The mixture was cooled to 0−5 °C, and it was held at that temperature for 1 h. The solid was removed by filtration. The filtrate was extracted with 2 × 240 L of water, 270 L of 10% aqueous H_2SO_4, and 250 L of 8% aqueous $NaHCO_3$. Approximately half of the organic layer was removed by distillation. To the residual mixture was added 240 L of CH_3CN, and the volume was reduced by half. The dilution/distillation process was repeated. The volume was adjusted to approximately 500 L with CH_3CN. The CH_3CN solution was assayed and found to contain 36 kg of **5**, 86% yield, >96% pure by HPLC: Symmetry C18, 4.6 mm i.d. × 250 mm, 5 μ; conditions, isocratic 80% A/10% B [A = 90:10: 0.1 H_2O/CH_3CN/TFA, B = 90:10:0.1 CH_3CN/H_2O/TFA], run time = 15 min, flow rate = 1.0 mL/min, λ = 220 nm. ^{1}H NMR (400 MHz, d_6-DMSO): δ 2.48, 2.60 (dd, 2 H), 2.94 (m, 1 H), 3.13 (m, 1 H), 3.48 (s, 3 H), 3.54 (s, 3 H), 6.98 (dd, 1 H), 7.09 (d, 1 H), 7.21 (d, 1 H), 9.75 (bs, 1 H),

10.10 (s, 1 H). ^{13}C NMR (75 MHz, d_6-DMSO) δ 193.3, 174.4, 172.1, 157.0, 135.2, 133.5, 131.3, 121.5, 117.8, 57.9, 51.9, 43.5, 35.5, 33.0 ppm. MS (Ion Mode: ESI) $m/z = 303$ $[M + Na]^+$.

[(*S*)-9-Hydroxy-3-oxo-2-(2,2,2-trifluoro-ethyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-4-yl]acetic Acid Methyl Ester (4). To (*S*)-2-(2-formyl-4-hydroxybenzyl)succinic acid dimethyl ester **5** (56 kg, 200 mol, 1.0 equiv) in 562 L of CH_3CN was charged trifluoroethylamine-HCl (32.5 kg, 240 mol, 1.2 equiv) and $ZnCl_2$ (13.5 kg, 100 mol, 0.5 equiv). The mixture was heated at reflux, while water and hydrochloric acid were azeotropically removed. After 2−3 h the water content was found to be <1.0%. The mixture was cooled to 20−25 °C. To the imine solution was added $NaBH(OAc)_3$ (92.5 kg, 436 mol, 2.2 equiv) that was dissolved in 244 L of DMA. After 30 min the reaction was deemed complete by HPLC. The mixture was quenched with 160 L of 8.0% aqueous $NaHCO_3$. The mixture was then further diluted with 1120 L of 8% aqueous $NaHCO_3$ and 372 L of TBME. After the layers were separated, approximately half the volume of the organic layer was removed by distillation. The residual mixture was diluted with 265 L of toluene, and it was distilled until approximately half volume. The dilution/distillation process was repeated. The residual mixture was diluted with toluene to approximately 400 L. To the mixture was added TFA (15.4 kg, 135 mol, 0.7 equiv). The mixture was heated at reflux for 4 h at which point the reaction was deemed complete by HPLC. The mixture was cooled to 20−25 °C and then distilled to approximately half volume. To the mixture was added 270 L of EtOAc. The mixture was washed with 270 L of 10% aqueous H_2SO_4, 270 L of 5% aqueous $NaHCO_3$, and 270 L of water. The organic layer was distilled to approximately one-third volume. To the residual mixture was added 230 L of toluene. The mixture was distilled to approximately half volume. The dilution/distillation process was repeated twice. The mixture was cooled to 0−5 °C and held at that temperature for 30 min. The precipitate was collected, washed with toluene, and oven dried in vacuo (40 °C, 20 in. Hg) to afford 47.6 kg of **4**, 72% yield, 99% pure by HPLC: Ultrasphere ODS 150 mm × 4.6 mm i.d., 5 μ; conditions, isocratic 80% A/20% B [A = 90% H_2O/10% CH_3CN/0.1% TFA, B = 90% CH_3CN/10% H_2O/0.1% TFA], run time = 20 min, flow rate = 1.0 mL/min, λ = 240 nm, 98% ee by chiral HPLC: Chiralpak AD 250 mm × 4.6 mm i.d., 10 μ; conditions, isocratic 85% hexane/IPA, run time = 20 min, flow rate = 1.0 mL/min, λ = 230 nm. ^{1}H NMR (400 MHz, d_6-DMSO): δ 2.48, 2.71 (dd, 2 H), 2.64, 2.93 (dd, 2 H), 3.77 (m, 1 H), 3.58 (s, 3 H), 4.14, 4.30 (dq, 2 H), 4.07 (d, 1 H), 5.26 (d, 1 H), 6.57 (d, 1 H), 6.63 (dd, 1 H), 6.90 (d, 1 H), 8.29 (bs, 1 H). ^{13}C NMR (75 MHz, d_6-DMSO) δ 174.6, 172.0, 154.9, 134.8, 131.2, 125.9, 124.7, 115.5, 114.7, 52.1, 51.2, 46.7, 36.2, 36.0, 33.7 ppm. MS (Ion Mode: ESI) $m/z = 354$ $[M + Na]^+$.

***S*-(−)-9-[2-[6-(Methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-(2,2,2-trifluoroethyl)-1,2,4,5-tetrahydro-2-benzaepine-4-acetic Acid (1).** To [(*S*)-9-hydroxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-4-yl]acetic acid methyl ester (50 kg, 151 mol, 1.0 equiv) was added 500 L of TBME. To the heterogeneous mixture was added 6-(methylamino)-2-pyridineethanol (25.3 kg, 166 mol, 1.1 equiv) that was dissolved in 250 L of TBME. To the mixture was added PPh_3 (43.5 kg, 166 mol, 1.1 equiv). The heterogeneous mixture was cooled to 0−5 °C. To the cooled mixture was added DIAD (33.5 kg, 166 mol, 1.1 equiv). The mixture was stirred at 20−25 °C for 2−3 h at which point the reaction was deemed complete by HPLC. The mixture was concentrated to approximately one-third of its original volume. The mixture was cooled to 0−5 °C and stirred at that temperature for 30 min. The solids were removed by filtration. The filtrate was extracted with 100 L of 3 N NaOH and 100 L of brine. To the organic layer was added $LiOH\cdot H_2O$ (13.9 kg, 332 mol, 2.2 equiv) that was dissolved in 125 L of water. The mixture was heated at 50−55 °C for 2−3 h at which point the reaction was deemed complete by HPLC. The mixture was cooled to 20−25 °C, and it was diluted with 375 L of water. The layers were separated, and the aqueous layer was washed with 250 L of TBME. To the aqueous layer was added 125 L of MeOH. The aqueous methanolic mixture was acidified with 10−12 L of concentrated HCl until the pH = 6.0−7.0. The mixture was seeded with authentic product. The mixture was further acidified with 10−12 L of concentrated HCl until pH = 5.0−5.5. The mixture was cooled to 0−5 °C and stirred at that temperature for 30 min. The crude precipitate was collected by filtration. The crude product was dissolved in 450 L of hot MeOH, seeded with pure product, and then allowed to stand at 20−25 °C for 16 h. The recrystallized product was collected by filtration. The product was then oven dried in vacuo (40 °C, 20 in. Hg) to afford 44.9 kg of **1**, 66% yield, 98% pure by HPLC: YMC Basic, 4.6 mm i.d. × 150 mm, 5 μ; conditions, gradient 80% H_2O/CH_3CN to 20% H_2O/CH_3CN over 10 min, run time = 15 min, flow rate = 2.0 mL/min, λ = 233 nm. >98% ee by chiral HPLC: Chiralcel OJ 250 mm × 4.6 mm i.d., 10 μ; isocratic 70% hexane/30% H_2O/0.1% TFA/0.1% diethylamine, run time = 20 min, flow rate = 1.0 mL/min, λ = 234 nm. ^{1}H NMR (400 MHz, d_6-DMSO): δ 2.37, 2.66 (dd, 2 H), 2.66, 2.98 (dd, 2 H), 3.74 (m, 1 H), 4.19 (m, 2 H), 4.13, 5.28 (d, 2 H), 6.78 (m, 1 H), 6.79 (m, 1 H), 7.00 (d, 1 H), 2.93 (t, 2 H), 4.25 (t, 2 H), 2.73 (d, 3 H), 6.32 (q, 1 H), 6.25 (dd, 1 H), 6.41 (dd, 1 H), 7.28 (dd, 1 H), 11.90 (bs, 1 H). ^{13}C NMR (75 MHz, d_6-DMSO) δ 174.7, 173.1, 159.3, 156.2, 155.9, 137.0, 135.1, 131.3, 128.0, 124.7, 114.9, 113.9, 110.6, 105.1, 66.9, 52.0, 46.7, 37.3, 36.4, 36.1, 33.7, 27.9 ppm. MS (Ion Mode: ESI) $m/z = 452$ $[M + 1]^+$.

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