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Preparation of a HMG-CoA Reductase Inhibitor via an Optimized Imidazole-Forming Condensation Reaction

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Abstract:

Development work toward an enabling synthesis of preparative scale batches of an imidazole-based HMG-CoA reductase inhibitor is described. The desired target was synthesized in 16% yield over 7 steps, highlighted by an imidazole-forming condensation reaction in which the yield was improved from 20% to >70% via modification of the solvent, acid, and amine equivalents. The step 2 acylation was improved, and a problematic benzyl ester in step 4 was converted into the corresponding benzyl amide to decrease trans-amidation during the step 5 imidazole formation. A highly effective salt formation and crystallization protocol was also developed.

Introduction

Statins, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors,[1] are widely prescribed in the fight against coronary heart disease[2] for their ability to moderate hypercholesterolemia.[3] Unfortunately, many marketed statins, albeit effective in lowering levels of LDL-C (so-called "bad cholesterol"),[4] have been linked to a variety of musculoskeletal problems, such as cramping, myalgia,[5] and rhabdomyolysis.[6] Imidazole **1** (Figure 1) is a HMG-CoA reductase inhibitor with potential for improved efficacy and tolerability[7] in comparison to those currently available.

When analyzing the existing synthesis of **1** for potential process improvements, it was determined that identification of an efficient synthesis of the key imidazole core was paramount.

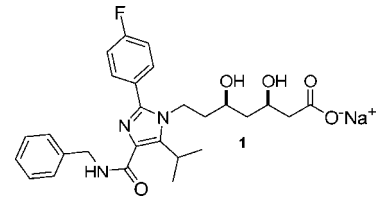
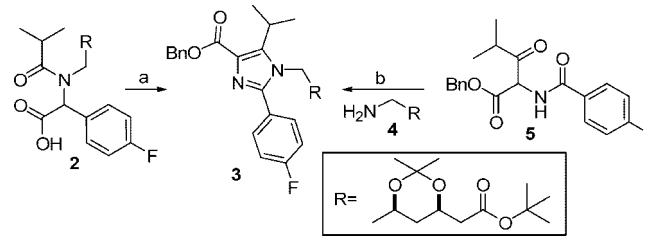


Figure 1. **Imidazole 1, a potential HMG-CoA reductase inhibitor.**

Scheme 1. **Two approaches to imidazole 3**[a]



[a] Reagents and conditions: (a) $NCCO_2Bn$, Ac_2O, $CF_3C_6H_5$, reflux, 24 h, 15%; (b) **4**, xylene, AcOH, TsOH (cat.), reflux, 16 h, 20%.

The original discovery synthesis[8] was based on a Münchnone cyclization[9] of α-amino acid **2**(Scheme 1), but imidazole **3** was formed as the minor regioisomer and proved challenging to isolate cleanly by chromatography. An alternate preparation from α-amino β-ketoester **5** also afforded low conversion to **3** but avoided the formation of regiochemical isomers. Thus, **3** could be readily isolated from other byproduct via flash chromatography, which enabled the second-generation synthesis (Scheme 2) capable of providing gram quantities of **1** for preclinical toxicological studies. However, it became evident that several steps of the process would need to be significantly improved to provide larger quantities of API.

Acylation of glycine diphenylimine **7** with isobutyryl chloride originally required three cryogenic reactors and a tedious workup. Amine salt **8** was typically isolated by crystallization from water, making the subsequent moisture-sensitive amide formation extremely difficult. To make matters worse, **8** was prone to decomposition upon vacuum drying

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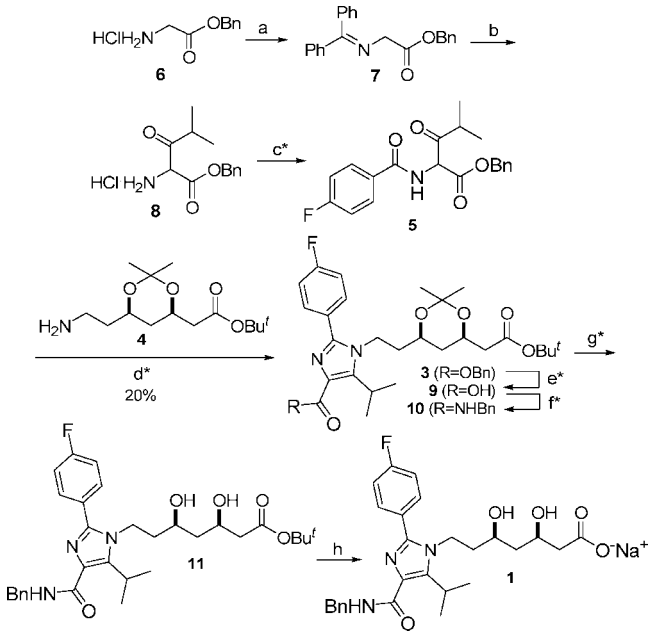
Scheme 2. **Second-generation synthesis of 1[a]**



[a] Reagents and conditions: (a) benzophenone imine, CH_2Cl_2, 20 °C, 8 h, 99%; (b) i. KO^{t}Bu, isobutyryl chloride, THF, −78 °C, 30−70 %; ii. HCl (aq); (c) 4-fluorobenzoyl chloride, Et_3N, CH_2Cl_2, 0 °C, 30 min, 45−85%; (d) xylene, AcOH, TsOH (cat.), reflux, 16 h, 20%; (e) Pd/C, H_2, 50 psi, 25 °C, 4 h, 91%; (f) benzylamine CDI, DMF, 0 °C to 20 °C, 2 h, 90%; (g) TFA, CH_2Cl_2, 0 °C, 30 min, 52%; (h) NaOH (aq), THF, 50 °C, 2 h, 92%; * step required chromatography.

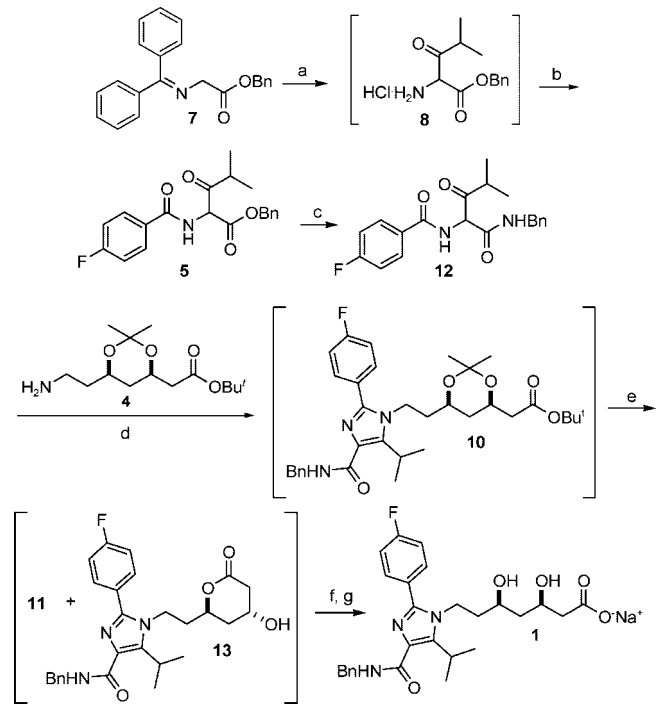
above 35 °C, so the overall conversion of imine **7** to ketoamide **5** was not robust. Cyclization of **5** with amine **4**[10] afforded **3**, but this reaction suffered from a variety of side reactions, resulting in a poor overall yield (<20%). Debenzylation and CDI coupling afforded smooth conversion to the amide **10**, but acetonide deprotection with trifluoroacetic acid resulted in formation of a variety of impurities stemming from β-hydroxy elimination. Sodium salt **1** was isolated as a mixture of amorphous and crystalline solids, and excess sodium hydroxide contaminated the final product. A total of five chromatography steps were also necessary via the original synthetic pathway.

In this paper we report a series of practical refinements of the second-generation synthesis of **1** that proved more amenable to preparative scale-up. The acylating, amide-forming, and imidazole-forming steps were all significantly improved and simplified from the original procedure. An improved protocol for isolation of crystalline **1** allowed all chromatography steps to be removed from the synthesis.

Results and Discussion

The second-generation route was modified to enable the synthesis of several hundred grams of **1**, in 16% yield over seven steps (Scheme 3). The preparation of masked glycine **7** was not altered from the original procedure and was readily isolated from the imine exchange reaction of HCl salt **6**[11] with benzophenone imine. The subsequent acylation of imine **7**,

Scheme 3. **Optimized second-generation synthesis of 1[a]**



[a] Reagents and conditions: (a) i. KO^{t}Bu, isobutyryl chloride, THF, −70 °C; ii. HCl (aq); (b) K_2CO (aq), CH_2CL_2, 4-fluorobenzoylchloride, 0 °C, 0.5 h, 75% (2 steps); (c) benzylamine, Et_3N, heptane 70 °C, 6 h, 80%; (d) **4**, benzoic acid, heptane, 82 °C, 48 h; (e) MeOH, HCl (aq), 45 °C, 12 h; (f) i. NaOH (aq), IPA, 95 °C, 6 h; ii. HCl (aq) to pH = 4, MTBE, 50 °C, 1 h; iii. NaOH (aq), IPA; (g) IPA (aq), reflux to 18 °C, 57% from **12**; [] not isolated.

however, proved to be difficult. Acidic workup of the reaction mixture obtained using the second-generation chemistry resulted in isolation of approximately 20% of hydrolyzed glycine ester **6** as an unwanted byproduct. However simply charging 1.0 equiv of both reagents led to the optimized results: a 93:5 ratio of **8** to **6** in 83% yield. In this procedure, imine **7** was added slowly to a −70 °C slurry potassium *tert*-butoxide in THF, and the resulting anion was transferred into a solution of isobutyryl chloride. Acylated intermediate **14** was hydrolyzed with aqueous HCl, and benzophenone was removed by extraction with MTBE. Amine salt **8** was either crystallized from the aqueous layer in 83% yield (99% (area %) HPLC purity) or was more preferably carried forward as a crude aqueous solution.

The problematic anhydrous amidation conditions were replaced with a more effective Schötten−Baumann procedure in which the aqueous solution of **8** was treated with potassium carbonate and dichloromethane, followed by slow addition of 4-fluorobenzoyl chloride. This made it unnecessary to dry and isolate **8** before amidation, as ketoamide **5** was isolated by crystallization from MTBE/heptane in 90% yield (>98% HPLC purity).

The second-generation synthesis (Scheme 2) had required a three-step sequence including (i) cyclization to afford imidazole **3**, (ii) debenzylation to produce acid **9**, and (iii) CDI coupling with benzylamine to produce amide **10**. However, the benzyl ester in ketoamide **5** was prone to *trans*-amidation with amine **4** during the formation of **3**, resulting in a poor yield (<20%) for this key step. We reasoned that installation of the desired benzyl amide prior to the cyclization might "block" this site to the undesired side reaction, potentially improving the formation

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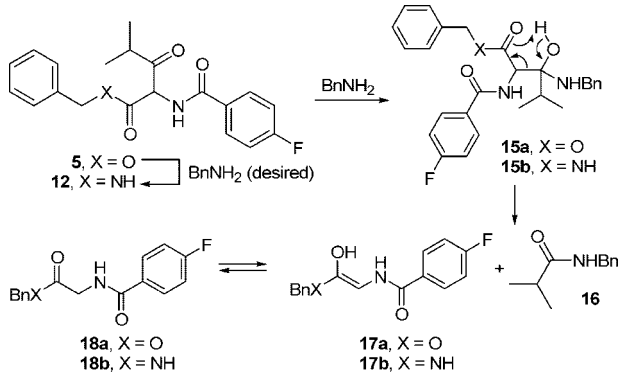
(11) The corresponding tosylate and mesylate salts, ethyl and methyl esters, and benzyl amide were also investigated.

Scheme 4. **Retro-Claisen dealkylation of ketoamides 5 and 12**



of the imidazole. However, the desired *trans*-amidation resulting from treatment of **5** with benzylamine resulted primarily in retro-Claisen dealkylation (Scheme 4) to produce **18**.

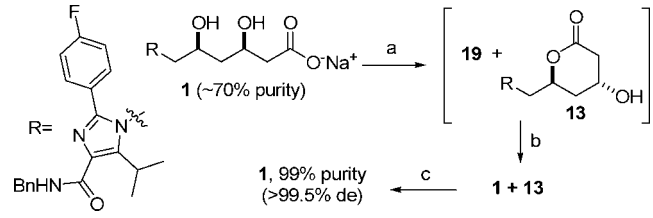
The conversion of **5** to **12** (Scheme 3) was further examined in a variety of solvents. Highly polar solvents such as DMF, DMSO and benzylamine resulted in complete consumption of **5** but exacerbated the decomposition. Nonpolar solvents such as hexane, heptane and methyl cyclohexane appeared to minimize formation of **18**, but conversion often stalled due to poor solubility of both **5** and **12**. Use of non-nucleophilic amines such as Hunig's base and triethylamine as cosolvents improved solubility and conversion without significantly increasing dealkylation. Under the most effective conditions screened, **5** was treated with 2 equiv of benzylamine in 2:1 heptane/triethylamine to afford **12** as a fluffy solid that was easily filtered away from the crude reaction mixture in good purity.

With **12** in hand, our focus turned toward optimization of the original condensation conditions (refluxing xylenes, acetic acid, 72 h). A variety of solvent and acid combinations were studied. Installation of the amide functionality in **12**, as predicted, immediately improved the isolated yield of **10**[12] (Scheme 3) in the cyclization from 20% to 41%. Several nonpolar solvents performed well, and heptane was especially effective. Most polar solvents afforded poor conversion to desired product.

During the course of this study, it was determined that a mild acid additive was crucial for stabilization of amine **4** against dimerization. We discovered that under the original cyclization conditions, acetic acid was inadvertently removed via its azeotrope with heptane and was trapped in the aqueous layer in the Dean−Stark apparatus, resulting in poor conversion to **10**. Cyclization in neat acetic acid failed. A variety of carboxylic acids with increased resistance to azeotropic distillation, including pivalic, benzoic, tosic, and solid-supported acid resins were screened, and benzoic acid, which was easily washed away afterward, enabled significant improvement. As an added benefit, replacement of the original reagents xylenes and acetic acid with heptane and benzoic acid, respectively, allowed the necessary equivalents of amine **4** to be optimized from 5 down to 1.1. The isolated yield of **10** was improved to 72%, an increase of >50% over the original procedure with benzyl ester **5**.

(12) Isolated by column chromatography in >98% HPLC purity for this study.

Scheme 5. **Lactone 13, a useful intermediate toward the purification of 1**[a]



[a] Reagents and conditions: (a) HCl (aq), 50 °C, 1 h; (b) NaOH (aq), IPA; (c) 98:2 IPA/water, 80 °C to 18 °C.

Despite these improvements, it seemed that flash chromatography would have still been required to isolate imidazole **10** in high purity. Instead, as a general practice this intermediate was carried forward as a crude concentrate (60−75% HPLC purity), and critical impurities were removed downstream. Substitution of methanolic HCl (aq) for TFA resulted in smooth conversion of acetonide **10** to diol **11**, while retaining the chiral integrity.[13] The *tert*-butyl ester was cleaved with excess sodium hydroxide, and free acid **19** (Scheme 5) was extracted into MTBE following pH adjustment with HCl. The organic solvents were replaced with 2-propanol via vacuum distillation to produce a 15:1 ratio of **19** (free acid) to lactone **13** (Scheme 5).[14] As a result, the end point of the subsequent sodium hydroxide addition (1.0 molar equiv) was easily reached by slowly metering in caustic until the level of **13** fell to <1% by HPLC analysis.[15] Residual water was removed to 2%[16] via azeotropic distillation, and sodium salt **1** was isolated by filtration.

Conclusions

A low yield second-generation synthetic route was transformed into a synthesis capable of manufacturing multiple kilograms of API within a scale-up facility, provided cryogenic capability is available. The acylating and amide-forming steps were combined into a one-pot procedure, resulting in improved robustness and yield. Replacing the benzyl ester of **5** with the corresponding benzyl amide increased the stability of downstream intermediates. The key imidazole-forming step was optimized to improve the yield from 20% to >70%, and the number of equivalents of amine **4** was decreased from 5 to 1.1. All five chromatographic purification steps were removed, enabling increased throughput and decreased processing time. Overall, the synthesis of imidazole **1** was improved from 4% to 16% yield over seven steps and was isolated in >99% HPLC purity (>99.5% de).[17]

Experimental Section

All reagents were purchased from commercial suppliers and used as received unless otherwise specified. All reactions were

(13) No β-elimination observed under these conditions.
(14) Lactone **13** was not crystallized despite repeated efforts.
(15) Sodium hydroxide selectively consumes free acid **19**, followed by reaction with lactone **13**, in that order. This phenomenon allowed careful titration to the desired addition endpoint.
(16) Determined by Karl Fischer analysis.
(17) A laboratory-scale batch was carried forward from raw materials to >250 g of **1** within 2 weeks time. Nearly 600 g of non-cGMP API was prepared by this method.

performed under a dry nitrogen atmosphere. NMR spectra were measured at 400 and 376 MHz, for ^{1}H and ^{19}F, respectively. HPLC analyses of chemical purity were carried out using a YMC Pack Pro C18 column (150 mm × 4.6 mm, 3 μm) with 0.2% $HClO_4$ in 95:5 water/acetonitrile (mobile phase A) and acetonitrile (mobile phase B) with a gradient method: 20% eluent B linearly increased to 95% eluent B over 20 min, 1.0 mL/min, 235 nm. Chiral purity analyses were carried out using a Daicel Chiralpak AD column (250 mm × 4.6 mm, 10 μm) with an isocratic mobile phase of hexanes/2-propanol, 85:15; 1.0 mL/min, 210 nm.

(Benzhydrylidene-amino)acetic Acid Benzyl Ester (7). A 5-L round-bottom flask equipped with an overhead stirrer and nitrogen inlet was charged with glycine benzyl ester hydrochloride **6** (505.2 g, 2.51 mol) and CH_2Cl_2 (3.0 L). To this mixture was charged benzophenone imine (471.1 g, 2.60 mol) in one portion. The reaction was stirred at 20 °C for 8 h until TLC analysis (1:1 ethyl acetate/heptane) confirmed full consumption of **6**. The precipitated ammonium salt was removed with a short pad of Celite, and the filter cake was rinsed with CH_2Cl_2 (0.5 L). The filtrates were concentrated under reduced pressure, and the resulting solid was dried for 12 h at 35 °C under vacuum to afford **7** (837.3 g, 101%) as a white solid that was carried on without further purification. ^{1}H NMR(DMSO-d_6): δ 7.53−7.25 (m, 13H), 7.12 (m, 2H), 5.10 (s, 2H), and 4.17 (s, 2H). MS *m*/*z* calcd for $C_{22}H_{19}NO_2$ 329.14, found 330.36 (M^+).

2-Amino-4-methyl-3-oxo-pentanoic Acid Benzyl Ester Hydrochloride (8). A 3-L round-bottom flask equipped with an overhead stirrer, cooling bath, and nitrogen inlet was charged with a slurry of potassium *tert*-butoxide (120.0 g, 1.07 mol) in THF (600 mL). The slurry was cooled to below −70 °C and was charged with a solution of **7** (350.3 g, 1.06 mol) in THF (800 mL) over 0.5 h, maintaining the reaction temperature below −40 °C. The reaction mixture was recooled to −70 °C and was then transferred into a second 5 L reactor containing a −70 °C solution of isobutyryl chloride (114.0 g, 112.1 mL, 1.07 equiv) in THF (300 mL), maintaining the reaction temperature in the receiving reactor below −55 °C. The reaction was stirred for 3 h between −55 and −65 °C and was then removed from the cold bath and quenched with HCl (3 M, 3.18 mol) in one portion. The reaction was allowed to warm to −10 °C, and was diluted with water (1 L) followed by extraction with MTBE (2 × 1 L). The aqueous layer was separated and distilled at 40 °C for 1 h under vacuum (60 Torr) to remove any residual MTBE. The resulting aqueous mixture was placed in the refrigerator between 0 and 3 °C for 12 h and was filtered to produce **8** (238.5 g, 83%) as a white solid that was carried forward without additional drying. Alternatively, crude **8** can be carried forward without crystallization. ^{1}H NMR (CD_3OD): δ 7.37−7.30 (m, 5H), 5.29−5.18 (dd, J = 23.8 and 12.2 Hz, 2H), 3.16−3.00 (m, 2H), 1.13 (d, J = 7.1 Hz, 3H), 1.00 (d, J = 6.9 Hz, 3H). MS *m*/*z* calcd for $C_{13}H_{18}NO_3Cl$ 271.10, found 236.31 (M^+ less HCl).

2-(4-Fluorobenzoylamino)-4-methyl-3-oxo-pentanoic Acid Benzyl Ester (5). A 5-L round-bottom flask equipped with an overhead stirrer, cooling bath, addition funnel, and nitrogen inlet was charged with **8** (427.8 g, 1.57 mol), water (1.0 L) and dichloromethane (1.0 L). The mixture was cooled to between −10 and 0 °C, and a solution of potassium carbonate (546.0 g, 3.95 mol) in water (1.5 L) was added at a rate of 2.5 mL/min, maintaining the reaction temperature below 5 °C. The reaction was recooled to 0 °C and was charged with a solution of 4-fluorobenzoyl chloride (209 mL, 1.74 mol) in dichloromethane (500 mL) at a rate of 1.5 mL/min, maintaining the reaction temperature below 5 °C. The reaction layers were separated after 30 min, and the aqueous portion was extracted with dichloromethane (500 mL). The combined organic layers were washed sequentially with HCl (0.1 M, 500 mL) and water (2 L) and then concentrated under vacuum to produce a yellow solid that was reconcentrated[18] from MTBE (0.5 L) and crystallized from a mixture of refluxing MTBE (1 L) and heptane (2.5 L). The resulting solid was collected by filtration and washed with heptane (0.5 L) and then dried for 12 h at 35 °C under vacuum to afford **5** (504.0 g, 90%) as a fluffy white solid. ^{1}H NMR ($CDCl_3$): δ 7.81 (dd, J = 7.0 and 4.8 Hz, 2H), 7.38−7.29 (m, 5H), 7.09 (dd, J = 8.5 and 8.6 Hz, 2H), 5.60 (d, J = 6.5 Hz, 1H), 5.22 (dd, J = 21.2 and 12.2 Hz, 2H), 3.07−3.02 (m, 1H), 1.20 (d, J = 7.0 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H). ^{19}F NMR ($CDCl_3$): δ −107.54. HPLC (area %) purity: 99.2%. MS *m*/*z* calcd for $C_{20}H_{20}FNO_4$ 357.14, found 358.36 (M^+).

***N*-(1-Benzylcarbamoyl-3-methyl-2-oxo-butyl)-4-fluorobenzamide (12).** A 3-L round-bottom flask equipped with an overhead stirrer, heating mantle, reflux condenser, and nitrogen inlet was charged with a slurry of **5** (500.0 g, 1.4 mol) in heptane (1.5 L) and triethylamine (750 mL). Benzylamine (375.0 g, 3.5 mol) was added in one portion, and the resulting slurry was heated to 70 °C for 6 h. The reaction was cooled to 18 °C and was filtered to produce a wet cake that was recrystallized from refluxing heptane (1.5 L). The resulting solids were collected by filtration and dried at 55 °C under vacuum for 12 h to afford **12** (401.2 g, 80%) as a pale-yellow, fluffy solid. ^{1}H NMR ($CDCl_3$): δ 7.85−7.80 (m, 2H), 7.70, (d, J = 6.5 Hz, 1H), 7.41−7.10 (m, 7H), 5.33 (d, J = 7.0 Hz, 1H), 4.42 (m, 2H), 3.17−3.14 (m, 1H), and 1.10 (m, 6H). ^{19}F NMR ($CDCl_3$): δ −106.95. MS *m*/*z* calcd for $C_{20}H_{21}FN_2O_3$ 356.15, found 357.12 (M^+).

7-[4-Benzylcarbamoyl-2-(4-fluorophenyl)-5-isopropyl-imidazol-1-yl]-3,5-dihydroxyheptanoic Acid, Sodium Salt (1). *Cyclization.* A 5-L round-bottom flask outfitted with an overhead stirrer and Dean−Stark apparatus was charged sequentially with benzyl amide **12** (356.7 g, 1.0 mol), amine **4** (183.0 g, 1.5 mol), benzoic acid (183.0 g, 1.5 mol), and heptane (3 L). The resulting slurry was heated to reflux for 18 h, and any water generated during the course of the reaction was removed via the Dean−Stark apparatus. The reaction progression was monitored by water collection and by HPLC analysis over 48 h, until less than 0.5% of **12** remained. The reactor was refitted with a distillation head and a total of 1.8 L of heptane was distilled out under ambient pressure. The reactor was cooled to 40 °C and charged with MTBE (1 L). The resulting solution was extracted with saturated sodium carbonate

(18) Azeotropic drying.

solution (2 × 750 mL) followed by HCl (0.5 N, 1 L). Crude **10** was carried forward in the organic phase without further purification.

Acetonide Removal. The organic layer was returned to the reactor and was diluted with methyl alcohol (1.8 L) and a solution of HCl (12 N, 34.0 g) in water (1.3 L). The mixture was heated to 45 °C for 3.5 h, until acetonide **10** was fully consumed by HPLC analysis. A crude solution of diol **11** and lactone **13** was carried forward into the next step.

tert-Butyl Ester Cleavage. The previous reaction mixture was charged with aqueous sodium hydroxide (50 wt %/wt) to pH = 13,[19] and was heated to 50 °C for 2 h, until *tert*-butyl ester **11** was determined to be fully consumed by HPLC analysis. The reaction was cooled to 35 °C, diluted with water (1 L), and extracted with MTBE (2 × 1 L). The aqueous product-containing layer was distilled under ambient pressure to a reaction temperature of 97 °C, and the resulting solution was cooled to 50 °C and held at this temperature while adding HCl (6 N) until the pH reached 7. The reactor was charged with MTBE (1 L) and the pH of the mixture was further adjusted to pH 4 ± 0.5 with HCl (1 N). The product-containing organic layer[20] was distilled under ambient pressure down to a volume of 0.6 L, and 2-propanol (1.5 L) was added. Distillation was continued, refilling with additional 2-propanol as necessary, until the pot temperature reached 82 °C, and the resulting crude mixture of free acid **19** and lactone **13** was distilled to a reaction volume of 0.5 L.

Salt Formation/Isolation. Aqueous sodium hydroxide (50 wt %/wt) was added to the reaction mixture in portions, and the level of lactone **13** was carefully monitored by HPLC analysis. Addition of sodium hydroxide was halted when only 0.2 to 0.5% of **13** remained after 10 min of stirring.[21] Additional anhydrous isopropyl alcohol (0.5 L) was added, the distillation head was refitted, and the solution was distilled under ambient pressure until Karl Fischer analysis indicated between 1 and 2% water (solution wt %) remaining.[22] The reaction volume was readjusted to a total volume of 1.0 L with additional 2% aqueous 2-propanol as necessary, and the reactor was cooled at a rate of 5 °C/h to 20 °C. The resulting slurry was stirred for an additional 3 h, and the solids were collected by filtration and rinsed with anhydrous 2-propanol (300 mL) to produce crude **1** (92% (area %) HPLC purity) that was carried forward into the recrystallization.

Recrystallization. Sodium salt **1** was redissolved into 80:20 2-propanol/water (700 mL) at reflux under a distillation head, and 2-propanol (500 mL) was added in one portion. The mixture was reheated to reflux, and additional 2-propanol was added, as necessary, while continuously distilling, until Karl Fischer analysis indicated between 1−2% of water (wt %) remained. The reactor was cooled at a rate of 5 °C/h to 20 °C, and the resulting slurry was stirred for 3 h and filtered. The solid product cake was rinsed with anhydrous 2-propanol (300 mL) and dried at 75 °C under vacuum for 12 h to afford 294.8 g (57%, > 99% (area %) HPLC chemical purity, > 99.5% de) of **1** as a crystalline white solid. ^{1}H NMR (CD_3OD): δ 7.62 (m, 2H), 7.33−7.19 (m, 7H), 4.95 (bs, 1H), 4.51 (s, 2H), 4.21 (ddd, J = 14.85, 11.33 and 5.08 Hz, 1H), 4.11−3.92 (m, 2H), 3.73 (m, 1H), 3.46 (m, 1H), 2.29 (dd, J = 15.24 and 5.47 Hz, 1H), 2.23 (dd, J = 15.04 and 7.42, Hz, 1H), 1.89−1.76 (m, 1H), 1.73−1.61 (m, 1H), 1.61−1.54 (m, 1H), 1.48 (m, 7H). ^{19}F NMR (CD_3OD): δ −113.88. Anal. Calculated for $C_{27}H_{31}F_1N_3NaO_5$: C, 62.42; H, 6.01; N, 8.09; Na, 4.40. Found: C, 62.32; H, 5.93; N, 8.05; Na, 4.39. Karl Fischer: 0.36% water. IR(neat) ν_{max} = 1657, 1574, 1512, 1411, 1223, 846, and 700 cm^{-1}.

(19) Additional sodium hydroxide was added, as necessary, to maintain the pH at 13 until this step was completed.
(20) As much as 10% of **19** was converted to lactone **13** during this pH adjustment.
(21) Any unreacted **13** was selectively purged in the subsequent crystallization step.
(22) Additional anhydrous isopropyl alcohol was added, as necessary, to maintain the reaction volume near 1 L.

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Supporting Information Available

Tables showing solvent effects on formation of amide **12** and influence of solvent and acid on yield of imidazole **10**. This information is available free of charge via the Internet at http://pubs.acs.org.

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