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Asymmetric Synthesis of the Cholesteryl Ester Transfer Protein Inhibitor Torcetrapib

David B. Damon, Robert W. Dugger, Stephen E. Hubbs, Jill M. Scott, and Robert W. Scott*,†

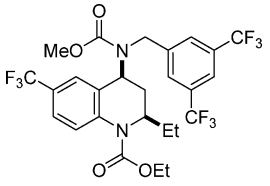
Pfizer Chemical Research and Development, Eastern Point Road, Groton, Connecticut 06340, U.S.A.

Abstract:

Previously our group reported synthetic efforts used to synthesize kilogram quantities of the cholesteryl ester transfer protein (CETP) inhibitor torcetrapib, 1, via a mid-stage resolution. This account describes research conducted to develop an asymmetric route to this clinical candidate suitable for long-term manufacturing. The first asymmetric center is established via coupling of (*R*)-3-aminopentanenitrile to a trifluoromethylarene. After elaboration of the nitrile to a suitable precursor, a key step in the synthesis is diastereoselective cyclization of immonium ion 7 to provide the tetrahydroquinoline core. This approach also permitted a streamlined sequence to complete the synthesis of 1. Development of the process and synthetic rationale are described.

Introduction

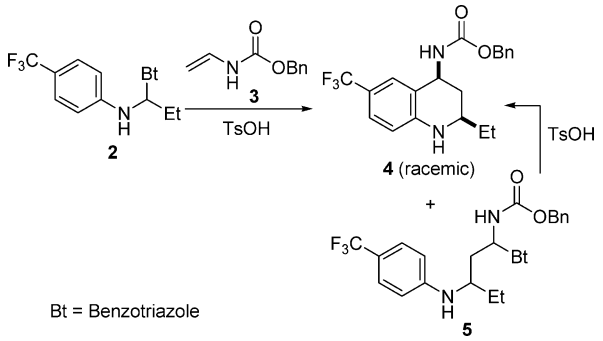
Current therapies for the treatment of atherosclerosis focus primarily on the reduction of low-density lipoprotein cholesterol (LDL-C). Cholesteryl ester transfer protein (CETP) is an agent responsible for the transfer of cholesterol from high-density lipoprotein cholesterol (HDL-C) to LDL-C. A compound that inhibits CETP may therefore be effective at increasing the levels of HDL-C as a treatment of cardiovascular diseases. Torcetrapib (**1**) is a molecule currently undergoing clinical trials as a CETP inhibitor, thereby necessitating a synthetic route amenable to multikilogram-scale synthesis.



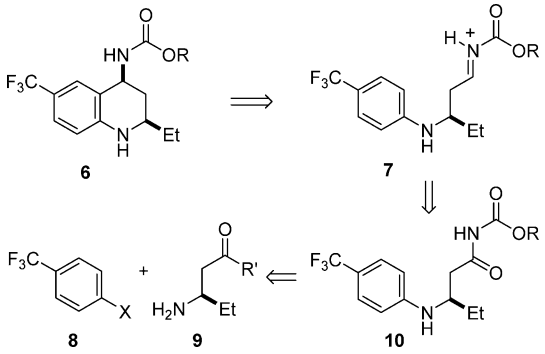
torcetrapib (1)

The preceding paper outlined process research and scale-up for the clinical candidate **1**.[1] The key step in the production of asymmetric material was a diastereomeric salt resolution. Although several multikilogram lots were produced by this resolution route, synthetic efficiency favored development of an asymmetric route to synthesize the tetrahydroquinoline core. The asymmetric route was based on a key discovery during research to develop the cyclization to produce **4** (Scheme 1). From the crude reaction mixture, a byproduct (**5**) was isolated as a 1:1 mixture of diastereomers. Resubjecting **5** to acidic cyclization conditions resulted in clean formation of the desired racemic **4**. The exclusive formation of the desired cis orientation suggested that assembly of a precursor with the C-2 center of defined stereochemistry would provide the desired *syn*-tetrahydroquinoline upon cyclization. In development of a new synthesis, two other factors were considered. First, the continued use of *N*-vinylbenzylcarbamate **3** was undesirable, due to varying quality of this material because of its low stability. Second, we hoped to avoid the use of trifluoromethylaniline as a starting material due to safety issues with long-term storage.[2]

Scheme 1



Scheme 2



We set out to synthesize an intermediate such as **7** and verify that the absolute stereochemistry at the 2-carbon would transfer to the C-4 center to form the tetrahydroquinoline core **6** as a single enantiomer (Scheme 2). Retrosynthetically, the acyl-immonium ion could be generated from the imide,[3]

* Author for correspondence. E-mail: bobscottorg@sbcglobal.net.

† Current address: Chemical Research and Development, Pfizer Global R&D, 10578 Science Center Drive, San Diego, CA 92121.

(1) Damon, D. B.; Dugger, R. W.; Magnus-Aryitey, G.; Ruggeri, R. B.; Wester, R. T.; Tu, M. Abramov, Y. *Org. Process Res. Dev.* **2006**, *10*, 464−471.

(2) Tickner, D.; Kasthurikrishnan *Org. Process Rev. Dev.* **2001**, *5*, 270−271.

(3) DeNinno, M. P.; Eller, C. *Tetrahedron Lett.* **1997**, *38*, 6545−6548.

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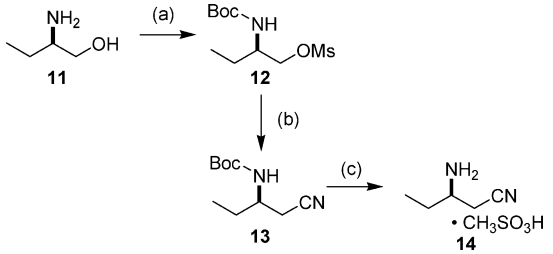
Scheme 3[a]



[a] Reagents and conditions: (a) i. BOC_2O; ii. MsCl, TMEDA (86%); (b) Bu_4NCN (93%) or NaCN, Bu_4NBr (74%); (c) MsOH, THF (81%).

which in turn could be formed via Pd-catalyzed condensation of an enantiomerically pure amine and aryl halide.

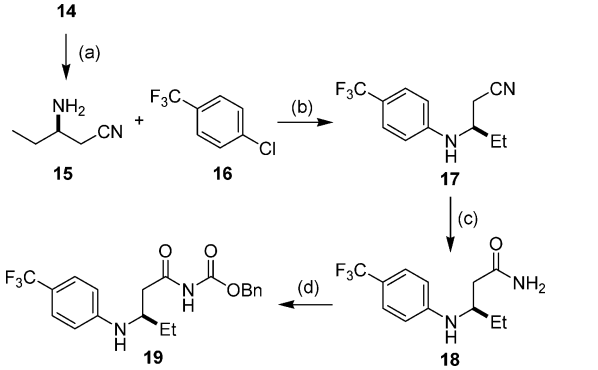
Results and Discussion

To develop a scalable synthetic strategy around the asymmetric β-amino acid functionality, we searched for readily available compounds that contained the desired stereocenter. A commercially available raw material that incorporates the desired chiral amine center, the required ethyl group, and a handle for further elaboration was (*R*)-2-amino-1-butanol. Using standard transformations for one-carbon homologation, we developed the following synthesis for the chiral nitrile **14** (Scheme 3). Starting with **11**,[4] we protected the amine followed by conversion of the alcohol to a mesylate. TMEDA was used as the amine base, which provided an insoluble amine·HCl salt in the reaction solvent (EtOAc) and was thus removed from the reaction by crystallization. After workup, mesylate **12** was isolated as a crystalline solid, providing a convenient purification point. The first two steps could be further streamlined into one reaction by the stepwise addition of reagents to a single reactor.

Initial attempts to displace the mesylate of **12** with simple cyanide sources (NaCN, KCN) led to disappointing results, mainly due to lack of solubility of the cyanide salts and the negative effects on the reaction profile upon prolonged heating.[5] In contrast, displacement of the mesylate with Bu_4NCN was very clean in EtOAc. To complete the sequence, the nitrogen protecting group was removed under acidic conditions. Due to the high water solubility of the aminonitrile, the acid for deprotection of the BOC group was chosen so as to avoid the need for aqueous workup. The methanesulfonic acid salt of **14** was a crystalline solid, so deprotection with methanesulfonic acid in THF provided the salt via direct filtration from the reaction mixture.

Difficulty in sourcing and handling Bu_4NCN and high cost forced us to reevaluate this approach, and a facile cyanide displacement utilizing readily available materials was sought to develop this route into a large-scale process. Several attempts to generate Bu_4NCN "in situ" using Bu_4NF/TMSCN provided a reagent mixture that was significantly less reactive than the purified commercial Bu_4NCN. We were able to achieve a compromise using NaCN in DMF containing Bu_4NBr as a solubilizing counterion. The NaCN chemistry was not as clean or high yielding but did provide the desired product in decent conversion at a low cost with readily available reagents. Impurities formed in this step were purged in the subsequent BOC-removal/salt formation step. This procedure was transferred to pilot plant facilities to produce 6 kg of **14**. This key raw material represented a useful cGMP starting material for the first campaign, and further production research was not pursued.[6] This allowed us to focus our efforts on the remaining steps of the synthesis.

Scheme 4[a]



[a] Reagents and conditions: (a) Na_2CO_3; (b) $Pd(OAc)_2$, 2-$(Cy)_2$P-2′-(Me_2N)biphenyl), $PhB(OH)_2$, Cs_2CO_3; (c) H_2SO_4, H_2O (77%); (d) $ClCO_2Bn$, LiOtBu (85%).

The next two-step sequence was coupling of chiral amine **15** to the trifluoroarene followed by hydrolysis of the nitrile to produce amide **18** (Scheme 4). We chose the reaction sequence in this order since the nitrile provided a nonbasic and nonligating functionality, limiting potential problems in the Pd-catalyzed amination. We examined many variables for the Pd-mediated amination reaction of **15** with **16**.[7] Among the variables examined were different bases and base combinations (NaOtBu, Cs_2CO_3, K_2CO_3, K_3PO_4); solvents (toluene, CH_3CN, THF, dioxane, DMF, DMAC, DME); ligands [binap, $(o\text{-tol})_3P$, DPPE, DPPB, DPPF, (biphenyl)$P(Cy)_2$, (biphenyl)$P(tBu)_2$, (dimethylaminobiphenyl)$P(Cy)_2$]; catalyst activation protocols (in situ activation or preactivation using $PhB(OH)_2$, NEt_3, $(^iPr)_2NH$); and Pd source [$Pd_2(dba)_3$ or $Pd(OAc)_2$]. The extensive list of permutations will not be reproduced here, but the optimal conditions elucidated within our research time frame are described below.

Although the chiral amine **14** was isolated as a salt, cleaner reactions resulted from the use of the free amine **15**. We originally developed this coupling using 1-bromo-4-(trifluoromethyl)benzene, and upon optimization we were able to switch to the much cheaper and readily available aryl chloride **16**. Typical catalyst loading to ensure complete consumption is at the 0.5% Pd level, with 1.5 equiv of ligand relative to Pd. For larger-scale reactions, the catalyst load was increased by 50% from normal lab conditions to 0.75% Pd and 1.12% ligand. A reaction temperature of 80 °C was utilized, as higher temperatures led to a slight erosion of

(4) This material was purchased from Fisher Scientific.

(5) The main impurity is (*R*)-4-ethyloxazolidin-2-one formed from cyclization of the BOC-protected mesylate.

(6) In time, other vendors were identified to provide this key raw material using variations of the described method or alternate technologies.

(7) For overviews of the literature coupling conditions, see: (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144−1157. (b) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158−1174.

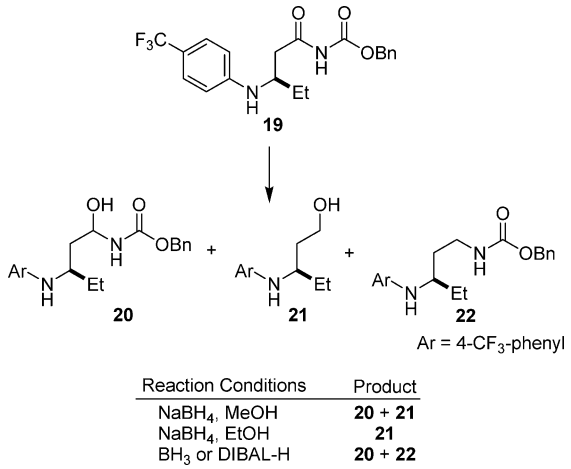
enantiomeric purity.[8] Unfortunately, the amination product **17** is an oil, eliminating the opportunity to purify at this stage for large-scale manufacturing.

With successful amination our focus was turned to elaboration of the C-4 carbon to the desired imide. We focused our approach on generation of the primary amide at this carbon, which required hydrolysis of the nitrile to the desired amide. Both acidic and basic hydrolysis conditions were explored. Several acids were examined to hydrolyze the nitrile (CH_3SO_3H, HCl, HBr, TFA/acetic acid) to the amide, but varying amounts of byproducts or hydrolysis to the carboxylic acid were observed. However, hydrolysis in sulfuric acid (2.2 mL/g **17**) with a small amount of water (4 equiv) present provided a robust procedure. Overreaction to the acid was not detected even when the reaction was heated overnight. Basic hydrolysis conditions were also screened (with or without H_2O_2) but were not competitive with the sulfuric acid hydrolysis method due to lower yield and consistent byproduct resulting from overreaction to produce the carboxylic acid.

To address the issue that intermediate **17** is an oil, we successfully telescoped the Pd-mediated amination reaction and hydrolysis together. After completion of the Pd-mediated amination reaction, the toluene solution was filtered to remove the salts, and the sulfuric acid/water mixture was added to the filtrate. The bilayer was stirred at 35 °C overnight to provide clean hydrolysis. The product **18** was completely soluble in the sulfuric acid layer (presumably as the sulfuric acid salt), and after the reaction was complete the toluene layer was discarded. After neutralization and extraction with diisopropyl ether (IPE), amide **18** was isolated via crystallization by addition of cyclohexane as an anti-solvent.[9] This procedure routinely provided an 85% yield over the two-step sequence under laboratory conditions. When the reaction was performed on kilogram scale, the Pd-catalyzed reaction was slightly slower than expected based on our previous experience on smaller scale. The two bulk-scale reactions had 6−7% of **16** remaining after 20 h, whereas on multihundred-gram scale the reactions were complete in this time frame. We propose that differences in mixing due to the heterogeneous nature of the reaction led to this lower rate for the multikilogram-scale reactions. The high density of Cs_2CO_3 led to this material being agitated only near the bottom of the reactor, and poor agitation in laboratory experiments also exhibited slower reactivity. Upon further scale-up, reactors with more efficient stirring could be chosen to minimize this effect. The two-step yields for two bulk runs were 79% (3.2 kg) and 74% (3.0 kg). The main difference in yield is in recovery from the crystallization. The second run had a higher concentration of IPE, and therefore the mother liquor retained more product.

Our strategy was to access the desired cyclization precursor **7** via reduction of an imide followed by elimination of water.[3] This approach required conversion of amide **18** to a suitable imide (Scheme 4). This transformation turned out to be more complicated than expected, as benzylchloroformate was reacted with the amide under a variety of basic conditions (LDA, NaH, DMAP, KOtBu, and NaOtBu) in different solvents. In each case, significant starting material would remain after multiple additions of base/chloroformate, leading to an unacceptably low overall yield. We discovered a satisfying balance in base strength and counterion to provide primarily the desired transformation using a solution of lithium *tert*-butoxide in THF. When this base was added to **18** in the presence of the chloroformate, a very rapid and clean reaction produced the desired imide **19**.

Scheme 5



Reaction Conditions	Product
$NaBH_4$, MeOH	**20** + **21**
$NaBH_4$, EtOH	**21**
BH_3 or DIBAL-H	**20** + **22**

With the key imide in hand, we set out to explore the reduction/cyclization protocol outlined in the retrosynthesis. Initially, the reduction was effected with $NaBH_4$ in MeOH (Scheme 5). Large amounts of borohydride (∼15 equiv) in multiple charges were used to consume the starting material. We attempted to use ethanol as solvent to minimize reagent decomposition and found that the desired aminal was formed in only small amounts and the imide starting material mainly converted to overreduced product **21**. Interestingly, when we performed the reaction in methanol on larger scale, desired aminal **20** was the major product, but overreduction to **21** remained a significant problem.

We also examined the use of DIBAL-H[3] and borane·DMS. Borane gave the desired aminal, but with a new overreduction product **22** resulting from reduction of the acylimide before fragmentation. DIBAL-H exhibited an improved profile but still gave significant overreduction with this system.

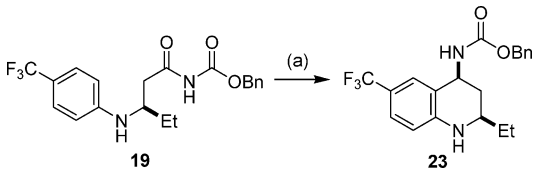
We decided to examine $NaBH_4$ reduction combined with acid activation, as described by Speckamp to mono-reduce succinimides.[10] Use of this methodology dramatically increased the rate and selectivity of the reduction, but the protocol was not ideal for large-scale production. Since the addition of acid to the imine/borohydride mixture led to significant evolution of hydrogen, careful addition of the acid was warranted and would be a difficult operation on larger

(8) Comparison of reactions at 85 and 110 °C showed 3 times as much enantiomer by chiral HPLC at the higher temperature. Typically, 0.2−0.6% of enantiomer was detected at the end of reactions at 85 °C.

(9) Cyclohexane can be replaced with hexanes or heptane, but cyclohexane is the solvent of choice based on the consistent physical characteristics of the amide thus obtained.

(10) (a) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437−1441. (b) Dijkink, J.; Speckamp, W. N. *Tetrahedron Lett.* **1975**, *46*, 4047−4050.

Scheme 6[a]



[a] Reagents and conditions: (a) i. $NaBH_4$, $CaCl_2$ or $MgCl_2$; ii. H^+.

scale. We found that it took several additions of acid to drive the reduction to completion, but using this activation the reaction gave very little (<5%) overreduction as long as the temperature was carefully controlled.

In hopes of developing a more scalable acid-catalyzed procedure, we reasoned that Lewis acid should activate the imide for reduction with less borohydride decomposition. Calcium borohydride is a known mild reducing agent, with greater ester reduction properties as compared to sodium borohydride.[11] The addition of $CaCl_2$ to our imide-reduction reaction caused a significant rate increase similar to that seen with the addition of protic acid. Under the $CaCl_2/NaBH_4$ conditions, we did not observe the extensive borohydride decomposition, which eliminated the need to add acid in multiple portions. Using the Lewis acid-activated conditions, nearly quantitative reduction of imide **19** was achieved in a single operation, and this was readily telescoped into the desired cyclization to produce **23** (Scheme 6). After aqueous workup with toluene as the organic solvent, catalytic $TsOH \cdot H_2O$ was added to the organic layer, and the solution was stirred at room temperature until cyclization was complete (usually 10−30 min). We were only able to detect the cis isomer in our reaction by ^1H NMR analysis, and the compound was >99% ee by chiral HPLC analysis.

A concern we had for scale-up was that the reduction required careful monitoring and was temperature sensitive. Warmer temperatures or prolonged reaction times led to significant overreduction products. We attributed the significantly higher yield of the desired aminal with calcium-ion activation in comparison to proton activation to its ability to chelate the aminal oxygen of the product and the carbamate carbonyl, providing a more stable intermediate. Following this rationale, it was further reasoned that a stronger chelating cation might provide a product with enhanced stability toward overreduction relative to calcium (Figure 1). This led us to the use of stoichiometric magnesium chloride, which provided a very clean reaction in ~30 min to the desired aminal with less than 1% overreduction. Remarkably, the product solution could be held at 0 °C for several hours in the presence of excess $NaBH_4$ with no further overreduction. Under these conditions, the majority of the product in the calcium chloride-activated reactions was lost to overreduction. After $NaBH_4$ reduction with $MgCl_2$ activation, the reaction was simply quenched with aqueous acid and the bilayer stirred for 3−4 h to effect the desired cyclization.

With the successful synthesis of tetrahydroquinoline **23**, we have relayed a common intermediate in the previously

(11) Kollonitsch, J.; Fuchs, O.; Gabor, V. *Nature* **1955**, 346.

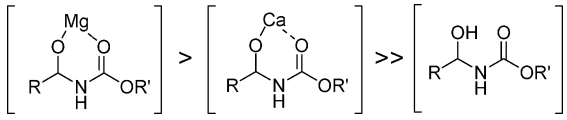
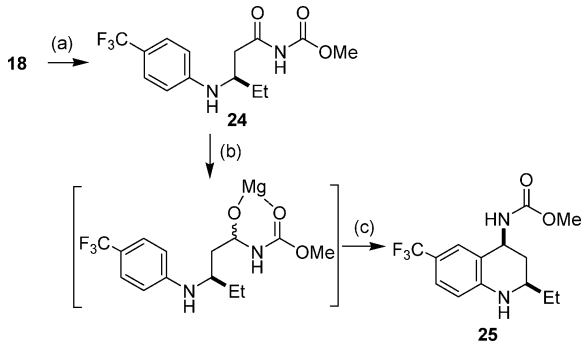


Figure 1. **Relative stability of in situ reduction intermediates.**

Scheme 7[a]



[a] Reagents and conditions: (a) $ClCO_2CH_3$, LiOtBu (94%); (b) $NaBH_4$, $MgCl_2$; (c) aq HCl (80%).

reported resolution route, but in asymmetric form (in the resolution route, the benzylcarbamate protected material is racemic).[1] It would require four steps to complete the synthesis from **23** to **1** via the previously reported chemistry: (1) conversion of the aniline nitrogen to the ethyl carbamate, (2) removal of the benzyl carbamate, (3) reductive alkylation of the amine with 3,5-bis(trifluoromethyl)benzaldehyde, (4) and conversion of the resultant amine to the methyl carbamate. Attempts to further shorten the sequence are described in the next sections.

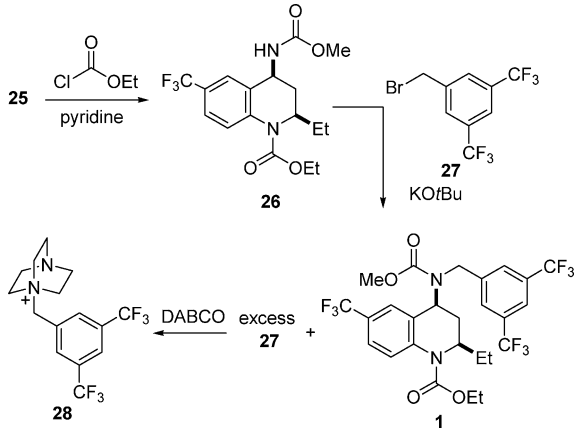
Alternate Imide Strategy. The route described in the previous section met the initial goals of the project in developing an asymmetric synthesis and intersecting a common intermediate in the synthetic sequence of the resolution route. However, some inefficiency was present as the developed route incorporated the benzylcarbamate-protected tetrahydroquinoline (**23**). In the new asymmetric route, the benzyl carbamate is not actually necessary for the synthesis, and the extra steps to remove this group and replace with one of the final nitrogen substituents is inefficient. This provided us an opportunity to further shorten the sequence by incorporation of the methyl carbamate as the cyclization activator, which then can remain until the end of the synthesis.

Utilizing the chemistry we developed for the benzylcarbamate **19**, amide **18** was acylated with methylchloroformate using lithium *tert*-butoxide as previously described to provide imide **24** (Scheme 7). Upon reaction completion and extractive workup the organic layer is distilled and displaced by cyclohexane to crystallize the product. The yield for the bulk run to produce 7 kg of **24** was 94%.

The key reduction/cyclization sequence was run using the previously described procedure. For added process safety and ease of handling on large scale, $NaBH_4$ was used as 11-mm pellets.[12] Imide **24** was mixed with $NaBH_4$ in $EtOH/H_2O$, as there is virtually no background reaction of the substrate

(12) This material was purchased from Aldrich Chemical Co. Due to lower activity of the pellets, the surface was "preactivated" by stirring the pellets in the solvent for 20 min at room temperature.

Scheme 8



with $NaBH_4$ without Lewis acid catalysis under the reaction conditions (−10 to 0 °C). To this mixture, a solution of aq $MgCl_2$ was then added. Upon reaction completion, the solution was quenched into an aq HCl/citric acid/CH_2Cl_2 mixture and stirred for ∼2 h at room temperature to effect the acid-catalyzed cyclization to produce **25**. The citric acid was added to complex Mg salts; without citric acid severe emulsions were encountered. After further extractions, the product was crystallized from the CH_2Cl_2 by displacement with hexanes. The bulk yield to produce 5.3 kg of **25** was 80%. Note that the diastereoselectivity for this cyclization is comparable to that seen in the benzyl carbamate case, with no trans isomer detected by NMR analysis.

Development of the Endgame. With a reliable synthesis of the chiral tetrahydroquinoline core, we set out to develop the chemistry for the final two transformations. To complete the synthesis, the N-1 position must be converted to the ethyl carbamate and the C-4-nitrogen must be alkylated with the required 3,5-bis(trifluoromethyl)benzyl group. One drawback to the approach is the use of an alkylating agent in the final step.[13] In developing this chemistry, careful attention was given to the levels of alkylating agent present as an impurity in the final product.

Using a procedure analogous to that previously described,[1] ethyl chloroformate was added to a solution of **25** in the presence of pyridine (Scheme 8). During prior bulk campaigns, multiple charges of chloroformate were often used to drive the reaction to completion. During our research on this step, slow bubbling was noticed during the reaction; as a result, we proposed that reagent decomposition could explain the stalled reactions.[14] It was visually determined that this bubbling is significant only at temperatures above ∼15 °C. Thus, by conducting the reaction at 0 °C with careful temperature monitoring, the reaction could be driven to completion without additional charges of chloroformate. Upon reaction completion, acidic workup followed by solvent distillation provided crystalline **26**. The bulk yield was 88% to produce 5.6 kg of **26**.

The final step alkylation was examined under a variety of base (various metal alkoxides and hydroxides, carbonates, and amines), solvent (THF, DMAC, CH_2Cl_2, toluene, DMSO, DME, IPE, MTBE, alcohols, and hexanes, or combinations of the above), and stoichiometry conditions. The optimal base was *tert*-butoxide; however, the use of excess base also leads to a stilbene byproduct [(*E*)-1,2-bis(3,5-bis(trifluoromethyl)-phenyl)ethane, **29**], in some cases to the extent of several percent.[15] The formation is minimized with the weaker hydroxide bases, or by the use of stoichiometric *tert*-butoxide. The best conditions elucidated were the use of potassium *tert*-butoxide in toluene or CH_2Cl_2. Employing stoichiometric base minimized the formation of stilbene **29** to nearly undetectable levels at the expense of ∼5% unreacted **26**.

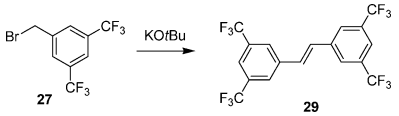
After the reaction is complete, excess alkylating agent **27** was quenched with DABCO. The nucleophilic amine was efficient at converting the excess alkylating agent to the quaternary salt **28**. The quaternary salt was very stable and not readily hydrolyzed by acidic or basic water under the time frame required for large-scale processing, allowing efficient removal via aqueous HCl extractions. After extractions, the IPE organic layer was displaced by distillation with denatured EtOH[16] and reduced in volume to crystallize **1**. Filtration was followed by further concentration and reseeding to obtain a second crop. Both crops had no detectable alkylating agent (**27** present at <10 ppm). The bulk run provided 6.0 kg from two crops for a 73% yield, with purities >99%. No enantiomer or diastereomer was detected by HPLC analysis.

Last-Step Alkylation Purge Tests. Since this material was designated for clinical use, extra attention was given to the use of an alkylating agent in the final step, and the subsequent removal is described in the last section. We have addressed the fate of the excess alkylating agent: the DABCO quaternary salt is washed out in the aqueous layer. We also demonstrated the purge of the alkylating agent in the final crystallization: a sample of **1** produced by the alkylation route was spiked with 30 000 ppm of **27** in EtOH. The solution was then subjected to the standard crystallization procedure, and the resultant product was isolated free from detectable bromide **27** (<10 ppm). This purge experiment further confirms that we can control the level of the benzyl halide in the final steps: the fate of the material under normal reaction conditions is the quaternary salt that is washed out with the water, and additional purge is provided by the crystallization procedure.

(13) To circumvent a final-step alkylation, we also examined the alternate permutation: alkylation of **25** first with bis(trifluoromethyl)benzyl bromide followed by conversion of the tetrahydroquinoline nitrogen to the ethyl carbamate. Although the major product from this sequence was the desired compound, the alkylation step was not completely selective for the desired nitrogen, leading to significant impurities.

(14) A reasonable possibility is that the acyl pyridinium is formed, displacing chloride. The chloride then attacks the ethyl group, forming ethyl chloride and CO_2, and releasing pyridine.

(15) This impurity arises from deprotonation at the benzyl center of **27**, which displaces the bromide of a second molecule of **27**. The intermediate can then undergo base-catalyzed elimination to provide **29**. Formation of this material must be minimized as it is difficult to purge in the final crystallization.



(16) Anhydrous ethanol denatured with 0.5% toluene was used.

Conclusion

The work presented describes a scalable asymmetric synthesis of compound **1**. The six-step synthesis from chirally pure amine **14** was demonstrated on multikilogram scale, providing the title compound in 37% overall yield.

Experimental Section

All materials were purchased from commercial suppliers and used without further purification. All reactions were conducted under an atmosphere of nitrogen unless noted otherwise.

Methanesulfonic Acid (*R*)-2-*tert*-Butoxycarbonylaminobutyl Ester (12). *Run 1*. BOC anhydride (515.9 g, 2.364 mol) in ethyl acetate (400 mL) was added to a solution of *R*-(−)-2-amino-1-butanol (**11**, 200.66 g, 2.251 mol) in ethyl acetate (1500 mL) via an addition funnel. The reaction mixture was stirred for approximately 30 min. TMEDA (360 mL, 2.39 mol) was added, and the reaction mixture was cooled to approximately 10 °C. Methanesulfonyl chloride (184.7 mL, 2.386 mol) was added to the reaction mixture over a 30-min period. After stirring for 1 h, the reaction mixture was filtered to remove the TMEDA salts, and the filtrate was collected.

Run 2. BOC anhydride (514.5 g, 2.357 mol) in ethyl acetate (400 mL) was added to a solution of *R*-(−)-2-amino-1-butanol (200.12 g, 2.245 mol) in ethyl acetate (1100 mL) via an addition funnel. The reaction mixture was stirred for approximately 30 min. TMEDA (359.1 mL, 2.379 mol) was added, and the reaction mixture was cooled to approximately 10 °C. Methanesulfonyl chloride (184.1 mL, 2.379 mol) was added to the reaction mixture over a 30-min period. After stirring for 1 h, the reaction mixture was combined with the filtrate from Run 1 and the combined mixture was filtered. The solids were washed with ethyl acetate (400 mL), which was collected with the reaction filtrate. Hexanes (12 L) was added to the combined filtrates, and the mixture was cooled in an ice/water bath. After 2.5 h the solids were isolated by filtration, washed with hexanes (2 L), and dried under vacuum to afford 971.57 g (81%) of **12**: mp 89.9−90 (sub). ^{1}H NMR (300 MHz, d_6-DMSO) δ 0.86 (t, 3, J = 7.4), 1.25−1.57 (m, 2), 1.39 (s, 9), 3.15 (s, 3), 3.49−3.63 (m, 1), 4.04 (dd, 1, J = 6.3, 10.0), 4.10 (dd, 1, J = 5.3, 10.0), 6.85 (br d, 1, J = 8.3). ^{13}C NMR (75 MHz, d_6-DMSO) δ 10.0, 23.4, 28.1, 36.6, 50.8, 71.0, 77.8, 155.4. Anal. Calcd for $C_{10}H_{21}NO_5S$: C, 44.93; H, 7.92; N, 5.24. Found: C, 45.21; H, 8.02; N, 5.12.

(*R*)-*N*-*tert*-Butyloxycarbonyl-3-aminopentanenitrile (13). NaCN (24.05 g, 0.4907 mol) was added to DMF (500 mL), and the mixture was stirred at 35 °C for 30 min. Tetrabutylammonium bromide (120.59 g, 0.3741 mol) was added, and the reaction mixture was stirred at 35 °C for 2 h. **12** (101.23 g, 0.3787 mol) was added, and the reaction mixture was stirred at 35 °C overnight. The mixture was then partitioned between water (2 L) and diisopropyl ether (IPE, 1 L). The aqueous layer was extracted with IPE (1 L). The combined organic layers were extracted sequentially with water and a saturated solution of sodium chloride in water. The organic layer was dried over magnesium sulfate, filtered, and concentrated to afford a solid (65.22 g). A portion of the solid (61.60 g) was transferred to a flask equipped with an overhead stirrer. Hexanes (186 mL) was added, and the flask was heated to 65 °C. After all the solids were in solution, the mixture was cooled to ambient temperature and stirred overnight. The resulting solids were isolated by filtration to afford 52.32 g (74%) of **13**. Note: for reaction on larger scale, the water washes were replaced with 2% aq K_2CO_3, and the extractions were performed with EtOAc in place of IPE: mp 62.4−63.3. ^{1}H NMR (300 MHz, d_6-DMSO) δ 0.84 (t, 3, J = 7.4), 1.40 (s, 9), 1.37−1.52 (m, 2), 2.53 (dd, 1, J = 7.4, 17.0), 2.67 (dd, 1, J = 5.2, 16.8), 3.48−3.62 (m, 1), 7.00 (br d, 1, J = 8.0). ^{13}C NMR (75 MHz, d_6-DMSO) δ 10.1, 22.6, 26.5, 28.1, 48.7, 77.8, 118.5, 155.2. Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.40; H, 9.17; N, 14.12.

(*R*)-3-Aminopentanenitrile Methanesulfonic Acid Salt (14). Methanesulfonic acid (48 mL, 0.74 mol) was added to a solution of **13** (52.32 g, 0.2639 mol) in THF (530 mL). The reaction mixture was heated to 40 °C for 30 min. The temperature was raised to 45 °C, and the reaction mixture was stirred for 1 h. The temperature was raised again to 65 °C, and the reaction mixture was stirred for 5 h. The solution was allowed to cool to room temperature, and upon cooling the product crystallized. The resulting solids were isolated by filtration to afford 41.53 g (81%) of the title compound: mp 125.1−126.0. ^{1}H NMR (300 MHz, d_6-DMSO) δ 0.95 (t, 3, J = 7.5), 1.60−1.75 (m, 2), 2.39 (s, 3), 2.89 (dd, 1, J = 6.2, 17.4), 2.97 (dd, 1, J = 5.5, 17.4), 3.35−3.45 (m, 1), 8.16 (br s, 3). ^{13}C NMR (75 MHz, d_6-DMSO) δ 9.3, 20.4, 25.0, 39.8, 48.3, 117.2. Anal. Calcd for $C_6H_{14}N_2O_3S$: C, 37.10; H, 7.26; N, 14.42. Found: C, 37.34; H, 7.27; N, 14.61.

(3*R*)-3-(4-Trifluoromethylphenylamino)pentanenitrile (17). To a clean, dry 100-L glass reactor was charged **14** (3000 g, 15.44 mol), sodium carbonate (2.8 kg, 26.4 mol), and methylene chloride (21 L). The heterogeneous mixture was stirred well for at least 2 h. The mixture was filtered and rinsed with methylene chloride (3 × 2 L). The resulting filtrate was placed in a clean, dry, and nitrogen gas-purged 50-L glass reactor. The methylene chloride was removed by distillation until the internal temperature reached 50−53 °C to provide the free-based amine as a thin oil. The reactor was then cooled to room temperature and charged with toluene (20 L), chloro-4-(trifluoromethyl)benzene (4200 g, 23.26 mol), and cesium carbonate (7500 g, 23.02 mol). The solution was sparged with nitrogen gas for 1 h. Near the time of completion of the sparging, fresh catalyst solution was prepared by charging a 2-L round-bottom flask, equipped with stir bar and flushed with nitrogen gas, with 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (68 g, 0.17 mol), phenylboronic acid (28 g, 0.23 g), and THF (1.2 L) followed by palladium acetate (26 g, 0.12 mol). The catalyst solution was stirred at room temperature under nitrogen atmosphere for 15 min. The catalyst solution was added to the 50-L reactor with a cannula (excluding air). The mixture was heated to 79 °C internal temperature under nitrogen atmosphere for 16 h. The reaction solution was cooled to room temperature and filtered through Celite. The solids were

rinsed with toluene (3 × 2 L), and the filtrate was collected. All filtrates were combined to afford a crude solution of **17**.

(3*R*)-3-(4-Trifluoromethylphenylamino)pentanoic Acid Amide (18). Aqueous acid (8.2 L concentrated sulfuric acid and 1.1 L water premixed and cooled to 35 °C or less) was added to the crude toluene solution of **17** from the above procedure. The resulting bilayer was stirred well and heated to 35 °C for 17 h. The lower aqueous layer was collected and the upper toluene layer discarded. The aqueous layer was quenched with aq NaOH (95 L water and 10.7 kg NaOH) and IPE (40 L). After extraction and removal of the aqueous layer, the organic layer was extracted with saturated aqueous $NaHCO_3$ (10 L). The layers were separated and the organic phase concentrated by distillation to a volume of 19 L. The solution was cooled to room temperature and seeded with **18** and allowed to granulate for 3 h while stirring. To the heterogeneous mixture was added cyclohexane (38 L), and the mixture granulated for an additional 11 h. The solids were filtered, rinsed with cyclohexane (4 L), and dried under vacuum at 40 °C to provide 3173 g (79%) of **18**. A repeat of the above procedure provided 3021 g (75%) for an average yield over two runs of 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, 3, J = 7.5), 1.60−1.76 (m, 2), 2.45 (d, 2, J = 5.8), 3.73−3.80 (m, 1), 5.53 (br s, 1), 5.63 (br s, 1), 6.65 (d, 2, J = 8.7), 7.39 (d, 2, J = 8.7). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.7, 27.8, 40.0, 51.9, 112.6, 118.9 (q, J = 32.7), 125.2 (q, J = 271.0), 126.9 (q, J = 3.8), 150.2, 174.3. Anal. Calcd for $C_{12}H_{15}F_3N_2O$: C, 55.38; H, 5.81; N, 10.76. Found: C, 55.25; H, 5.98; N, 10.59.

(3*R*)-[3-(4-Trifluoromethylphenylamino)pentanoyl]-carbamic Acid Benzyl Ester (19). To a clean, dry flask was charged **18** (20.11 g, 77.27 mmol) and IPE (100 mL), and the mixture was cooled to −12 °C. Benzyl chloroformate (13.25 mL, 92.8 mmol) was then added followed by the slow addition of 1.0 M lithium *tert*-butoxide in THF solution (185.5 mL, 185.5 mmol). Lithium *tert*-butoxide solution was added at such a rate that the internal temperature remained below 0 °C. This addition took 1 h. Fifteen minutes after the completion of base addition, the reaction was quenched by adding the mixture to IPE (100 mL) and 1.5 M HCl (130 mL). The phases were separated, and the organic layer was washed with sat. aqueous NaCl solution (130 mL). The phases were separated, and the organic layer was dried ($MgSO_4$), filtered, and concentrated under partial vacuum (at 40 °C) to a total volume of 100 mL. Additional IPE (200 mL) was added, and the solution was again concentrated under partial vacuum (at 40 °C) to a total volume of 100 mL. After cooling, the solution was seeded with **19** and allowed to stir at room temperature overnight. The remaining solvent was displaced with cyclohexane using partial vacuum distillation (45 °C bath, 200 mL followed by 100 mL). The resultant slurry was cooled and stirred for 40 min and filtered, and the solids were dried to provide 25.8714 g (85%) of **19**: mp 100.6−101.4. ^{1}H NMR (400 MHz d_6-acetone) δ 0.96 (t, 3, J = 7.5), 1.57−1.75 (m, 2), 2.87 (dd, 1, J = 6.6, 16.2), 2.97 (dd, 1, J = 6.2, 16.2), 3.94−4.00 (m, 1), 5.16 (s, 2), 5.50 (br s, 1), 6.75 (d, 2, J = 5.7), 7.33−7.43 (m, 7), 9.52 (br s, 1). ^{13}C NMR (100 MHz $CDCl_3$) δ 10.7, 28.1, 40.3, 51.5, 68.3, 112.5, 118.9 (q, J = 32.3), 125.2 (q, J = 269.9), 126.9 (q, J = 3.8), 128.6, 128.98, 129.04, 135.1, 150.1, 152.1, 173.5. Anal. Calcd for $C_{20}H_{21}F_3N_2O_3$: C, 60.91; H, 5.37; N, 7.10. Found: C, 60.96; H, 5.22; N, 7.07.

(2*R*,4*S*)-(2-Ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamic Acid Benzyl Ester (23). A clean, dry flask was charged with **19** (11.51 g, 29.18 mmol) and 95% ethanol (80 mL), and the solution was cooled in an ice/acetone bath (−12 °C). $NaBH_4$ (0.773 g, 20.4 mmol) was then added to the solution. The internal temperature of the reaction was −11.5 °C. To the reaction flask was slowly added a solution of $MgCl_2 \cdot 6H_2O$ (6.23 g, 30.6 mmol, in 13 mL of H_2O). The internal temperature was maintained below −5 °C by adjusting the addition rate. The total addition time was 15 min. Once all of the magnesium chloride solution was added, the solution temperature was raised to 0 °C and stirred for 30 min. The reaction was then quenched by addition of the reaction solution to a mixture of CH_2Cl_2 (115 mL), 1 N HCl (115 mL), and citric acid (14.02 g, 72.97 mmol). The resulting bilayer was stirred at room temperature. After 3.75 h, the phases were separated. Water (58 mL) and citric acid (8.41 g, 43.77 mmol) were added to the organic layer, and the mixture was stirred at room temperature for 45 min. The phases were separated, and G-60 Darco activated charcoal (1.52 g) was added to the organic layer. After stirring for 45 min, the solution was filtered through Celite and washed with CH_2Cl_2 (2 × 15 mL). The filtrate was then displaced with hexanes by distillation under atmospheric pressure (used ∼350 mL hexanes) and concentration of the mixture to a total volume of 230 mL. The mixture was stirred at room temperature for 14 h and filtered, and the solids were dried to provide 9.0872 g (82%) of **23**: mp 154.0−155.2. ^{1}H NMR (400 MHz d_6-acetone) δ 1.00 (t, 3, J = 7.5), 1.51−1.69 (m, 3), 2.17−2.26 (m, 1), 3.46−3.54 (m, 1), 4.96 (ddd, 1, J = 5.4, 9.5, 11.6), 5.14 (d, 1, J = 12.9), 5.20 (d, 1, J = 12.9), 5.66 (br s, 1), 6.65 (d, 1, J = 8.3), 6.71 (br d, 1, J = 9.1), 7.20 (dd, 1, J = 1.9, 8.9), 7.30−7.43 (m, 6). ^{13}C NMR (100 MHz $CDCl_3$) δ 9.9, 29.2, 35.3, 48.2, 52.4, 67.3, 113.7, 118.9 (q, J = 32.7), 121.4, 124.1 (q, J = 3.8), 125.1 (q, J = 270.6), 125.7 (q, J = 3.8), 128.4, 128.5, 128.9, 136.6, 147.7, 156.7. Anal. Calcd for $C_{20}H_{21}F_3N_2O_2$: C, 63.48; H, 5.59; N, 7.40. Found: C, 63.08; H, 5.50; N, 7.46.

(3*R*)-[3-(4-Trifluoromethylphenylamino)pentanoyl]-carbamic Acid Methyl Ester (24). To a clean, dry 100-L glass reactor was charged **18** (6094 g, 23.42 mol), isopropyl ether (30 L), and methylchloroformate (2.7 kg, 29 mol). The resulting slurry was cooled to 2 °C and the reactor jacket set at −8 °C. The reactor was then charged with lithium *tert*-butoxide solution (18−20% in THF, 24.6 kg, ∼58 mol) at such a rate as to maintain the internal temperature below 10 °C and preferably at a temperature of about 5 °C. Ten minutes after addition of base was complete, the reaction was quenched by the addition of 1.5 M HCl (36 L). The aqueous layer was removed, and the organic phase was extracted with saturated aq NaCl solution (10 L). The aqueous layer was removed, and the organic phase was concentrated by distillation under vacuum and at a temperature of about 50 °C until the volume was reduced to about

24 L. Cyclohexane (48 L) was added to the reaction vessel, and distillation was again repeated at an internal temperature of 45−50 °C under vacuum until the volume of solution in the vessel was reduced to 24 L. A second portion of cyclohexane (48 L) was added to the reaction vessel, and distillation was again repeated at an internal temperature of 45−50 °C under vacuum until the volume of solution in the vessel was reduced to 24 L. While the temperature was held at 50 °C, the solution was seeded with **24** and allowed to granulate while stirring 2 h. The solution was then cooled slowly (over 1.5 h) to room temperature and allowed to granulate while stirring for 15 h. The mixture was filtered. The resulting solids were rinsed with cyclohexane (10 L) and dried under vacuum at 40 °C to afford 7504 g of solids that contained 7 wt % of residual cyclohexane; further drying was not necessary for continuation of the process. This provided a theoretical recovery of 6979 g (94%) of **24**; analytical data is presented for a solvent-free sample: mp 142.3−142.4. ^{1}H NMR (400 MHz, d_6-acetone) δ 0.96 (t, 3, J = 7.4), 1.55−1.75 (m, 2), 2.86 (dd, 1, J = 6.6, 16.2), 2.96 (dd, 1, J = 6.2, 16.2), 3.69 (s, 3), 3.92−3.99 (m, 1), 5.49 (br d, 1, J = 8.7), 6.76 (d, 2, J = 8.7), 7.37 (d, 2, J = 8.7), 9.42 (br s, 1). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.6, 28.1, 40.2, 51.5, 53.4, 112.5, 119.0 (q, J = 32.70), 125.2 (q, J = 270.2), 126.9 (q, J = 3.8), 150.1, 152.7, 173.4. Anal. Calcd for $C_{14}H_{17}F_3N_2O_3$: C, 52.83; H, 5.38; N, 8.80. Found: C, 52.71; H, 5.37; N, 8.80.

(2*R*,4*S*)-(2-Ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamic Acid Methyl Ester (25). To a clean, dry 100-L glass reactor was charged **24** (7474 g of a lot that contains 7% solvent, theoretical 6951 g, 21.84 mol) followed by EtOH (46 L, denatured with 0.5% toluene) and water (2.35 L). $NaBH_4$ (620 g, 11-mm pellets, 16.4 mol) was added to the solution in one portion. Some off-gassing of hydrogen occurred; nitrogen gas purging was maintained. The mixture was stirred at room temperature for 20 min and then cooled to −10 °C. A solution of 3.3 M aq $MgCl_2$ solution (4.68 kg of $MgCl_2$·$6H_2O$, 23.0 mol in 7 L of water) was added at such a rate that the internal temperature did not exceed −5 °C. Once addition was complete, the reaction solution was warmed to 0 °C for 45 min. The reaction was quenched by transferring the reaction mixture to a 200-L reactor containing methylene chloride (70 L), and 1 M HCl/citric acid solution (5.8 L of concentrated HCl, 64 L of water, and 10.5 kg of citric acid). The headspace of the reactor was purged with nitrogen gas since the quench liberates some H_2. This bilayer was stirred at room temperature for 2 h. The phases were separated, and the lower organic product layer was removed. After aqueous layer removal, the organic phase was returned to the reaction vessel and extracted with an aqueous citric acid solution (6.3 kg of citric acid, 34 L of water). The mixture was stirred for 1 h and allowed to settle overnight. The layers were separated, and to the organic phase was added Darco activated carbon (G-60 grade, 700 g), and the solution was stirred for 30 min. The mixture was filtered through Celite, and the carbon was rinsed twice with methylene chloride (14 and 8 L). The filtrate was distilled while periodically adding hexanes so as to displace the methylene chloride with hexanes to a total final volume of 70 L (the internal volume was kept at approximately 65−70 L, total hexanes used = 112 L). Product crystallized during the displacement. Once a stable distillation temperature was reached, the solution was cooled and granulated at room temperature for 10 h. The solids were filtered off, rinsed with hexanes (14 L), and dried at 40 °C under vacuum to provide 5291 g (80%) of **25**: mp 139.0−140.5. ^{1}H NMR (400 MHz, d_6-acetone) δ 1.00 (t, 3, J = 7.5), 1.51−1.67 (m, 3), 2.19 (ddd, 1, J = 2.9, 5.4, 12.4), 3.44−3.53 (m, 1), 3.67 (s, 3), 4.89−4.96 (m, 1), 5.66 (br s, 1), 6.56 (br d, 1, J = 8.7), 6.65 (d, 1, J = 8.7), 7.20 (d, 1, J = 8.7), 7.30 (br s, 1). ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.9, 29.2, 35.5, 48.1, 52.4, 52.6, 113.7, 118.9 (q, J = 33.1), 121.4, 124.1 (q, J = 3.8), 125.1 (q, J = 270.6), 125.7 (q, J = 3.8), 147.7, 157.3. Anal. Calcd for $C_{14}H_{17}F_3N_2O_2$: C, 55.62; H, 5.67; N, 9.27. Found: C, 55.68; H, 5.78; N, 9.31.

(2*R*,4*S*)-2-Ethyl-4-methoxycarbonylamino-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic Acid Ethyl Ester (26). To a clean, dry 100-L glass reactor was charged **25** (5191 g, 17.17 mol), methylene chloride (21 L), and pyridine (4.16 L, 51.4 mol). The reaction vessel was cooled to −10 °C. Ethyl chloroformate (4.10 L, 42.9 mol) was slowly added at such a rate that the internal temperature did not exceed −5 °C (jacket temperature was set at −25 °C to absorb exotherm). The reaction solution was brought to 0 °C and held for 20 h. The reaction was quenched by adding to a mixture of IPE (36 L), CH_2Cl_2 (6.2 L), and 1.5 M HCl solution (52 L). The resulting phases were separated, and the organic layer was extracted with 1 M NaOH solution (15 L). The resulting phases were separated, and the organic layer was extracted with a sat. aq NaCl solution (15 L). The resulting phases were separated, and the organic layer was concentrated by distillation to a volume of 40 L. Crystallization initiated at the lower volume. The CH_2Cl_2 was displaced with IPE by distilling the mixture and periodically adding IPE to maintain a constant volume at ∼40 L until a distillation temperature of 68 °C was maintained (46 L total IPE used). The mixture was cooled and allowed to granulate with stirring at room temperature for 19 h. The solids were filtered, rinsed with IPE (8 L), and dried under vacuum at 40 °C to provide 5668 g (88%) of **26**: mp 157.3−157.6. ^{1}H NMR (400 MHz, d_6-acetone) δ 0.84 (t, 3, J = 7.5), 1.26 (t, 3, J = 7.0), 1.44−1.73 (m, 3), 2.59 (ddd, 1, J = 4.6, 8.3, 12.9), 3.67 (s, 3), 4.14−4.28 (m, 2), 4.46−4.54 (m, 1), 4.66−4.74 (m, 1), 6.82 (br d, 1, J = 9.1), 7.53 (s, 1), 7.58 (d, 1, J = 8.3), 7.69 (d, 1, J = 8.3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.9, 14.6, 28.5, 38.1, 46.9, 52.6, 53.7, 62.4, 120.8 (q, J = 3.4), 124.32 (q, J = 271.7), 124.36 (q, J = 3.4), 126.38, 126.46 (q, J = 32.7), 134.7, 139.7, 154.7, 156.9. Anal. Calcd for $C_{17}H_{21}F_3N_2O_4$: C, 54.54; H, 5.65; N, 7.48. Found: C, 54.50; H, 5.68; N, 7.55.

(2*R*,4*S*)-4-[(3,5-Bis(trifluoromethyl)benzyl)methoxycarbonylamino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic Acid Ethyl Ester (1). To a clean, dry 100-L glass reactor was charged **26** (5175 g, 13.82 mol), CH_2Cl_2 (20 L), and potassium *tert*-butoxide (1551 g, 13.82 mol) at room temperature. The mixture was stirred for 5 min.

3,5-Bis(trifluoromethyl)benzylbromide (3.50 L, 19.1 mol) was added to the mixture in one portion. The internal temperature was maintained between 20 and 25 °C for 1.5 h. After 2.3 h of reaction time, an additional charge of potassium *tert*-butoxide (46.10 g, 0.41 mol) was added. After a total reaction time of 4.5 h, the reaction was quenched. 1,4-Diazabicyclo[2.2.2]octane (DABCO, 918 g, 8.18 mol) was added to the reaction solution, and the mixture was stirred 1 h. IPE (40 L) and 0.5 M HCl (30 L) were added to the reaction mixture. The resulting organic and aqueous phases were separated, and the organic layer was extracted with 0.5 M HCl (2 × 30 L). The resulting organic and aqueous phases were then separated, and the organic layer was extracted with sat. aq NaCl (15 L), and the layers were separated. Anhydrous magnesium sulfate (3.5 kg) was added to the organic layer, and the mixture was stirred for 30 min. The mixture was then filtered (0.5 μm filter) into a 50-L glass reactor with IPE wash (8 L) in two portions. The filtrate was concentrated under vacuum to a total volume of 12 L (jacket temp 45 °C, max internal temp 35 °C). EtOH (25 L, denatured with 0.5% toluene) was added to the oil, and the solution was concentrated under vacuum to a volume of 12 L. To the solution was added EtOH (15 L, with 0.5% toluene), and the solution was again concentrated under vacuum to a volume of 12 L. The solution was cooled to room temperature and seeded with **1** (3 g). The solution was granulated for 38 h and filtered, and the solids were rinsed with EtOH (4 L + 2 L, each with 0.5% toluene). The solids were dried under vacuum (no heat) to provide 4610 g (55%) of the title compound **1**. The mother liquor from the above filtration was concentrated under vacuum (solution temp = 62 °C) to a final volume of 6 L and cooled to 38 °C. The solution was seeded with **1** (0.5 g) and allowed to cool and granulate while stirring for 19 h. The mixture was filtered, and the solids were rinsed with EtOH (2.5 L containing 0.5% toluene). The resulting cake was dried under vacuum (no heat) to provide 1422 g (17%) of the title compound as the second crop. Combined recovery of **1** was 6032 g (73%). The final material was identical to previously prepared material[1] by chiral and achiral HPLC analysis. ^{1}H NMR (600 MHz, $CDCl_3$, 55 °C) δ 0.75 (br s, 3), 1.29 (t, 3, J = 7.1), 1.40−1.47 (m, 2), 1.65−1.69 (m, 1), 2.26 (br s, 1), 3.80 (br s, 3), 4.17−4.29 (m, 3), 4.32−4.37 (m, 1), 5.2 (br s, 2), 7.13 (s, 1), 7.51 (br d, 1, J = 8.3), 7.58 (br d, 1, J = 8.3), 7.74 (br s, 2), 7.80 (s, 1). ^{13}C NMR (150 MHz, $CDCl_3$, 55 °C) δ 9.5, 14.6, 29.4, 37.1, 47.2, 53.7 (2 C), 54.7, 62.5, 119.8, 121.7, 123.5 (q, J = 273), 124.3 (q, J = 272), 126.7, 127.1, 127.6, 132.5 (q, J = 33.4), 133.8, 140.6, 141.9, 154.7, 157.5. Anal. Calcd for $C_{26}H_{25}F_9N_2O_4$: C, 52.01; H, 4.20; N, 4.67. Found: C, 51.97; H, 4.08; N, 4.55.

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