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A Practical Enantioselective Synthesis of Odanacatib, a Potent Cathepsin K Inhibitor, via Triflate Displacement of an α-Trifluoromethylbenzyl Triflate

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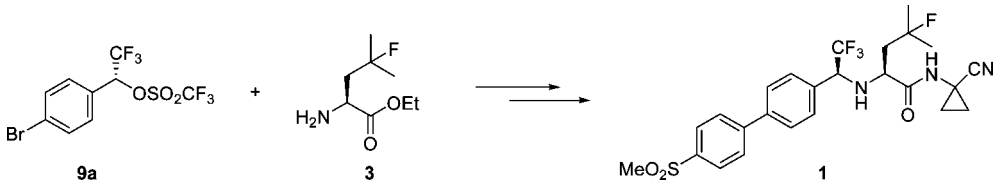

An enantioselective synthesis of the Cathepsin K inhibitor odanacatib (MK-0822) **1** is described. The key step involves the novel stereospecific S_N2 triflate displacement of a chiral α-trifluoromethylbenzyl triflate **9a** with (*S*)-γ-fluoroleucine ethyl ester **3** to generate the required α-trifluoromethylbenzyl amino stereocenter. The triflate displacement is achieved in high yield (95%) and minimal loss of stereochemistry. The overall synthesis of **1** is completed in 6 steps in 61% overall yield.

Introduction

Osteoporosis is a disease characterized by excessive bone loss causing skeletal fragility and an increased risk of fracture. One in two women and one in eight men over the age of 50 will have an osteoporotic fracture.[1] Cathepsin K is a recently discovered[2] member of the papain superfamily of cysteine proteases that is abundantly expressed in osteoclasts, the cells responsible for bone resorption.[3] Bone is a living tissue that is remodeled every five to seven years in a dynamic process governed by the balance between bone formation and resorption in which osteoblasts and osteoclasts play a pivotal role. The abundant and selective expression of Cathepsin K in osteoclasts has made it an attractive therapeutic target for the treatment of osteoporosis.[4]

Odanacatib (MK-0822) **1** has been identified as a potent and selective inhibitor of Cathepsin K.[5] We were interested in developing chemistry suitable for preparing kilogram quantities of **1** in an effort to further explore its pharmacological properties. Herein, we report our efforts to develop a practical, enantioselective, chromatography-free synthesis of **1** on a multikilogram scale.

We envisioned three possible routes for the preparation of **1** and the retrosynthetic analysis is outlined in Figure 1. The first route (A) requires an unprecedented nucleophilic displacement of an appropriately activated chiral α-trifluoromethylbenzyl alcohol with an α-amino ester. The second approach (B) relies on the diastereoselective reductive amination of an aryl trifluoromethyl ketone with an amino acid derivative. The third approach (C) requires nucleophilic displacement of an activated chiral α-hydroxy ester[6] with a chiral α-trifluoromethylbenzyl amine. Previous reports from our laboratories have described methodologies attesting to the viability of approaches B[7] and C[8] for the synthesis of **1**. Therefore, herein we report our efforts to investigate the nucleophilic displacement approach A for the preparation of **1**.

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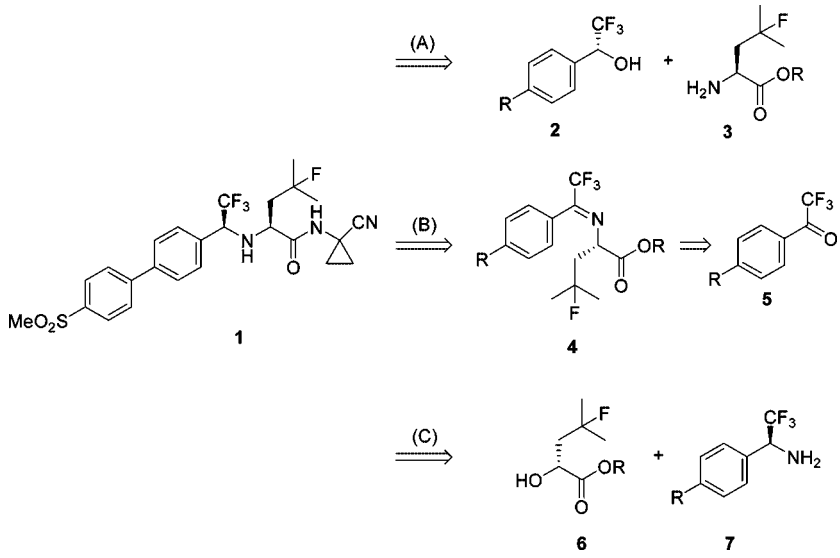

FIGURE 1. Retrosynthetic analysis.

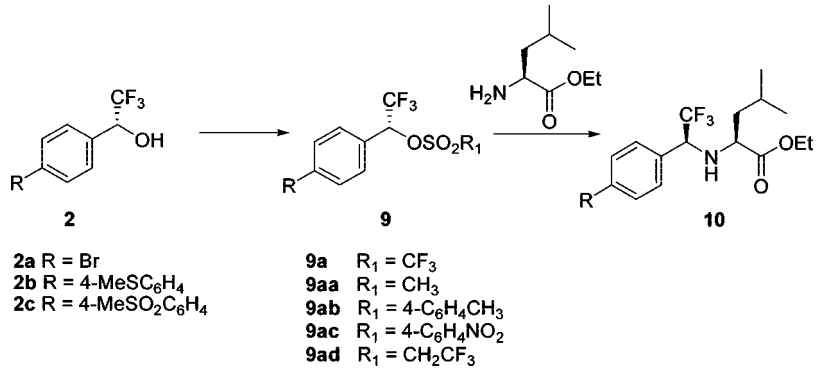

FIGURE 2. Displacement of activated alcohols.

Results and Discussion

The introduction of a fluorine in place of a hydrogen in an organic molecule can have a profound effect on its biological properties.[9] Recently, the trifluoroethylamine functionality has been proposed as an amide bond surrogate in peptidomimetics.[10] As such, the synthesis of chiral fluoroalkyl amines has received considerable attention in the literature and a number of methodologies have been reported.[11] The nucleophilic displacement of activated benzylic alcohols is a well-studied transformation in organic chemistry.[12] The stereospecific S_N2 displacement of activated chiral secondary benzylic alcohols is an attractive strategy for the preparation of optically active substrates. However, despite some reported successes,[13] its practical use remains limited due to racemization as a result of competing S_N1 and S_N2 pathways. Stereospecific displacements have been reported with use of electron-deficient aromatic or heteroaromatic[14] substrates where S_N1 pathways are disfavored through generation of destabilized carbocation intermediates. Due to the strong electron-withdrawing property of the CF_3 group, we were particularly interested in nucleophilic displacements of activated chiral alcohols such as **9**, which would provide easy access to the desired functionalized amino esters **10** (Figure 2). A survey of the literature revealed scant reference to displacement reactions of α-trifluoromethyl benzyl substrates. Tidwell and co-workers[15] have reported solvolysis studies of 1-aryl-2,2,2-trifluoroethyl sulfonates. β-Trifluoromethyltyrosine derivatives have been reported in racemic fashion via displacement of 1-chloro-2,2,2-trifluoroethyl phenols.[16] Fuchikami et al. have reported[17] clean S_N2 displacement of optically active alkyl-trifluoroalkyl triflates under mild conditions using benzoic acid

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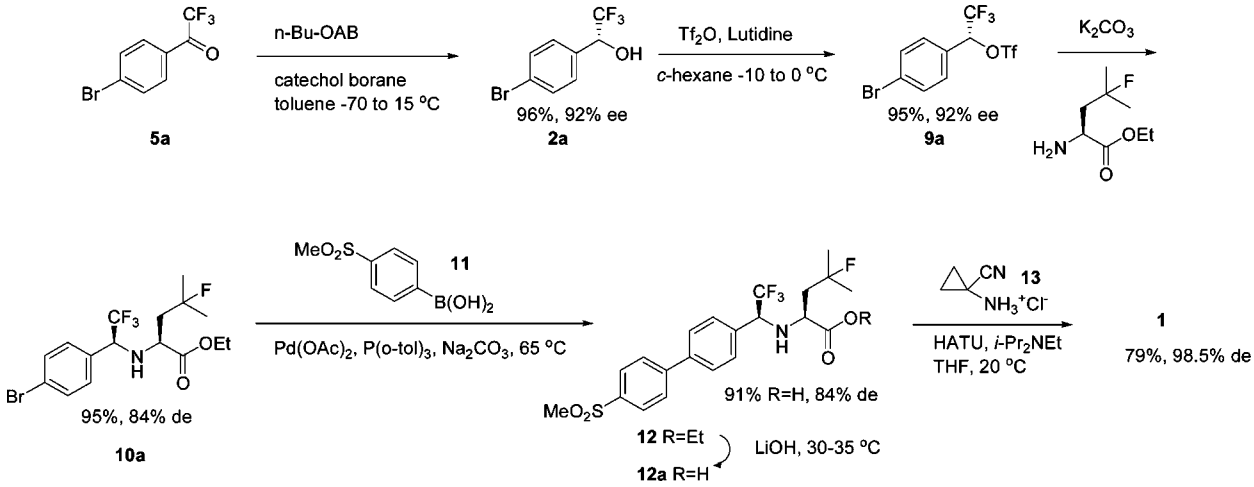
SCHEME 1. S_N2 Displacement Route to 1



as a nucleophile. In addition, the displacement of secondary benzylic mesylates has been reported; however, there are no details describing the stereospecificity of these reactions.

Chiral alcohol **2a** was accessed in a straightforward manner via oxazaborolidine-catalyzed enantioselective reduction[18] of ketone **5a**. Thus, treatment of a solution of **5a** with 2.5 mol % of *n*-Bu-OAB and catechol borane gave **2a** in 96% isolated yield and 92% ee. To study the effect of the aromatic ring substitution on the activation and subsequent amino ester displacement, biphenyl methylsulfide alcohol **2b** and methyl sulfone **2c** were also prepared in high yield via Suzuki[19] cross coupling with the requisite boronic acids. We began our studies with an investigation of various activating groups using commercially available L-leucine ester as a model amino ester (Figure 2).

We first evaluated biaryl sulfone alcohol **2c** as a substrate for the S_N2 reaction. Activation of alcohol **2c** as its corresponding mesylate or tosylate and reaction with 2 equiv of L-leucine methyl ester gave none of the desired product in a variety of solvents at temperatures from 25 to 100 °C. Higher temperatures (150 °C) led to rapid (<10 min) and complete decomposition of the starting material. Activation of the alcohol **2c** (90% ee) as its corresponding triflate followed by reaction with L-leucine methyl ester (2 equiv) with K_2CO_3 in 1,2-dichloroethane (DCE) at 50 °C did give the desired displacement product; however, significant erosion of stereochemistry at the benzylic center (20% ee) was observed. An evaluation of various solvents (*i*PAc, CH_3CN, THF) and bases (TEA, DIEA) failed to improve the outcome of this reaction and in most cases led to multiple byproducts with either decreased conversion and/or nearly complete erosion of optical purity.

Activation of alcohol **2b** with triflic anhydride or triflic chloride proved problematic, presumably due to competing thioether sulfonylation and subsequent decomposition. By comparison, the corresponding mesylate, tosylate, brosylate, nosylate, and tresylate were readily prepared in high yield and evaluated directly in the nucleophilic displacement reaction. The mesylate and tosylate were unreactive toward displacement under a variety of conditions, with hydrolysis or decomposition occurring at higher temperatures. Moderate to good conversion was observed in acetonitrile with K_2CO_3 at 40−80 °C for the brosylate (50%), nosylate (80%), and tresylate (82%); however, in all cases the product obtained was racemic at the benzylic center.

We then focused our efforts on the displacement of 1-(4-bromophenyl)-2′,2′,2′-trifluoroethanol **2a**. As in the case of **2b** and **2c**, the corresponding mesylate **9aa** and tosylate **9ab** were unreactive under a variety of reaction conditions. Therefore, we investigated more reactive leaving groups. The nosylate-activated alcohol **9ac** afforded hydrolysis product under a variety of reaction conditions. The corresponding tresylate **9ac** afforded a 42% conversion to the desired compound in a 5:1 diastereomeric ratio; however, all attempts to improve the conversion resulted in lower selectivity and/or decomposition. High conversion was observed with the triflate **9a**; however, in the initial experiments significant erosion of enantiometic excess was observed at the benzylic center. In an effort to improve on the stereochemical outcome, a number of reaction parameters were evaluated. Solvents such as DMSO, DMF, NMP, DMPU, and toluene were found to be unsuitable due to their reaction with the triflate. The reaction did proceed in *i*PAc, CH_3CN, $PhNO_2$, THF, PhCl, CH_2Cl_2, *c*-hexane, and *n*-Bu_2O to varying degrees of success. An evaluation of bases indicated that *i*-Pr_2NEt, Et_3N, 2,6-lutidine, K_3PO_4, and K_2CO_3 all gave high conversion. Stability studies on the triflate **9a** with chiral HPLC to measure the ee of unreacted triflate indicated that the loss of ee at the benzylic center was due to racemization of the triflate as the reaction progressed. The racemization was promoted by increasing temperature, the use of more polar solvents, and the presence of soluble triflate salts. Therefore, we were delighted to find that treatment of triflate **9a** with (*S*)-γ-fluoroleucine ethyl ester **3**[20] and K_2CO_3 in *c*-hexane at 70 °C led to high conversion to the desired product with minimal erosion of ee at the benzylic center. Thus treatment of **2a** (92% ee) with Tf_2O in *c*-hexane with 2,6-lutidine at 0−10 °C gave the desired triflate **9a** in >95% yield with no loss of ee as a *c*-hexane solution after aqueous workup. Addition of K_2CO_3 and **3** followed by heating at 65−70 °C for 18−24 h yielded **10a** in 95% yield and 84% de (Scheme 1).

An evaluation of cross-coupling conditions between bromo ester **10a** and boronic acid **11** with $Pd(OAc)_2$ and various ligands Ph_3P, $(o\text{-tol})_3P$, $(2\text{-furyl})_3P$, $(Cy)_2P$-biaryl, and $(t\text{-Bu})_2$-biaryl

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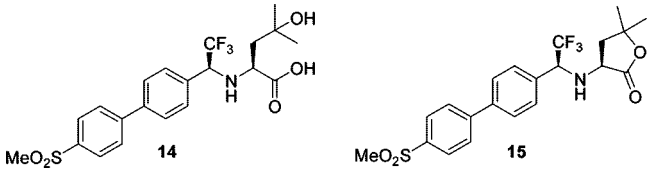

FIGURE 3. Ester hydrolysis impurities.

revealed high conversion and purity with use of $(o\text{-tol})_3P$. Thus treatment of bromide **10a** with boronic acid **11** in the presence of $Pd(OAc)_2$ (0.5 mol %), $(o\text{-tol})_3P$ (1.25 mol %), and aqueous Na_2CO_3 in THF at 65 °C for 2 h gave >99% conversion (93% assay yield by HPLC) of the desired biaryl **12** (Scheme 1).

Several reagents were investigated for the hydrolysis of the ethyl ester **12**. Potassium trimethylsilanolate (TMSOK) in THF at 20 °C afforded good conversion to the desired acid **12a** but caused extensive epimerization (~10%) at the amino ester stereocenter. Lithium hydroperoxide afforded only low conversion (~20%) even after extended reaction time. NaOH gave the desired acid but generated up to 10% of hydroxyl acid **14** (Figure 3). KOH led to a much slower hydrolysis and caused 1−5% epimerization of the amino ester stereocenter. Interestingly, LiOH gave complete conversion to the desired acid within a few hours at reflux in THF with a lower amount of hydroxy acid **14** and no epimerization was observed with HPLC analysis. We focused our efforts on a one-pot Suzuki coupling/hydrolysis procedure to increase the efficiency of the process. Thus, on completion of the Suzuki reaction powdered $LiOH \cdot H_2O$ (5 equiv) was added to the reaction mixture at 20 °C. The saponification was completed after 18 h at 35 °C and following extractive workup, the desired acid **12a** was isolated in 91% yield (over two steps) and 84% de (Scheme 1). It was necessary to store the acid at <4 °C to prevent formation of the undesired lactone **15** (Figure 3).

A number of conditions were investigated for the amidation of acid **12a** with cyclopropylaminonitrile **13**. Activation of the acid **12a** with oxalyl chloride or thionyl chloride followed by treatment with amine hydrochloride **13** led to low yields of **1**. Similarly, activation as a mixed anhydride with pivaloyl chloride did not give useful yields of **1**. High conversion and yields were obtained with a number of peptide coupling agents most notably phosphonium coupling reagent PyBOP and uronium coupling reagents TBTU and HATU. Thus, treatment of **12a** and **13** with HATU and DIEA in DMAc at 5 °C led to high conversion to the desired amide **1**. Addition of water directly to the reaction mixture crystallized **1** in 79% isolated yield with an efficient rejection of the minor diastereoisomer to give an upgrade in de from 84% to 98.5%. A final recrystallization from THF/water provided an additional purity and diastereomeric upgrade yielding **1** with 97% recovery and >99.5% de.

Conclusion

Odanacatib (MK-0822) **1** was synthesized in six steps and 61% overall yield from commercially available 1-(4-bromophenyl)-2,2,2-trifluoroethanone (**5a**) without the need for chromatography. The key step is a novel triflate displacement of (1*R*)-1-(4-bromophenyl)-2,2,2-trifluoroethyl trifluoromethanesulfonate (**9a**) with (*S*)-γ-fluoroleucine ethyl ester **3**, which provides **10a** with minimal loss of ee at the benzylic center. Subsequent Suzuki cross coupling, saponification, and amidation complete the synthesis.

Experimental Section

(1*R*)-1-(4-Bromophenyl)-2,2,2-trifluoroethanol (2a). Catecholborane (9.49 L, 2.0 M in toluene, 18.97 mol, 1.6 equiv) was cooled to −50 °C. (*S*)-Butyloxazaborolidine (988 mL, 0.3 M solution in toluene, 0.30 mol, 2.5 mol %) was added over 30 min and the mixture was cooled to −70 °C. A solution of 1-(4-bromophenyl)-2,2,2-trifluoroethanone **5a** (3.00 kg, 11.86 mol) in toluene (9.0 L) was added to the reaction mixture over 3 h. The reaction mixture was warmed to −55 °C over 2 h, maintained at this temperature for 4 h, then gradually warmed to 15 °C over 14 h. The reaction mixture was cooled to −20 °C then toluene (2 L) was added, followed by aqueous 1 N HCl (30 L) over 10 min. The batch was warmed to 20 °C and the layers were separated. The organic layer was successively washed with aqueous 2 M Na_2CO_3 (3 × 15 L), aqueous 1 N HCl (15 L), and H_2O (2 × 15 L). The batch was concentrated under reduced pressure (35 °C), flushed with toluene (8 L), and kept as a toluene solution. HPLC assay indicated 2.9 kg of trifluoromethyl alcohol **2a** in 96% yield, 92.4% ee: mp 55−56 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, 2H, J = 8.5 Hz), 7.35 (d, 2H, J = 8.3 Hz), 5.02−4.98 (m, 1H), 2.64 (d, 1H, J = 4.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.2, 132.2, 129.5, 124.3 (q, J = 282.1 Hz), 124.2, 72.6 (q, J = 32.4 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ −78.5; IR (NaCl cm^{-1}) 3374, 3075, 2945, 2880, 1593, 1492, 1402, 1335, 1247, 1195, 1124, 1096; $[\alpha]^{20}_D$ −27.5 (*c* 1.06, EtOH); HPLC Zorbax Rx-C8 4.6 mm × 25 cm column; eluants (A) 0.1% aqueous H_3PO_4 and (B) acetonitrile; 2 mL/min; gradient A/B 70:30 to 5:95 over 25 min; λ = 220 mn; temperature 35 °C; t_R(ketone) = 7.4 min, t_R(alcohol) = 9.4 min; SFC (chiral) Chiralcel OJ 4.6 mm × 25 cm column; eluants (A) 2-propanol and (B) CO_2; 2 mL/min; gradient A/B 1:99 for 4 min to 20:80 over 12.7 min; λ = 220 mn; temperature 35 °C; t_R((*R*)-**2a**) = 10.2 min, t_R((*S*)-**2a**) = 10.9 min, 92.4% ee. Anal. Calcd for $C_8H_6BrF_3O$: C, 37.68; H, 2.37. Found: C, 37.44; H, 2.10.

(1*R*)-1-(4-Bromophenyl)-2,2,2-trifluoroethyl Trifluoromethanesulfonate (9a). A solution of bromo alcohol **2a** (2.13 kg, 5.15 mol, 1.0 equiv, 92% ee) and 2,6-lutidine (0.88 kg, 8.24 mol, 1.6 equiv) in *c*-hexane (5 L) was cooled to −10 °C. Triflic anhydride (2.18 kg, 7.7 mol, 1.5 equiv) was added over ~30 min at a rate to maintain the temperature <10 °C. The reaction mixture was aged for 90 min maintaining the temperature at 0−10 °C. Water (5.6 L) and *c*-hexane (5.6 L) were added. The aqueous layer was separated and the organic layer was washed with aqueous 1 N HCl (1 × 5.6 L, 2 × 2.6 L) and water (5.6 L). Following layer separation the *c*-hexane was removed under reduced pressure to yield 3.12 kg of **9a** in *c*-hexane, 95% yield, 91.7% ee: ^{1}H NMR (400 MHz, acetone-d_6) δ 7.83−7.79 (m, 2 H), 7.70 (d, 2H, J = 8.4 Hz), 6.74 (q, 1 H, J = 5.9 Hz); ^{13}C (125 MHz, benzene-d_6) δ 132.5, 129.4, 126.8, 126.2, 121.6 (q, J = 280 Hz), 118.6 (q, J = 323 Hz), 81.9 (q, J = 36 Hz); ^{19}F NMR (377 MHz, acetone-d_6) δ −80.3 (s, 3F), −81.7 (d, 3F, J = 31 Hz); HRMS (ESI) calcd for $C_9H_6BrF_6O_3S$ $[MH]^+$ 388.0976, found 388.0976; $[\alpha]^{20}_D$ −84 (*c* 1.7, hexanes); HPLC Zorbax SBC18 4.6 mm × 25 cm column; eluants (A) 0.1% aqueous H_3PO_4 and (B) acetonitrile; 2 mL/min; gradient A/B 50:0 to 5:95 over 10 min, hold 5 min; λ = 220 nm; temperature 25 °C; t_R(alcohol) = 4.0 min, t_R(triflate) = 7.9 min: chiral HPLC Chiralpak AD 4.6 mm × 25 cm column; eluant hexane 100%; 1 mL/min; λ = 220 nm; temperature 25 °C; t_R((*S*)-**9a**) = 10.4 min, t_R((*R*)-**9a**) = 11.6 min, 91.7% ee.

Ethyl *N*-[(1*S*)-1-(4-Bromophenyl)-2,2,2-trifluoroethyl]-4-fluoro-L-leucinate (10a). Potassium carbonate (1.19 kg, 8.59 mol, 1.5 equiv) was added to a mixture of triflate **9a** (3.12 kg, 5.7 mol, 1.0 equiv, 91.7% ee), *c*-hexane (2 L), and amino ester (1.48 kg, 8.02 mol, 1.4 equiv, 96% ee). The mixture was heated to 65−70 °C and aged for 24 h. The mixture was cooled to 20 °C and *c*-hexane (5.6 L) and water (5.6 L) were added, then the mixture stirred for 10 min. The layers were separated; the organic layer was washed with aqueous 1 N HCl (1 × 5.6 L, 2 × 2.5 L) and water (5 L). The organic layer was concentrated under reduced pressure to yield 2.6

kg of **10a**, 95% yield, 84% de (^{19}F NMR). A sample was purified by flash chromatography (5% EtOAc/hexanes) for purposes of characterization: mp 34.5−35.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, 2H, J = 8 Hz), 7.26 (d, 2H, J = 8 Hz), 4.10−3.97 (m, 3H), 3.61 (br s, 1H), 2.13 (br s, 1H), 2.07 (ddd, 1H, J = 18.5, 14.7, 5 Hz), 1.87 (ddd, 1H, J = 21, 14, 8 Hz), 1.46 (d, 3H, J = 17 Hz), 1.42 (d, 3H, J = 18 Hz), 1.18 (t, 3H, J = 7 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 174.1, 133.6, 131.8, 130.0, 125.1 (q, J = 282 Hz), 123.2, 94.7 (d, J = 156 Hz), 62.7 (q, J = 27 Hz), 61.1, 57.0 (d, J = 4 Hz), 44.4 (d, J = 23 Hz), 27.5 (d, J = 24 Hz), 26.5 (d, J = 25 Hz), 13.9; ^{19}F (377 MHz, $CDCl_3$) δ −78.5 (d, 3F, J = 7 Hz), −140.4 (nonet, 1F, J = 21 Hz); IR (film, cm^{-1}) 1729, 1490, 1370, 1258, 1158, 1123; $[\alpha]^{20}_D$ +37.5 (*c* 1.9, $CHCl_3$); HPLC Zorbax SB-C18 4.6 mm × 25 cm column; eluants (A) 0.1% aqueous H_3PO_4 and (B) acetonitrile; 2 mL/min; gradient A/B 50:50 to 5:95 over 10 min, hold 5 min; λ = 220 nm; temperature 25 °C; t_R(bromo amine **10a** (major diastereoisomer)) = 5.5 min, t_R(bromoamine **10a** (minor diastereoisomer)) = 5.8 min. Anal. Calcd for $C_{16}H_{20}BrF_4NO_2$: C, 46.39; H, 4.87; N, 3.38. Found: C, 46.22; H, 4.61; N, 3.47.

Ethyl 4-Fluoro-*N*-{(1*S*)-2,2,2-trifluoro-1-[4′-(methylsulfonyl)-biphenyl-4-yl]ethyl}-L-leucinate (12). A visually clean 5-necked 50-L round-bottomed flask was charged with crude bromo ester **10a** (1.85 kg, 4.46 mol) and THF (9.0 L). With stirring, *p*-methylphenylsulfone boronic acid (1.16 kg, 5.79 mol) and tri-*o*-tolylphosphine (17.0 g, 0.056 mol) were added. The solution was degassed with N_2 bubbling for 20 min. $Pd(OAc)_2$ (5.01 g, 0.022 mol) was added to the mixture and the solution was aged 20 min. Degassed 1 M aqueous Na_2CO_3 (6.7 L, 6.7 mol) was added to the THF solution. The biphasic mixture was heated to reflux (67 °C) under N_2 atmosphere and maintained at this temperature for 2 h. The reaction reached 99.8% conversion (by HPLC). The biphasic mixture was cooled to 35 °C and used directly for the hydrolysis of the ester. The HPLC assay yield of biaryl **12** was 1.98 kg, 92.7%, de 85% (by ^{19}F NMR): mp 102.9−103.6 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.03 (d, 2H, J = 8.4 Hz), 7.94 (d, 2H, J = 8.4 Hz), 7.79 (2H, d, J = 8.2 Hz), 7.62 (2H, d, J = 8.2 Hz), 4.46 (m, 1 H), 3.89 (qd, 2H, J = 5.9, 2.1 Hz), 3.65 (m, 1 H), 3.16 (s, 3 H), 2.69 (m, 1 H), 2.11−1.93 (m, 2 H), 1.46 (d, 3H, J = 21.5 Hz), 1.42 (d, 3H, J = 21.5 Hz), 1.08 (t, 3H, J = 7.1 Hz); ^{13}C NMR (126 MHz, acetone-d_6) δ 174.2, 145.4, 140.6, 139.9, 135.8, 129.7, 128.3, 128.1, 127.8, 126.2 (q, J = 282 Hz), 94.9 (d, J = 166 Hz), 63.0 (q, J = 29 Hz), 60.8, 57.9, 44.4 (d, J = 24 Hz), 43.9, 27.8 (d, J = 24 Hz), 26.1 (d, J = 24 Hz), 13.8; ^{19}F NMR (377 MHz, acetone-d_6) δ −78.0 (d, J = 8 Hz), −138.8 (m, J = 23 Hz); IR (NaCl cm^{-1}) 3339, 2984, 2933, 1733, 1598, 1482, 1374, 1304, 1262, 1150; HRMS (ESI) calcd for $C_{23}H_{28}F_4NO_4S$ $[MH]^+$ 490.1675, found 490.1673; $[\alpha]_D^{20}$ +47.8 (*c* 1.0, CH_2Cl_2); HPLC Zorbax Rx-C8 4.6 mm × 25 cm column; eluants (A) 0.1% aqueous H_3PO_4 and (B) acetonitrile; 1.8 mL/min; gradient A/B 90:10 to 10:90 over 15 min, hold 5 min; λ = 220 nm; temperature 35 °C; t_R(bromo amine **10a**) = 9.5 min, t_R(biaryl **12** (minor diastereoisomer)) = 12.8 min, t_R(biaryl **12** (major diastereoisomer)) = 13 min.

(2*S*)-4-Fluoro-4-methyl-2-(((1*S*)-2,2,2-trifluoro-1-(4′-(methylsulfonyl)biphenyl-4-yl))amino)pentanoic Acid (12a). $LiOH \cdot H_2O$ (935.7 g, 22.3 mol) was added to the crude biphenyl ethyl ester **12** (2.18 kg, 4.46 mol) from the Suzuki reaction. The resulting slurry was warmed to 35 °C and vigorously stirred for 19 h. The reaction mixture was cooled to 20 °C and heptane (9 L) and H_2O (9 L) were added. The layers were separated and the black emulsion was kept in the heptane layer. The organic layer was back-extracted with H_2O (4.5 L) and the black emulsion was kept in the organic layer. The combined aqueous layers were washed with toluene (9 L) and the black emulsion was kept in the toluene layer. The toluene layer was back-extracted with H_2O (4.5 L) and the black emulsion was kept in the toluene layer. The combined aqueous layers were washed with MTBE (9 L) and the black emulsion was kept in the MTBE layer. The MTBE layer was back-extracted with H_2O (4.5 L) and the black emulsion was kept in the MTBE layer. Fresh MTBE (9 L) was added to the combined aqueous layers. Aqueous 2 N HCl (15.9 L) was added over 15 min until the pH of the aqueous layer was 2.5. The layers were separated and the brown emulsion was kept in the MTBE layer. The aqueous layer was extracted with MTBE (9 L) and the brown emulsion was kept in the MTBE layer. The combined organic layers were washed with H_2O (9 L) and the brown emulsion was kept in the aqueous layer. Solka-floc (206 g) and activated carbon Darco KB-B (206 g) were added to the MTBE layer and the mixture was vigorously stirred for 1 h at rt. The suspension was then filtered through Solka-Floc and rinsed with MTBE (2 × 1 L). The brown filtrate was line concentrated under reduced pressure (30 °C), flushed with iPAc (4 L), and concentrated until a beige solid formed. HPLC analysis indicated 1.9 kg of acid **12a** in 91% yield over two steps, 84% de: mp 115−117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, 2H, J = 8.3 Hz), 7.78 (d, 2H, J = 8.3 Hz), 7.65 (d, 2H, J = 8.1 Hz), 7.53 (d, 2H, J = 8.1 Hz), 4.30 (q, 1H, J = 7.0 Hz), 3.72 (dd, 1H, J = 7.8, 4.3 Hz), 3.12 (s, 3H), 2.20 (ddd, 1 H, J = 23.3, 15.0, 4.2 Hz), 1.99 (ddd, 1 H, J = 18.4, 15.1, 8.0 Hz), 1.50 (d, 3H, J = 21.7 Hz), 1.48 (d, 3H, J = 21.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 146.1, 140.7, 140.0, 134.5, 129.7, 128.5, 128.4, 125.6 (q, J = 282.3 Hz), 95.8 (d, J = 165.4 Hz), 63.1 (q, J = 29.2 Hz), 56.9, 45.0, 44.1 (d, J = 21.9 Hz), 27.6 (d, J = 24.7 Hz), 27.3 (d, J = 24.4 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ −73.5, −136.9; HRMS (ES) calcd for $C_{21}H_{24}F_4NO_4S$ $[MH]^+$ 462.1362, found 462.1362; IR (NaCl, cm^{-1}) 3337, 3032, 2982, 2930, 1733, 1717, 1652, 1597, 1486, 1375, 1303, 1262, 1150; $[\alpha]^{20}_D$ + 42.9 (*c* 1.20, EtOH); conversion, diastereomeric excess and yield were determined by HPLC Phenomenex Synergy Max RP 4.6 mm × 25 cm column; eluants (A) 0.1% aqueous H_3PO_4 and (B) acetonitrile; 1 mL/min; gradient A/B 40:60 to 15:85 over 20 min; λ = 265 nm; temperature 30 °C; t_R(hydroxy acid **13**) = 3.8 min, t_R(biphenyl acid **12a** (minor diastereoisomer)) = 5.3 min, t_R(biphenyl acid **12a** (major diastereoisomer)) = 6.1 min, t_R(lactone **14**) = 6.6 min, t_R(biphenyl ester **12**) = 9.1 min.

(2*S*)-*N*-(1-Cyanocyclopropyl)-4-fluoro-4-methyl-2-({(1*S*)-2,2,2-trifluoro-1-[4′-(methylsulfonyl)biphenyl-4-yl]ethyl}amino)pentanamide (1). To a visually clean 5-necked 50-L round-bottomed flask equipped with a mechanical stirrer, a thermocouple, a dropping funnel, and a nitrogen inlet was added biaryl acid **12a** (1.87 kg, 4.0 mol) and DMAc (9.3 L). The solution was cooled to 3 °C and 1-aminocyclopropane carbonitrile hydrochloride (576 g, 4.86 mol) and HATU (1.85 kg, 4.86 mol) were charged to the reactor. The resulting slurry was stirred for 15 min and DIEA (2.1 L, 12.1 mol) was added over 1.5 h maintaining the temperature at <10 °C. HPLC indicated complete reaction at the end of the addition. Water (11.2 L) was added via dropping funnel over 70 min and the slurry that formed was aged for 1 h at 19−20 °C. The mixture was filtered and the filter cake was washed successively with a solution of DMAc:water (9.35 L, 1:1.2), water (18.7 L), 2-propanol (9.3 L), and MTBE (9.3 L). The batch was dried under vacuum at 35 °C to yield 1.67 kg of **1**, 79% yield, 98.38 area %, 98.5% de by HPLC.

A visually clean 5-necked 50-L round-bottomed flask equipped with a mechanical stirrer, a thermocouple, a dropping funnel, and a nitrogen inlet was charged with crude **1** (2.56 kg, 4.87 mol). THF (30.7 L) was added, then the batch was warmed to 30 °C and stirred for 1.2 h. Water (20.5 L) was added via dropping funnel. The batch was cooled to 22 °C and seeded with **1** (500 mg). The batch was aged for 1 h at 20−22 °C. A seed bed formed and addition of water (40.9 L) was continued over 1.5 h. The batch was aged at 20 °C for 12 h. The batch was filtered and washed with water (15 L) and dried under vacuum at 35 °C to yield **1** as a white solid (2.50 kg, 97% yield, 99.7 area %, 99.9% de by HPLC): mp 223−224 °C; ^{1}H NMR (CD_3OD) δ 8.17 (br s, 1H), 8.05 (d, 2H, J = 8.5 Hz), 7.96 (d, 2H, J = 8.5 Hz), 7.80 (d, 2H, J = 8.0 Hz), 7.64 (d, 2H, J = 8.0 Hz), 4.43 (m, 1H), 3.55 (ddd, 1H, J = 5.0, 8.5, 8.0 Hz), 3.18 (s, 3H), 2.84 (br m, 1H), 2.02 (m, 2H), 1.46 (d, 3H, J = 21.5 Hz), 1.43 (d, 3H, J = 22.0 Hz), 1.36 (m, 2H), 1.07 (m, 1H), 0.94 (m, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 175.2, 146.0, 141.2, 140.6,

136.1, 130.3, 128.9 (q, $J = 282.8$ Hz), 128.7, 128.6, 128.4, 120.9, 95.9 (d, $J = 164.3$ Hz), 63.5 (q, $J = 30.0$ Hz), 59.2 (d, $J = 3.5$ Hz), 44.8 (d, $J = 23.1$ Hz), 44.3, 27.5 (d, $J = 23.9$ Hz), 27.1 (d, $J = 24.9$ Hz), 20.7, 16.5; ^{19}F NMR (CD_3OD) δ −73.2, −136.8; IR (cm^{-1}) 3331, 2244, 1687, 1304, 1152; $[\alpha]^{20}_D$ + 23.3 (*c* 0.53, MeOH); HRMS calcd for $C_{25}H_{28}F_4N_3O_3S$ $[MH]^+$ 526.1782; found 526.1781; HPLC Phenomenex Spherisorb 4.6 mm × 25 cm column; eluants (A) 0.1% aqueous H_3PO_4 and (B) acetonitrile; 1 mL/min; gradient A/B 60:40 to 30:70 over 30 min; $\lambda = 265$ nm; temperature 45 °C; t_R(**1** (major diastereoisomer)) = 15.8 min, t_R(**1** (minor diastereoisomer)) = 16.4 min; HPLC (chiral) Chiralpak AD 4.6 mm × 15 cm column; eluants (A) hexanes, (B) ethanol, and (C) methanol; 1 mL/min; isocratic A/B/C 80:10:10 for 60 min; λ = 265 nm; temperature 40 °C; t_R((*S*,*S*)-**1**) = 14.5 min, t_R((*R*,*S*)-**1**) = 11.9 min, t_R((*S*,*R*)-**1**) = 18.2 min, t_R((*R*,*R*)-**1**) = 25.3 min, >99.5% (*S*,*S*).

Supporting Information Available: Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra for **2a**, **9a**, **10a**, **12**, **12a**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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