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Development of a Scalable Synthesis of a GPR40 Receptor Agonist

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Supporting Information

ABSTRACT: Early process development and salt selection for AMG 837, a novel GPR40 receptor agonist, is described. The synthetic route to AMG 837 involved the convergent synthesis and coupling of two key fragments, (*S*)-3-(4-hydroxyphenyl)hex-4-ynoic acid (**1**) and 3-(bromomethyl)-4′-(trifluoromethyl)biphenyl (**2**). The chiral *β*-alkynyl acid **1** was prepared in 35% overall yield via classical resolution of the corresponding racemic acid (±)-**1**. An efficient and scalable synthesis of (±)-**1** was achieved via a telescoped sequence of reactions including the conjugate alkynylation of an in situ protected Meldrum's acid derived acceptor prepared from **3**. The biaryl bromide **2** was prepared in 86% yield via a 2-step Suzuki−Miyaura coupling−bromination sequence. Chemoselective phenol alkylation mediated by tetrabutylphosphonium hydroxide allowed direct coupling of **1** and **2** to afford AMG 837. Due to the poor physiochemical stability of the free acid form of the drug substance, a sodium salt form was selected for early development, and a more stable, crystalline hemicalcium salt dihydrate form was subsequently developed. Overall, the original 12-step synthesis of AMG 837 was replaced by a robust 9-step route affording the target in 25% yield.

INTRODUCTION

Type 2 diabetes is a growing health concern that afflicts over 150 million people worldwide. Chronic hyperglycemia associated with diabetes can result in damage and dysfunction of various organs, including the eyes, kidneys, nerves, and heart. Activation of the G-protein coupled receptor GPR40 amplifies glucose-stimulated insulin secretion and lowers plasma glucose concentrations in multiple animal models of insulin resistance and obesity. Therefore, GPR40 agonists are being investigated as potential new therapeutic agents for the treatment of type 2 diabetes.[1] Herein we report the development of an efficient synthesis of AMG 837, a novel agonist of GPR40 that was selected for clinical development.

As shown in Scheme 1, AMG 837 possesses a chiral *β*-alkynyl acid fragment connected via an ether linkage to a trifluoromethyl-substituted biaryl. Thus, a convergent synthetic route would comprise the synthesis and coupling of two key fragments, (*S*)-3-(4-hydroxyphenyl)hex-4-ynoic acid (**1**) and 3-(bromomethyl)-4′-(trifluoromethyl)-biphenyl (**2**). Due to the paucity of scalable synthetic methods available for enantioselective alkynylation at the outset of this program,[2] efforts focused on the development of a racemic synthesis coupled with resolution to prepare the chiral intermediate **1**. Key to the success of this approach was the development of a practical synthesis of the Meldrum's acid derived acceptor **3**. Synthesis of the biaryl **2** via Suzuki−Miyaura cross-coupling was evaluated using various combinations of arylboronic acid−aryl halide coupling partners to minimize unit operations and cost-of-goods. The preparation and coupling of these intermediates posed a number of challenges for large-scale synthesis. This paper describes how these challenges were addressed during the development of a robust process for preparing a pharmaceutically acceptable salt form of AMG 837.

RESULTS AND DISCUSSION

Original Synthesis of Hexynoic Acid 1. The original 6-step synthesis of hexynoic acid **1** is summarized in Scheme 2.[1b] Knoevenagel condensation of 4-hydroxybenzaldehyde (**4**) with Meldrum's acid (**5**) in water provided benzylidene malonate **3**.[3] Protection of the phenol group of **3** as the corresponding THP ether[4] **6**, followed by addition of propynylmagnesium bromide, afforded the conjugate addition product **7**. Thermolysis of **7** in diethyl ketone/water resulted in decarboxylation with concomitant cleavage of the THP group to provide the racemic acid (±)-**1**. Resolution of (±)-**1** was accomplished by chiral chromatography or via diastereomeric salt formation with (1*S*,2*R*)-1-amino-2-indanol followed by salt break to furnish **1**.

In order to prepare sufficient quantities of **1** to supply the program, a number of limitations needed to be addressed. Although the initial Knoevenagel condensation reaction was reversible, it was driven forward in this case by the low solubility (<0.1 mg/mL) of the product **3** in water. In practice, a hot (50−60 °C) slurry of Meldrum's acid (**5**) in water was added to a solution of aldehyde **4** in water, and the resulting mixture was aged at 75 °C. This hetereogeneous (slurry-to-slurry) process produced a sticky suspension that filtered slowly and required recrystallization of **3** from acetone/water to increase the purity to >97%. Significantly, as the scale of the Knoevenagel condensation increased, the isolated yield of **3** decreased from 70% to 80% yield on 1−3 kg scale to 40−50% yield on 75−80 kg scale.

The THP protection step suffered from variable yields (<50−90%) and incomplete reaction, often stalling at 80−95% conversion. Charging additional catalyst (PPTS) or 3,4-dihydro-2*H*-pyran (DHP) did not improve conversion, and concomitant formation of black polymeric material was observed.[5] In addition, complete solvent switch from dichloromethane to acetone was required to isolate reasonable yields of solid **6**, necessitating a lengthy distillation. This process afforded **6** in relatively low purity (90−96%) and was not considered robust for scale-up due to the instability of the THP group.

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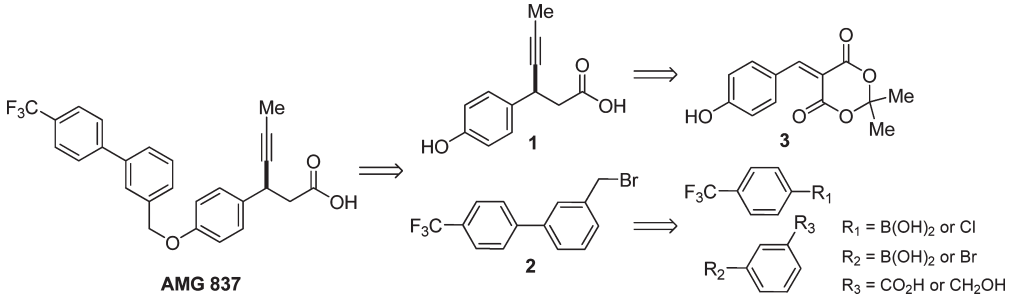
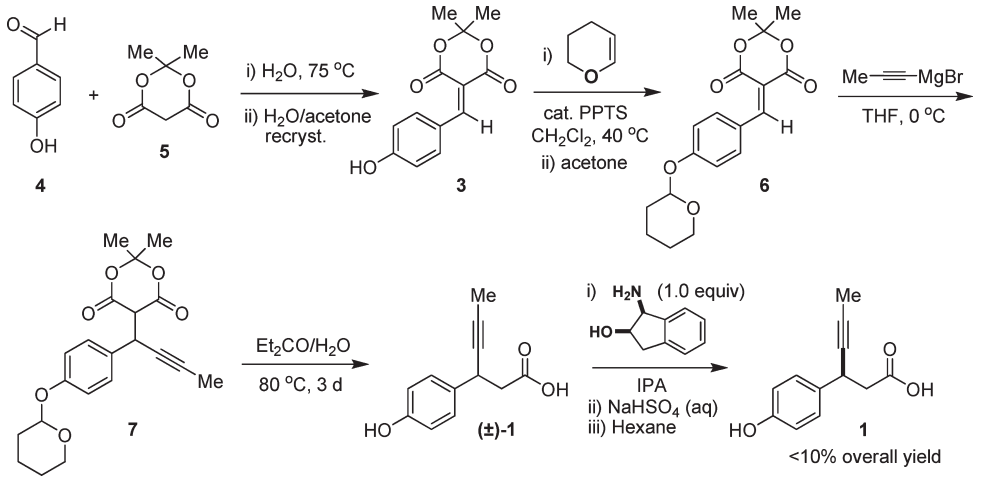
Scheme 1. Key Intermediates for the Synthesis of AMG 837



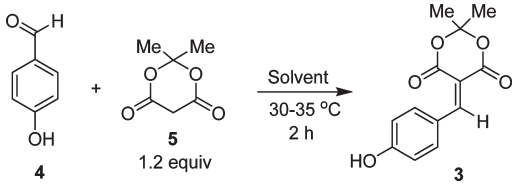
Scheme 2. Original Synthesis of 1



The conjugate addition of propynylmagnesium bromide to alkene **6** afforded **7** in 80−89% yield, depending on the purity of the starting material. However, during the extended reaction time (~3 days) required for hydrolysis−decarboxylation of **7**, several unidentified impurities were generated. The racemic acid (±)-**1** was isolated from this process in 67−74% yield and 85−95% purity. Recrystallization or purification via formation of a bis-diisopropylamine salt was used to provide (±)-**1** in >95% purity.[6] Resolution via diastereomeric salt formation with 1.0 equiv of (1*S*,2*R*)-1-amino-2-indanol in isopropyl alcohol (IPA) afforded **1** in ~93% ee (28% yield) after two crystallizations and a salt break. Further upgrade of the optical purity to our target of >97% ee was accomplished with chiral chromatography. The overall yield of **1** was <10%, and a more efficient and controlled process was required.

Optimized Synthesis of Hexynoic Acid 1. To investigate the reduction in yield as the scale of the Knoevenagel condensation increased, stability studies were conducted on both Meldrum's acid (**5**) and the condensation product **3**. It was determined that Meldrum's acid decomposed rapidly in water above ~35 °C, with a half-life of ~2 h at 50 °C.[7] Thus, the longer times required to heat up and transfer aqueous slurries of Meldrum's acid on larger scale resulted in partial hydrolysis and contributed to the decreased yields of **3**. Although **3** was stable in dry organic solvents including acetone, it readily hydrolyzed in miscible solvent/water mixtures.[8] Consequently, during recrystallization of **3** from acetone/water, a retro-Knoevenagel reaction pathway

Table 1. Reaction Conditions for the Knoevenagel Condensation



entry	solvent	conversion (%)	note
1	water	85	fine solids
2	organic solvents	<10	MTBE, IPAc,THF, toluene, MeCN
3	water/toluene (10/1)	>97	spherical beads (agglomeration)

was further eroding isolated yields. Studies directed at identifying milder condensation conditions revealed that the conversion was incomplete in water at 30−35 °C (Table 1, entry 1) and that the reaction did not proceed in dry organic solvents (entry 2).[9] However, addition of 10% of an immiscible organic solvent to water, including isopropyl acetate, toluene, *tert*-butyl methyl ether and 2-butanone, improved the reaction conversions to >97%. Among the solvent systems tested, toluene/water (entry 3) was unique in its ability to promote agglomeration of the product **3** into relatively uniform spherical beads (Figure 1).[10] These beads were easily filtered and dried quickly to provide **3** in

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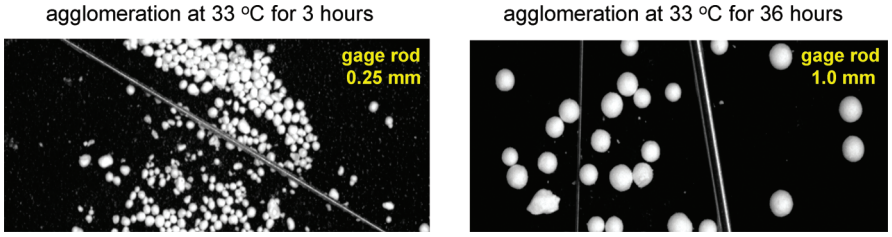


Figure 1. Spherical beads formed during agglomeration of **3** (size compared with standard gage rods).

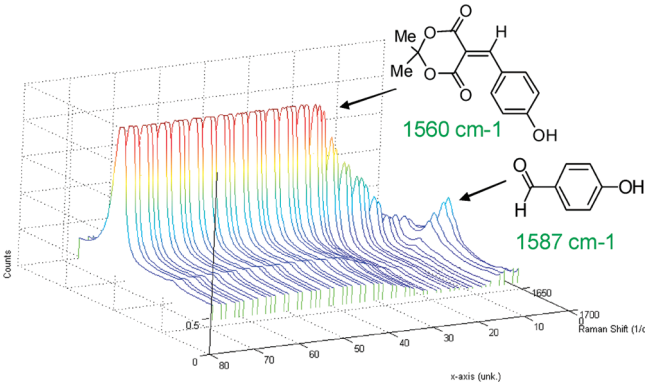
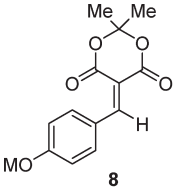


Figure 2. Representative waterfall plot (starting material and product absorptions at 2 min intervals) for in situ reaction monitoring via Raman spectroscopy.

99% yield (>99 wt % purity) with <0.03 wt % residual water by Karl Fischer titration (KF).[11] Due to the high quality of this material, recrystallization was not required.

In situ Raman spectroscopy was also used to monitor the course of the reaction, since the starting aldehyde and product **3** showed distinct absorptions at 1587 and 1560 cm^{-1}, respectively.[12] Under the optimized conditions the reaction was complete in <1 h at 33 °C (Figure 2); however, the batch was typically aged for 2−3 h to promote agglomeration before filtering.

Attention then turned to developing a through process to the racemic acid (±)-**1**. To circumvent difficulties associated with the labile THP protecting group, alternative protection strategies were investigated. In situ protection of the phenol group of **3** as the corresponding phenoxide salt[13] **8** was evaluated, but the subsequent addition of propynylmagnesium bromide typically stalled at <70% conversion.[14]

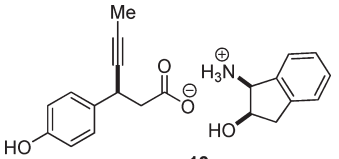


8
(M = Mg, Li, Na, K)

Further experimentation revealed that acetate **9** met our requirements as an inexpensive group that could be rapidly deployed and cleaved (Scheme 3). Treatment of **3** with acetyl chloride (1.1 equiv) in the presence of *N*-methylmorpholine (1.2 equiv) in THF (5 vol[15]) smoothly furnished **9**. The insoluble *N*-methylmorpholine hydrochloride produced in the reaction was conveniently removed via in-line filtration,[16] and the resulting salt-free solution of **9** was treated directly with propynylmagnesium bromide (1.1 equiv) to furnish the adduct **10**.[17] Aqueous 2 N NaOH (4 equiv) was then added to the crude solution of **10**, and the mixture was heated at 50 °C for 1−2 h to complete hydrolysis of the acetate group.[18] After pH adjustment, separation of the aqueous phase and solvent swap from THF to toluene, **11** was isolated via filtration as a white solid in 87% overall yield for the 3-step sequence. The purity of **11** by HPLC was 96 wt %, containing 3 wt % of the bis-acid **12** (see Scheme 4).[19]

Decarboxylation of **11** in 9:1 DMF/water (3 vol) at 100 °C for 1−2 h afforded a clean solution (>98% HPLC purity) of racemic acid (±)-**1** (Scheme 4). Formation of an intermediate diacid **12** was observed during the course of the reaction, which is consistent with a stepwise hydrolysis−decarboxylation pathway. The pure product (±)-**1** could be obtained via crystallization from IPAc/heptane, or the solution of (±)-**1** conveniently telescoped into the subsequent resolution step.

Classical resolution of (±)-**1** was studied with >20 commercially available chiral amines and confirmed the selection of (1*S*,2*R*)-1-amino-2-indanol as the optimum agent. It was found that using only 0.55 equiv of the amine in *n*-propanol (5 vol) gave chiral salt **13** with high diastereomeric excess (94−97% de). Slurrying the isolated salt in additional hot *n*-propanol (2.5 vol) improved the purity to >98% de with ∼28−34% overall yield (out of a maximum of 50%).



13

Additional studies revealed that the yield for the resolution could be increased to 39−41% (98% de) by performing the initial salt formation in acetonitrile (10 vol) and the hot slurry in acetonitrile containing 6−8 wt % water (5 vol total). Salt break with aqueous acid, extraction with ethyl acetate and crystallization (or solvent-swap to THF for the next step) afforded **1** in 35% overall yield. The optimized synthesis of hexynoic acid **1** is summarized in Scheme 5.

Original Synthesis of Bromide 2. The original 3-step synthesis of bromide **2** is shown in Scheme 6. Suzuki−Miyaura coupling (SMC) of 3-bromobenzoic acid (**14**) and 4-trifluoromethylphenylboronic acid (**15**) was carried out according to the method of Tiffin and co-workers[20] using catalytic palladium on carbon to provide biaryl **16**. Borane reduction of **16** afforded the benzylic alcohol **17**. Treatment of **17** with thionyl bromide in dichloromethane produced the bromide **2**, which was recrystallized from hexane or heptane. The overall yield of **2** was 72−82%, and early development work focused on modifications to make the route

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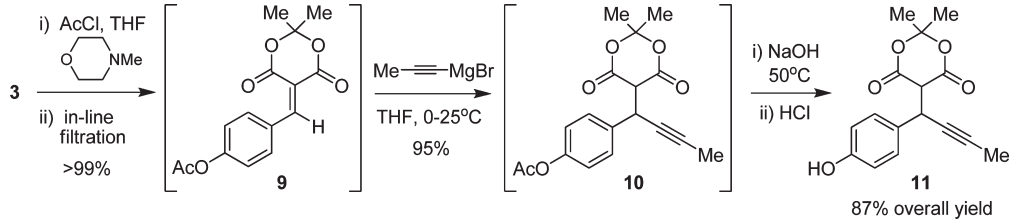
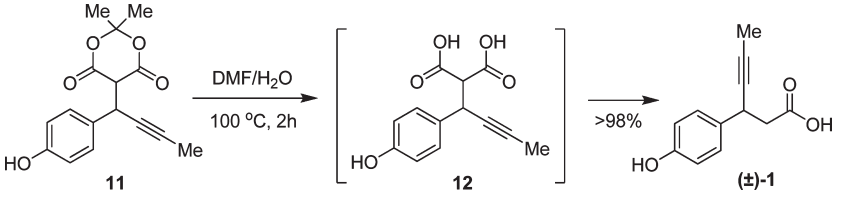
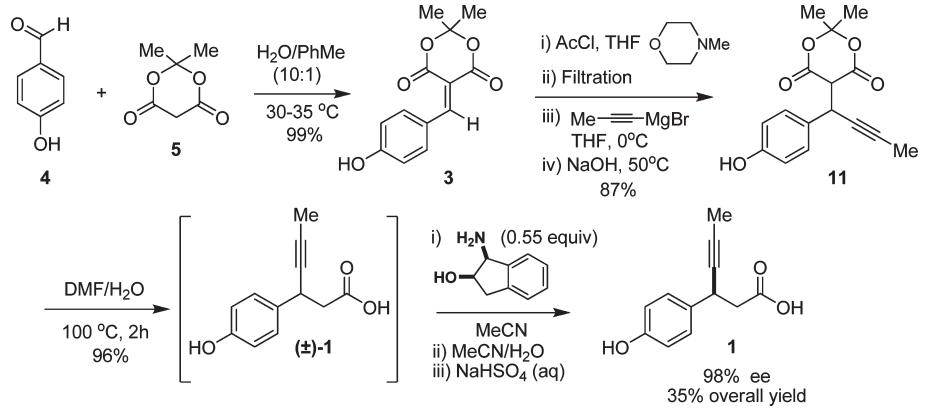
Scheme 3. Telescoped Process to 11



Scheme 4. Decarboxylation Pathway to (±)-1



Scheme 5. Optimized Synthesis of 1



more amenable to scale-up. The key issues identified were (i) during reagent charges for the SMC reaction, addition of aqueous Na_2CO_3 to a slurry of **14** and **15** resulted in vigorous CO_2 off-gassing and foaming of the batch; (ii) the bulk density of **16** was very low (~0.1 g/mL), which made handling and transfer of the powder difficult; (iii) during reduction of **16** to **17**, a delayed exotherm was observed after the addition of BH_3·THF was complete, which was considered potentially hazardous for scale-up; and (iv) the bromination reaction was performed in dichloromethane, and emulsions were frequently observed during aqueous workup.

Optimized Synthesis of Bromide 2. The catalyst loading in the SMC reaction was successfully lowered from 1.1 wt % to 0.13 wt % palladium[21] with complete conversion in 3 h at 75 °C. The issue with reaction foaming was addressed by changing the order of addition of reagents. By charging an aqueous solution of Na_2CO_3 to the reactor first followed by addition of the other reagents (**14** and **15**), the foaming was greatly suppressed and a stirrable slurry was obtained. After reaction completion, the mixture was filtered through a pad of Celite to remove the catalyst, the pH of the filtrate was adjusted to <2 with aqueous HCl, and the product **16** was directly isolated by filtration. The collected solids were dissolved in hot acetone (50 °C, 9 vol) and polish filtered, and water (12 vol) was added. The mixture was then cooled to 10 °C to crystallize **16**. Using this process, a 19.7 kg batch of acid **16** was prepared in 91% yield and >99% purity with improved bulk density (0.2 g/mL).

The reduction of **16** to **17** was originally carried out by slowly adding 1.2 equiv of BH_3·THF (1.0 M in THF) to a solution of **16** in THF at 0 °C, followed by gradual warming of the mixture to 30 °C over several hours.[22] A development run performed with 40 g of **16** demonstrated that when borane addition was complete, the initial exotherm subsided, but only 14% conversion to product had occurred. As the mixture was subsequently warmed, a second exotherm initiated at ~4 °C that rapidly heated the reactor contents to 9 °C despite jacket cooling. This result was consistent with the accumulation and exothermic sequential reduction of an acyloxyborane intermediate.[23] In order to achieve conditions in which accumulation of intermediates was not significant, the reduction was performed at higher temperature. Thus, addition of BH_3·THF over 1−2 h to a solution of **16** in THF at 45 °C smoothly afforded alcohol **17**. At this temperature the reaction was feed-controlled and reaction conversion was proportional to the fraction of BH_3·THF

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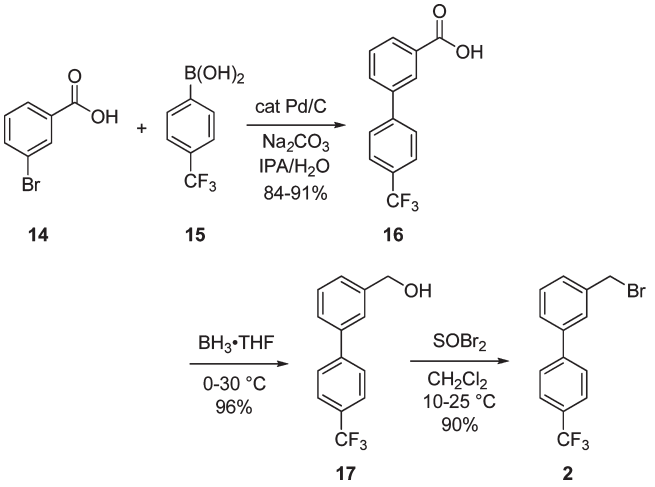
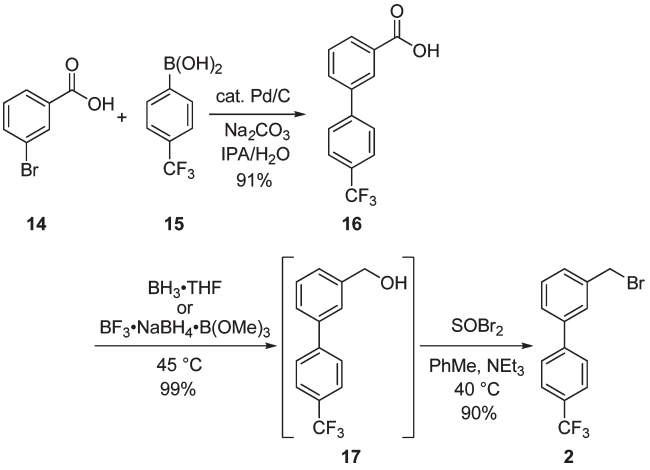
Scheme 6. Original Synthesis of 2



Scheme 7. Optimized Synthesis of 2



dosed. A modification of this process was also performed on 20 kg scale using borane generated in situ from $BF_3 \cdot THF$ and $NaBH_4$ (eq 1).

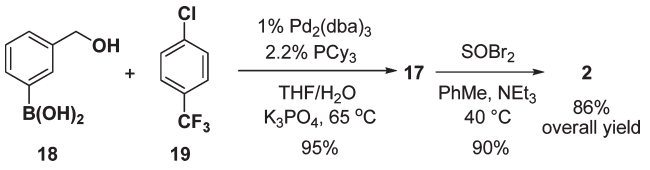
$$4BF_3 \cdot THF + 3NaBH_4 \rightarrow 4BH_3 \cdot THF + 3NaBF_4 \quad (1)$$

The controlled addition of borane was replicated by slowly adding $BF_3 \cdot THF$ to a mixture of **16**, $NaBH_4$, and $B(OMe)_3$ in THF.[24] Lab-scale development runs indicated that the reaction under these conditions was again feed-controlled and that reaction conversion (by HPLC) was proportional to the fraction of $BF_3 \cdot THF$ added. During large scale production, the progress of the reaction during the $BF_3 \cdot THF$ addition was confirmed by constant generation of heat (internal reactor temperature monitoring) to avoid the accumulation of starting material or intermediates. During the process, the reactor was vented to a scrubber containing 5% methanolic sodium methoxide to decompose any borane in the vent-gas. After aqueous workup, extraction with toluene and azeotropic drying via distillation, a solution of alcohol **17** (>99% purity, containing <200 ppm water) in toluene was obtained and used directly into the next step.

Bromination of **17** with $SOBr_2$ was slower in toluene than in dichloromethane solvent, and only 94% conversion was observed after 3 h at 40 °C. However, in the presence of 0.1 equiv of Et_3N, the reaction proceeded with >99% conversion to **2** via feed-controlled addition of $SOBr_2$ over 2 h to a warm (40 °C) solution of **17**.[25] After sequential washes with water and aqueous $NaHCO_3$, the organic phase was concentrated and solvent-swapped to heptane. The heptane phase was decolorized by filtration through a thin pad of silica gel, concentrated to 2.5 vol and cooled to crystallize **2**. Using this 3-step process, 21 kg of bromide **2** (99.9% purity, <4 ppm residual Pd) was prepared in 82% overall yield (Scheme 7).

Improved Synthesis of Bromide 2. Subsequent research focused on shortening the synthesis of **2**. In order to eliminate the reduction step, direct preparation of **17** from the less expensive raw materials **18** and **19** was investigated (Scheme 8).[26] A screen of Suzuki–Miyaura coupling conditions revealed that the reaction proceeded smoothly using a Pd/PCy_3 catalyst with potassium phosphate in 2:1 THF/water at 65 °C.[27] After extraction with isopropyl acetate, charcoal treatment, and azeotropic distillation from

Scheme 8. Improved Synthesis of 2



isopropyl acetate to heptane to crystallize the product, biaryl alcohol **17** was isolated in 95% yield (containing 6 ppm residual Pd). Bromination with thionyl bromide in toluene completed the 2-step sequence to **2**.

Synthesis of AMG 837. The Medicinal Chemistry route began with Fischer-esterification of **1** in methanol to afford **20**, followed by base-mediated phenol alkylation and ester hydrolysis to provide the free-acid form of AMG 837 (Scheme 9). Both intermediate esters **20** and **21** were isolated as oils after filtration through silica gel and concentration of the filtrate. The original conditions for alkylation of **20** employed cesium carbonate in acetone at room temperature, and the solid paste remaining at the end of the reaction was removed by filtration through Celite. The filtration was slow and was anticipated to be even more difficult on larger scale. We found potassium carbonate (1.5 equiv) to be a suitable alternative base for the alkylation of **20** (1.0 equiv) with **2** (1.1 equiv), and the reaction proceeded smoothly in 2 vol of refluxing acetone to provide **21**.[28] The resulting heterogeneous mixture was easily filtered to remove residual base, and then solvent switched to ethanol for the next step. Since the ester **21** was rather unstable,[29] solutions of the product were not held at this stage but instead processed forward. Aqueous sodium hydroxide (2.0 equiv) was added to the ethanolic solution of **21** to hydrolyze the ester as well as scavenge excess alkylating agent **2**.[30] The resulting mixture was neutralized with aqueous HCl, concentrated and extracted with isopropyl acetate.[31] The isopropyl acetate phase was washed with water and dried via azeotropic distillation to afford a solution of AMG 837 in 92–96% assay yield. Although this 3-step process was successfully employed in multiple batches to prepare ~20 kg AMG 837 overall, a chemoselective phenol alkylation process was subsequently developed that eliminated the need for the ester protection and hydrolysis steps. Extensive base and solvent screening revealed that treatment of **1** with 2.0 equiv

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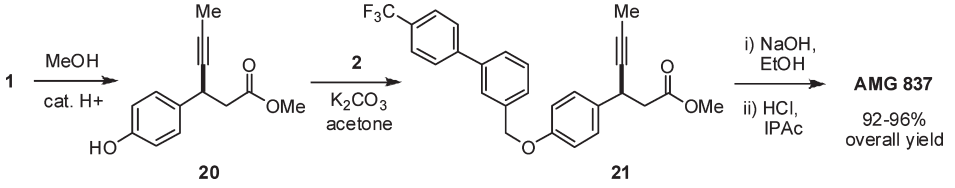
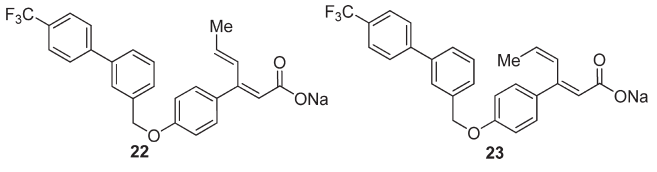
Scheme 9. Three-Step Synthesis of AMG 837



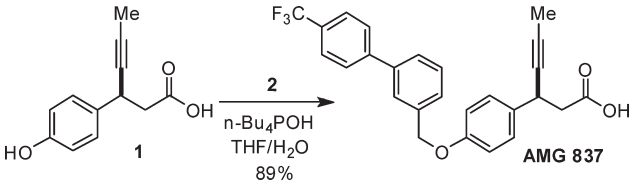
of 40% aqueous tetrabutylphosphonium hydroxide (*n*-Bu_4POH) in THF, followed by addition of 1.0 equiv bromide **2**, afforded AMG 837 in 89% assay yield (Scheme 10). Under these conditions, the alkylation was highly selective (>100:1) for the desired ether formation over competing esterification.[32] A homogeneous, single-phase mixture was maintained throughout the process and upon reaction completion the batch was concentrated and pH adjusted to liberate the free acid. Although a crystalline form (mp 83 °C) of AMG 837 free acid was identified, the molecule's fatty-acid-like structure made crystallization difficult, and the material exhibited poor stability during storage.[33] Consequently, formation of a pharmaceutically acceptable salt was pursued in order to improve the stability of the drug substance and provide a better control point for purification.

A lysine salt of AMG 837 was initially prepared by the Medicinal Chemistry team to enable screening and preliminary toxicology studies, but the severe hygroscopicity of this form precluded further development. After an intensive salt-screening effort, a sodium salt of AMG 837 was selected as a suitable form for early clinical development.[34] Although the sodium salt was poorly crystalline, it was significantly more stable than the free acid, could be reproducibly prepared in high yield and purity, and could rapidly supply the clinical program. In practice, after workup of the alkylation step, a solution of AMG 837 in isopropyl acetate was solvent-switched to acetonitrile and treated with aqueous NaOH. The resulting sodium salt of AMG 837 was isolated by filtration as a crystalline acetonitrile solvate.[35] The crystallization process was effective in rejecting process impurities (<90% pure acid could be converted to >99.5% purity sodium salt), but vacuum oven drying the product to attain low residual acetonitrile levels proved difficult on kilo-scale.[36] Use of higher drying temperatures (>70 °C) to accelerate desolvation was unsuccessful and resulted in the formation of diene impurities **22** and **23** (1−2% each) from alkyne isomerization.[37]



In contrast, it was noted that analytical samples left open to air for some time prior to testing showed consistently low residual acetonitrile levels. This finding was consistent with dynamic vapor sorption (DVS) data indicating sample weight loss at 35−55% relative humidity that corresponded to loss of acetonitrile from the sample and a form change (confirmed by XRPD) to the desired unsolvated form. Integrating this process knowledge, a mild "wet" drying approach was successfully scaled up (4−6 kg batches) via isolation of the salt by filtration and then drying on the filter by passing humidified nitrogen (dry nitrogen bubbled through deionized water) through the cake to remove acetonitrile. The filter cake was stirred periodically, and the moist nitrogen sweeps were alternated with dry nitrogen to control the water content of the solid and prevent it from becoming sticky and compacted.[38] Using this process, the sodium salt of AMG 837 was isolated in 88−95% yield with high chemical purity (>99% LCAP,[39] >96 wt %, 1−2% water) and contained <400 ppm residual acetonitrile. Although the sodium salt was suitable for this phase of development, a more crystalline, stable and non-hygroscopic form was preferred for long-term development. Additional final form screening identified a highly crystalline hemicalcium salt dihydrate that possessed these quality attributes.[34] However, physical characterization of the calcium salt by differential scanning calorimetry (DSC) showed a broad endotherm centered at 85 °C due to dehydration leading to an amorphous form. The amorphous material was less chemically stable than the crystalline dihydrate, so understanding and control of dehydration vs amorphous content was considered key to the development of a robust process.[40] Attempts at direct conversion of the free acid to the calcium salt using $Ca(OH)_2$ or $Ca(OAc)_2$ in a variety of solvents produced amorphous powders. However, it was noted that in contrast to the high solubility of the sodium salt in water (>100 mg/mL at pH 8), the calcium salt was poorly soluble (<0.005 mg/mL), and this difference was exploited in designing a salt-exchange crystallization process. Thus, slow addition of an aqueous solution of calcium chloride to a solution of the sodium salt of AMG 837 in 3:2 methanol/water (7 vol) at 25 °C, followed by aging and filtration, provided the hydrated hemicalcium salt wet cake (Scheme 11).[41] Conveniently, the initially isolated sodium salt MeCN-solvate could be used directly in this salt exchange process without the need for a prior drying/desolvation step.

Scheme 10. Chemoselective Coupling to AMG 837



Studies were then conducted to evaluate the impact of drying temperature on the amorphous content of the calcium salt, as determined by quantitative Raman spectroscopy.[42] As summarized in Table 2, the desired crystalline dihydrate form was maintained by drying the wet cake at 25−40 °C (entries 1 and 2), whereas partial conversion to amorphous form was observed at 60 °C (entry 3) and complete loss of crystallinity occurred at 85 °C (entry 4). During the process, bulk solvent and water were shown to be readily removed at ≤40 °C to reproducibly afford crystalline AMG 837 hemicalcium dihydrate in 89−94% overall yield (Scheme 11) with excellent

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Scheme 11. Final Salt Formation

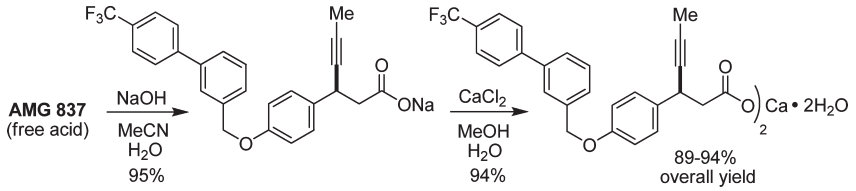

Table 2. Drying Studies on Hemicalcium Salt Dihydrate Wet Cake[a]

entry	drying temp (°C)	crystallinity (%)[b]	water content (wt %)[c]
1	25	≥97	4.3
2	40	≥97	4.0
3	60	89	3.7
4	85	≤3	<1.0

[a] 64 h drying time in vacuum oven with a nitrogen sweep. [b] Percentage target polymorph determined by quantitative Raman spectroscopy; see ref 42. [c] Determined by Karl Fischer titration; theoretical value for dihydrate = 3.9 wt % water.

chemical purity (>99% LCAP, >95 wt %, KF: 3.9−4.5 wt % water) containing <1500 ppm residual methanol.

CONCLUSIONS

Early process development, synthesis and salt selection for the GPR40 agonist AMG 837 has been described. Improvements to the original 12-step Medicinal Chemistry synthesis led to a process-enabled route that was satisfactory to supply preclinical and early clinical studies. Additional process research afforded an improved route (9 steps, 25% overall yield) and identified a stable, crystalline hemicalcium salt dihydrate form of the drug substance that was suitable for long-term development.

EXPERIMENTAL SECTION

Mass spectra analyses and high-resolution mass spec analyses were measured via fast-atom bombardment (FAB) or electrospray ionization (ESI). Optical rotations were recorded in cells with 1 dm path length. Enantiomeric excess was determined by chiral HPLC analysis. Assay yields were calculated by quantitative HPLC analysis against a purified reference standard. Isolated yields were corrected for product potency (wt % purity by quantitative HPLC). HPLC in-process-test method: YMC Pro C18 s-3 column (3.0 mm × 150 mm), 35 °C, flow rate 1.0 mL/min, UV detection at 220 nm. Gradient: mobile phase A, 40% MeOH, 60% water containing 0.1% perchloric acid; mobile phase B, 40% MeOH, 60% acetonitrile

time (min)	% B
0	25
10	50
28	65
35	95
36	95
37	25

HPLC purity method: YMC Pro C18 s-3 column (3.0 mm × 150 mm), 35 °C, flow rate 0.6 mL/min, UV detection at 220 nm. Gradient: mobile phase A, 40% MeOH, 60% water containing 0.1% perchloric acid; mobile phase B, 40% MeOH, 60% acetonitrile

time (min)	% B
0	10
5.0	10
15.0	50
35.0	65
45.1	95
50.0	95
50.1	10
55.0	10

5-(4-Hydroxy-benzylidene)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (3). 4-Hydroxybenzaldehyde (1.50 kg, 12.3 mol), Meldrum's acid (2.10 kg, 14.6 mol), water (18.0 L) and toluene (2.1 L) were stirred at 23 °C for 60 min, and the internal temperature was increased to 33 °C over 40 min and then aged for 60 min. A reaction aliquot was filtered, and HPLC analysis of the supernatant indicated complete reaction (<0.5 mg/mL 4-hydroxybenzaldehyde vs completion target of <2 mg/mL). The yellow suspension was aged at 33 °C for an additional 2 h to promote agglomeration of the product into spherical beads. The beads (diameter ~0.25 mm) were filtered and washed with water (2 × 6 L). The wet cake was dried at 50 °C under vacuum to constant weight to provide **3** as yellow solid beads (3.02 kg, 99%, >98 LCAP,[38] >98 wt %, <0.03 wt % water). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.95 (s, 1H), 8.26 (s, 1H), 8.18 (d, J = 8.80 Hz, 2H), 6.91 (d, J = 8.80 Hz, 2H), 1.73 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.83, 26.84, 103.90, 109.87, 115.80, 115.81, 123.03, 137.89, 137.90, 156.99, 163.35, 163.63. Anal. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 63.10; H, 4.84. IR: 3262, 1745, 1696, 1571, 1274, 1194, 1038 cm^{-1}; mp 202−203 °C.

5-(1-(4-Hydroxyphenyl)but-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (11). To a cold (5 °C), stirred solution of **3** (1.00 kg, 4.03 mol) and *N*-methylmorpholine (489 g, 4.83 mol) in anhydrous THF (5.0 L) was added acetyl chloride (348 g, 4.43 mol) at a rate that did not allow the internal batch temperature to rise above 25 °C. After the addition, the mixture was aged at 25 °C for 30 min (HPLC analysis showed >99% conversion to **9**). The mixture was in-line filtered (to remove *N*-methylmorpholine hydrochloride salt), rinsing with anhydrous THF (2 × 1.5 L). The filtrate was cooled to 15 °C, and a solution of 1-propynylmagnesium bromide (8.9 L, 0.5 M solution in THF, 4.45 mol) was added at a rate that did not allow the internal batch temperature to rise above 30 °C. After the addition was complete, the mixture was stirred at 25 °C for an additional 30 min (HPLC analysis showed >99% conversion to **10**). Aqueous 2 M NaOH (8.0 L) was added at a rate that did not allow the internal batch temperature to rise above 30 °C. The mixture was then heated to 50 °C and held for 30 min (HPLC analysis showed >99%

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conversion to **11**). The mixture was cooled to 0 °C, and aqueous 5 M HCl (~4.5 L) was added at a rate that did not allow the internal batch temperature to rise above 30 °C (final pH, 2−3). The layers were separated, and the organic phase was concentrated (45 °C) and solvent-swapped to toluene by distillation (~18 L distillate collected) until GC assay indicated <5 wt % THF in the reaction pot. The resulting mixture in toluene (~9 L) was cooled to 23 °C over 2 h and stirred for an additional 2 h. The batch was filtered, and the filter cake was washed with toluene (2 × 2 L). The filter cake was dried under vacuum at 50 °C to afford **11** as a white solid (1.01 kg, 87% yield, 96.5 LCAP, 96.2 wt %, 3.2 wt % bis-acid **12**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 2H); 6.78 (m, 2H); 4.85 (s(b), 1H); 3.82 (s, 1H); 1.88 (d, 3H, J = 2.5 Hz); 1.72 (s, 3H); 1.63 (s, 3H). For bis-acid **12**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (d, J = 2.34, Hz, 3H), 3.50 (d, J = 10.82 Hz, 1H), 4.02 (dd, J = 10.82, 2.48 Hz, 1H), 6.67 (d, J = 8.62, Hz, 2H), 7.12 (d, J = 8.62 Hz, 2H), 9.32 (s, 1H), 12.77 (s, 2H).

(3*S*)-3-(4-Hydroxyphenyl)-hex-4-ynoic acid (1*S*,2*R*)-1-Amino-2-indanol Salt (13). A solution of **11** (50.0 g, 0.173 mol) in DMF (137 mL) and water (13.7 mL) was heated to 100 °C over 30 min and then aged for an additional 60 min (**CAUTION**: carbon dioxide evolution). HPLC analysis of a reaction aliquot indicated >99% conversion. The mixture was cooled to room temperature, and *tert*-butyl methyl ether (250 mL) was added. The organic phase was washed with 50% aqueous brine (500 mL). The aqueous phase was separated and extracted with *tert*-butyl methyl ether (250 mL). The combined organic phases were washed with 50% aqueous brine (250 mL). The organic phase was distilled, and anhydrous acetonitrile was added until the water content in the acetonitrile phase was <1 wt % and GC analysis showed <1 wt % residual DMF. The resulting solution of (±)-**1** in acetonitrile (~205 mL) was added to a solution of (1*S*,2*R*)-1-amino-2-indanol (14.3 g, 0.095 mol, 0.55 equiv) in anhydrous acetonitrile (245 mL) at 65−70 °C over 1 h, and the mixture was aged for 3 h at 70 °C. The resulting suspension was cooled to room temperature over 2 h, and aged for 1 h. The mixture was cooled to 0−5 °C, aged for 1 h, and filtered, and the collected solid was washed with cold (0−5 °C) acetonitrile (2 × 40 mL). The wet cake (68% de **13**) was charged into a 500-mL round-bottom flask. Acetonitrile (225 mL) and water (20 mL) were charged. The mixture was heated to 70 °C over 0.5 h and held for an additional 3 h at 70 °C. The mixture was cooled to room temperature over 2 h and aged for 1 h. The mixture was cooled to 0−5 °C, aged for 1 h, and filtered, and the collected solid was washed with cold (0−5 °C) acetonitrile (2 × 60 mL). The wet cake was dried in a vacuum oven at 50 °C for 3 days to afford **13** as a white solid (24.5 g, 40% yield, >99 LCAP, 97.8% de). Chiral HPLC analysis: ChiralPak AD-H, 40 °C, mobile phase hexane/isopropyl alcohol/TFA (v:v:v) 850:150:2, flow rate 1.0 mL/min, UV detection at 226 nm, t_R (min) major: 9.5, minor: 6.7; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.76 (d, J = 2.54 Hz, 3H), 2.32−2.48 (m, 2H), 2.83 (dd, J = 16.04, 2.93 Hz, 1H), 3.02 (dd, J = 16.14, 5.77 Hz, 1H), 3.84 − 3.96 (m, 1H), 4.24 (d, J = 5.28 Hz, 1H), 4.36−4.42 (m, 1H), 6.67 (d, J = 8.61 Hz, 2H), 7.12 (d, J = 8.61 Hz, 2H), 7.17−7.28 (m, 4H), 7.33−7.48 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 3.30, 33.32, 45.43, 57.67, 71.47, 77.08, 82.05, 114.96, 114.97, 124.78, 124.79, 126.35, 127.87, 128.12, 128.13, 128.14, 132.44, 141.20, 141.28, 155.91, 174.03. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.48; H, 6.56; N, 3.95. IR: 2881, 1613, 1510, 1409, 1237, 1093 cm^{-1}; mp 202−203 °C.

(3*S*)-3-(4-Hydroxyphenyl)-hex-4-ynoic Acid (1). To a stirred suspension of **13** (1.57 kg, 4.44 mol) in ethyl acetate (6.0 L) was added a solution of $NaHSO_4 \cdot H_2O$ (714 g, 5.17 mol) in water (9.0 L). The mixture was stirred vigorously until all solids were dissolved (15−20 min.), the agitation was stopped, and the layers were separated (pH aqueous phase, 1−2). The organic phase was washed with water (2 × 1.0 L), dried over $MgSO_4$, filtered, and concentrated. The product can be solvent-swapped into THF for the next step or further dried (vacuum oven, 30 °C) to afford **1** as a white solid (900 g, 99% yield, >99 LCAP). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.77 (d, J = 2.48 Hz, 3H), 2.53−2.60 (m, 2H), 3.79−3.95 (m, 1H), 6.63−6.75 (m, 2H), 7.14 (d, J = 8.48 Hz, 2H), 9.31(s, 1H), 12.21 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 3.21, 32.68, 42.96, 77.90, 80.83, 115.08, 115.09, 128.15, 128.16, 131.35, 156.12, 171.85. HRMS (ESI) calcd for (M + H): 205.08592, found 205.08609. IR: 3232, 1693, 1598, 1512, 1216, 1157 cm^{-1}; $[\alpha]_D$ = +10.09 (c 0.11; $CHCl_3$); mp 127 °C.

[3-(4-Trifluoromethylphenyl)phenyl]methanol (17). To a solution of 3-(hydroxymethyl)phenylboronic acid **18** (46.3 g, 305 mmol, 1.1 equiv) in THF (400 mL) and water (200 mL) were added K_3PO_4 (117.6 g, 555 mmol, 2.0 equiv), 1-chloro-4-(trifluoromethyl)benzene **19** (50.0 g, 277 mmol, 1.0 equiv), $Pd_2(dba)_3$ (2.54 g, 2.7 mmol, 0.01 equiv) and PCy_3 (1.9 g, 6.6 mmol, 0.024 equiv). The mixture was degassed and refilled with N_2 four times and then heated at 65 °C for 20 h. The mixture was cooled to room temperature and filtered through a pad of Celite, washing with THF. The THF was removed via distillation at reduced pressure, and IPAc (600 mL) was added. The phases were separated, and the organic phase was washed with 10% aqueous Na_2CO_3 (300 mL) and water (2 × 300 mL). Charcoal (10 g) was added to the organic phase, and the mixture was heated at 70 °C for 0.5 h. The mixture was filtered through a pad of Celite, washing with IPAc. The IPAc solution was concentrated at reduced pressure and solvent-swapped to heptane by distillation (80−85 °C). The resulting heptane solution (~500 mL, containing <1 wt % IPAc) was cooled to 57 °C, seeded (1 wt %), and cooled to room temperature over 2 h, and the resulting slurry aged for 2 h. The mixture was cooled to 0−5 °C, aged for 0.5 h, and filtered. The filter cake was washed with cold (0−5 °C) heptane (2 × 100 mL) and dried in a vacuum oven at 50 °C overnight to afford **17** as a white solid (66.5 g, 95% yield, 98.3 wt %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (2H, d), 7.81 (2H, d), 7.68 (1H, s), 7.59 (1H, d), 7.47 (1H, t), 7.39 (1H, d), 5.28 (1H, t), 4.60 (2H, d); ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.3, 143.5, 138.3, 128.9, 127.4, 126.5, 125.7, 125.3, 125.0, 62.7. IR (neat): 3334, 1322, 1165, 1122, 1111, 1071, 1016, 843, 737 cm^{-1}. Anal. Calcd for $C_{14}H_{11}F_3O$: C, 66.66; H, 4.40. Found: C, 66.81; H, 4.41; mp 64−66 °C.

[3-(4-Trifluoromethylphenyl)phenyl]methanol (17) by in Situ Generated Borane Reduction of 16. To a mixture of sodium borohydride (3.15 kg, 83.3 mol) in tetrahydrofuran (35.0 kg) was added a solution of **16** (19.7 kg, 74.0 mol) in tetrahydrofuran (56.0 kg) over 2 h so as to maintain the internal temperature of the batch below 25 °C. Trimethyl borate (2.31 kg, 22.2 mol) was charged, and the mixture was heated to 44 °C. Then 45% $BF_3 \cdot$THF (13.2 kg, 87.6 mol) was slowly added to the reactor at a rate that did not allow the batch temperature to increase above 50 °C (addition of $BF_3 \cdot$THF occurred over 2 h with the reaction temperature between 41 and 49 °C during the addition, and constant heat generation was monitored to avoid accumulation of unreacted borane). The mixture was aged at 41−43 °C for 2 h, and the reaction was judged to be complete (<0.5% starting material detected vs target: <1.0% by HPLC analysis). The reaction was cooled to 10 °C, excess borane was quenched by the addition of acetone (8.59 kg), and water (47.2 kg) was added. After removal of the tetrahydrofuran by distillation under

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atmospheric pressure, toluene (51.1 kg) and water (9.9 kg) were added, the phases were allowed to separate, and the water layer was discarded. The upper organic layer was successively washed with a solution of $NaHCO_3$ (1.42 kg) in water (23.6 kg) and water (23.6 kg). The organic layer was concentrated under reduced pressure to remove about half of the toluene (26.9 kg distillate collected), and fresh toluene (21.3 kg) was added (water concentration of the resultant solution was 55 ppm). The mixture was filtered (washing with 8.5 kg toluene), and the filtrate was concentrated via distillation to afford a clear solution of **17** (18.5 kg assay, >99 LCAP, 99% yield) in toluene (55.4 kg) that could be used directly in the next step.

3-(Bromomethyl)-4′-(trifluoromethyl)biphenyl (2). To a solution of **17** (18.5 kg, 73.3 mol) in toluene (55.4 kg) was charged triethylamine (0.74 kg, 7.31 mol), and the resulting solution was heated to 35 °C. $SOBr_2$ (16.9 kg, 81.3 mol) was slowly added at a rate that did not allow the internal temperature of the batch to increase above 40 °C (addition of $SOBr_2$ occurred over 2.3 h with the reaction temperature between 35 and 40 °C during the addition). The mixture was aged for 0.5 h at 40 °C, and HPLC analysis indicated that the reaction was complete (<0.1% starting material detected vs target: <1.0% starting material). Excess $SOBr_2$ was quenched by addition of water (34.3 kg) and stirring for 45 min. (Note: addition of water is exothermic. A 7 °C temperature increase was observed during the quench). The phases were then allowed to separate, and the lower (aqueous) layer was discarded (aqueous layer pH < 1). The upper organic layer was washed twice with a solution of $NaHCO_3$ (2.05 kg) in water (34.3 kg) (aqueous layer pH after twice washing was 7.0). The organic layer was washed with water (37.3 kg), and after phase separation the upper organic layer was concentrated via distillation (53.6 kg distillate collected). Heptane (31.9 kg) was added, and the mixture was heated to 50 °C. The heptane solution was filtered through silica gel (2.9 kg), and the silica gel was washed with heptane (25.5 kg) preheated at 50 °C. The combined filtrate and washes were concentrated (54.4 kg distillate collected), additional heptane (25.5 kg) was added, and the mixture was heated to 50 °C. The resulting heptane solution was cooled to 40 °C, seeded with **2** (0.1 wt %, 0.019 kg), and cooled to 0 °C over 5 h for crystallization. The mixture was further aged at 0 °C for 4 h and then filtered. The filter cake was washed with cold (0 °C) heptane (8.29 kg) and then dried at 30 °C for 8 h, to afford **2** as a white solid (20.9 kg, 99.9 LCAP, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.68 (4H, m); 7.63 (1H, br s); 7.56−7.52 (1H, m); 7.50−7.43 (2H, m); 4.58 (2H, s); ^{13}C NMR (100 MHz, CDCl3) δ ppm 144.0, 140.4, 138.6, 129.8, 129.5, 128.7, 127.9, 127.4, 127.3, 125.8, 122.9, 33.1. IR (neat): 1327, 1265, 1166, 1122, 1112, 1070, 843, 735, 699 cm^{-1}. Anal. Calcd. for $C_{14}H_{10}BrF_3$: C, 53.36; H, 3.20. Found: C, 53.37; H, 3.22; mp 62−64 °C.

(*S*)-3-[4-(4′-Trifluoromethyl-biphenyl-3ylmethoxy)-phenyl]-hex-4-ynoic Acid (AMG 837). To a stirred solution of **1** (5.00 g, 24.5 mmol) in THF (35 mL) was added aqueous tetrabutylphosphonium hydroxide (34.5 g, 2.04 equiv, 40 wt % aqueous solution), and the resulting clear solution was cooled to −5 °C. A solution of **2** (7.71 g, 1.0 equiv) in THF (15 mL) was added over ∼30 min so as to maintain the internal temperature of the batch between −5 and 0 °C. The mixture was aged for an additional 30 min and then warmed to room temperature and aged for 20 h. The mixture was concentrated at reduced pressure (T < 40 °C) to remove THF, and the resulting aqueous solution was washed sequentially with hexane (20 mL) and 1:1 MTBE/hexane (30 mL). The aqueous phase was treated with 1 N aqueous HCl (33 mL) to adjust to pH to 2−3 and extracted with EtOAc (100 mL). The layers were separated, and the EtOAc phase was washed with water (50 mL) and then concentrated to dry azeotropically. The resulting solution of AMG 837 (9.50 g assay, 89% yield) could be further concentrated to dryness or solvent-swapped to acetonitrile for the next step.

AMG 837 Hemicalcium Salt Dihydrate. To a solution of AMG 837 free acid (113.1 g, 0.258 mol, 97.6 LCAP) in acetonitrile (250 mL) was added aqueous 5 N NaOH (51.6 mL, 0.258 mol, 1.0 equiv), and the clear yellow solution was stirred at 20 °C for 30 min. Additional acetonitrile antisolvent (1.60 L) was added over 2.5 h, and the resulting slurry was aged at 20 °C for 15 h. The mixture was filtered, and the filter cake was washed with acetonitrile (250 mL). The cake was dried on the filter under a nitrogen stream for 20 min and then further dried in a vacuum oven at 20 °C for 16 h to afford AMG 837 sodium salt (MeCN solvate) as a white solid (122.4 g, 99.1 LCAP, 90.1 wt %, containing 7.3 wt % acetonitrile, 95% corrected yield). An analytical sample was further dried for characterization and displayed: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, J = 8.2 Hz, 2H), 7.82 (d, J = 8.2 Hz, 2H), 7.81 (bs, 1H), 7.69 (dt, J = 6.3, 1.9 Hz, 1H), 7.53 (t, J = 6.3 Hz, 1H), 7.52 (d, J = 6.3 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H), 6.93 (d, J = 8.6 Hz, 2H), 5.15 (s, 2H), 4.01 (m, 1H), 2.33 (dd, J = 14.7, 6.9 Hz, 1H), 2.18 (dd, J = 14.7, 7.3 Hz, 1H), 1.74 (d, J = 2.3 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.2, 156.6, 143.9, 138.7, 138.3, 136.1, 129.3, 128.3, 127.9 (q, $^2J_{C-F}$ = 31.7 Hz), 127.6, 127.5, 127.0 (q, $^1J_{C-F}$ = 271.9 Hz), 126.5, 126.2, 125.8 (q, $^3J_{C-F}$ = 3.8 Hz), 114.4, 83.3, 76.4, 69.0, 47.5, 33.9, 3.3. HRMS (m/z): $[MH]^+$ calcd for $C_{26}H_{20}F_3NaO_3$, 461.1335 found, 461.1326. IR (KBr): 3590, 3064, 1640−1500, 1413, 1328, 1124, 1112, 1071, 789 cm^{-1}. The solvated AMG 837 sodium salt (120.5 g, 90.1 wt %, 0.235 mol, 1.0 equiv) obtained as described above was dissolved in methanol (578 mL) and water (289 mL) to afford a clear solution. A solution of calcium chloride dihydrate (17.3 g, 0.118 mol, 0.5 equiv) in water (35 mL) was added dropwise over 50 min at 20 °C, and the resulting slurry was aged for 16 h. The mixture was filtered, and the filter cake was washed with 2:1 methanol/water (2 × 150 mL). The cake was dried on the filter under a nitrogen stream for 2 h and then further dried in a vacuum oven at 40 °C with a nitrogen sweep for 36 h to afford AMG 837 hemicalcium salt dihydrate as a white solid (121.0 g, 99.2 LCAP, 99.4 wt %, 99.6% ee, 4.6 wt % water, 1600 ppm methanol, 94% overall yield from the free acid). Chiral HPLC analysis: ChiralPak AD-RH (150 mm × 4.6 mm), 40 °C, mobile phase: acetonitrile/methanol/water/TFA (v:v:v:v) 193:193:115:1, flow rate: 1.0 mL/min., UV detection at 254 nm, t_R (min) major: 9.0, minor: 5.4.; Ion Chromatography (IC): Dionex IonPac CS12A (250 × 4 mm), 35 °C, mobile phase: 30 mM MSA in water, flow rate: 1.0 mL/min. Calcd: 4.2% Ca, found 4.1% Ca. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (d, J = 8.2 Hz, 2H), 7.79 (d, J = 8.2 Hz, 2H), 7.77 (bs, 1H), 7.67 (bd, J = 6.8 Hz), 7.49 (m, 2H), 7.28 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H), 5.11 (s, 2H), 4.05 (m, 1H), 2.44 (dd, J = 15.2, 7.0 Hz, 1H), 2.28 (dd, J = 15.2, 7.2 Hz, 1H), 1.72 (d, J = 2.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.1, 156.7, 143.9, 138.7, 138.2, 135.5, 129.2, 128.4, 127.9 (q, $^2J_{C-F}$ = 32.1 Hz), 127.6, 127.5, 126.5, 126.2, 125.7 (q, $^3J_{C-F}$ = 4.3 Hz), 124.3 (q, $^1J_{C-F}$ = 271.4 Hz), 114.4, 82.7, 76.9, 69.0, 46.4, 33.1, 3.3. IR (KBr): 3545, 1562, 1509, 1436, 1327, 1241, 1126, 1016, 790 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) As a step to addressing this synthetic challenge we recently developed an asymmetric conjugate alkynylation of Meldrum's acid derived acceptors providing practical access to chiral β-alkynyl acids: (a) Cui, S.; Walker, S. D.; Woo, J. C. S.; Borths, C. J.; Mukherjee, H.; Chen, M. J.; Faul, M. M. *J. Am. Chem. Soc.* **2010**, *132*, 436. For a discussion of enantioselective approaches to AMG 837, see: (b) Woo, J. C. S.; Cui, S.; Walker, S. D.; Faul, M. M. *Tetrahedron* **2010**, *66*, 4730. (c) Yazaki, R.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2011**, *13*, 952. For Cu-catalyzed alkynylation of Meldrum's acid derived acceptors with aryl acetylenes see: (d) Knöpfel, T. F.; Carreira, E. M. *J. Am. Chem. Soc.* **2003**, *125*, 6054. For Rh-catalyzed alkynylation of Meldrum's acid derived acceptors with TMS-acetylenes see: (e) Fillion, E.; Zorzitto, A. K. *J. Am. Chem. Soc.* **2009**, *131*, 14608. For recent reviews of asymmetric conjugate alkynylation, see: (f) Fujimori, S.; Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Boyall, D.; Carreira, E. M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1635. (g) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963.

(3) Bigi, F; Carloni, S.; Farrari, L.; Maggi, A.; Satori, G. *Tetrahedron* **2001**, *42*, 5203.

(4) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

(5) This presumably results from polymerization of DHP; see: (a) Burrows, R. C. *Polym. Prepr.* **1965**, *6*, 600. (b) Kuethe, J. T.; Tellers, D. M.; Weissman, S. A.; Yasuda, N. *Org. Process Res. Dev.* **2009**, *13*, 471.

(6) The efficiency of the classical resolution step was highly dependent on the purity of the starting racemic acid. Consequently, a target purity of >95% was established.

(7) HPLC analysis indicated that <5% of Meldrum's acid hydrolyzed in water at 32°C after 2 h. In contrast, 48% hydrolyzed at 50 °C and >99% hydrolyzed at 79 °C over the same time period. Meldrum's acid is known to decompose to acetone and malonic acid in water: Kaczvinsky, J. R., Jr.; Read, S. A. *J. Chromatogr.* **1992**, *575*, 177.

(8) HPLC analysis indicated that 11% of **3** hydrolyzed in 1:1 acetone/water at room temperature after 1 h and 85% hydrolyzed after 16 h.

(9) Reaction conversion in THF could be increased to 75% by adding 10 mol% DMAP to the mixture.

(10) Product **3** readily agglomerated into beads in water that contained 10−20% vol of toluene. Agglomeration was not efficient in water that contained more than 20% or less than 5% toluene. For a discussion on agglomeration effects, see: Pietsch, W. *Agglomeration in Industry*; Wiley-VCH: Weinheim, 2005, Vols. 1 and 2. For a recent review of hydrophobic effects and reactions in/on water, see: Butler, R. N.; Coyne, A. G. *Chem. Rev.* **2010**, *110*, 6302.

(11) Since the next step employed a Grignard reagent, a target of <0.1% water was set.

(12) Raman spectroscopy is particularly useful here since it is suitable for analysis of heterogeneous mixtures and is insensitive to aqueous solvents.

(13) Bases screened to generate phenoxide **8** included: LiHMDS, LiH, KHMDS, K_2CO_3, NaHMDS, NaH, and Na_2CO_3.

(14) This was attributed to the low solubility of the phenoxide salts in THF. Addition of polar co-solvents (e.g., TMEDA, NMP, DMPU) did not improve conversions. Similar results were obtained using a TMS-ether protecting group.

(15) 1.0 vol = 1.0 L/kg.

(16) Solubility of *N*-methylmorpholine hydrochloride in THF at room temperature is <2 mg/mL as determined via turbidity measurements.

(17) 1,4-Addition occurred with >95% chemoselectivity with this addition mode. However, when a solution of acetate **9** was added to a solution of propynylmagnesuim bromide, HPLC analysis indicated a mixture containing 54% **10**, 20% **11** and 16% **9**.

(18) Although the saponification was typically complete in 1 h, stress tests indicated that the mixture could be aged for 24 h without loss of yield or purity. Apparently, formation of an enolate anion suppresses ester hydrolysis of the malonate moiety.

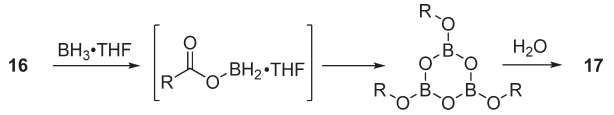
(19) The level of bis-acid in the product was dependent on the heating time during distillative solvent switch from THF to toluene. Small levels of bis-acid **12** are not a concern since **12** is also decarboxylated to (±)-**1** in the next step.

(20) Dyer, U. C.; Shapland, P. D.; Tiffin, P. D. *Tetrahedron Lett.* **2001**, *42*, 1765.

(21) A 5 wt % charge of NEChemcat E-type Pd/C (50% wet containing 5% Pd, corresponding to 0.125 wt% Pd overall)

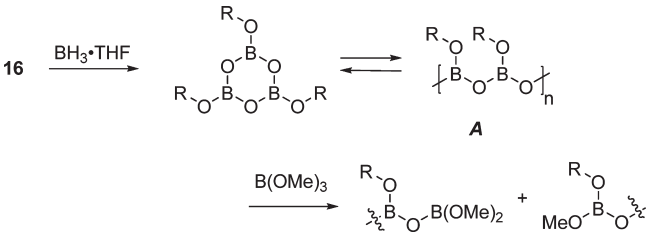
(22) BH_3-THF solutions were stored refrigerated and used shortly after being received. The titer of individual lots was confirmed by use-test prior to large-scale use. **CAUTION**: BH_3-THF solutions are known to decompose over time, particularly at room temperature and above. Thus, lots shipped or stored for extended periods at room temperature may have low borane titers and can accumulate pressure. See safety highlights in(a) Atkins, W. J., Jr.; Burkhardt, E. R.; Matos, K. *Org. Process Res. Dev.* **2006**, *10*, 1292. (b) Potyen, M.; Josyula, K. V. B.; Schuck, M.; Lu, S.; Gao, P.; Hewitt, C. *Org. Process Res. Dev.* **2007**, *11*, 210. (c) Guercio, G.; Manzo, A. M.; Goodyear, M.; Bacchi, S.; Curti, S.; Provera, S. *Org. Process Res. Dev.* **2009**, *13*, 489.

(23) Lobben, P. C.; Leung, S.S-W.; Tummala, S. *Org. Process Res. Dev* **2004**, *8*, 1072. Initial exotherm results from deprotonation of acid **16** to form an acyloxyborane intermediate that accumulates at low temperature. The second exotherm during warming can be explained by the sequential reduction of this acyloxyborane intermediate to a trialkoxyboroxine which librates **17** upon aqueous workup.



(24) In the absence of $B(OMe)_3$, thick gels were obtained which were difficult to stir. We postulate that the in situ borane reduction may produce a polymeric product such as **A** that is responsible for the gel. Thus, the role of $B(OMe)_3$ may be to cleave the polymeric chain to smaller fragments by disproportionation. Although $B(OMe)_3$ has been reported to accelerate borane reductions of carboxylic acids (e.g., see: Lane, C. F.; Myatt, H. L.; Daniels, J.; Hopps, H. B *J. Org. Chem.* **1974**,

39, 3052), in this case the reduction rates were similar in the presence or absence of $B(OMe)_3$.



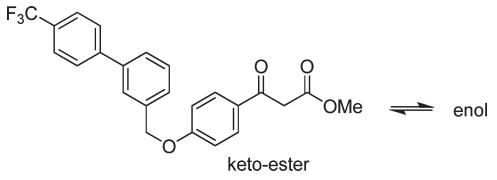
(25) The reactor was vented to a scrubber containing 5 N aqueous N_aOH to neutralize HBr and SO_2 off-gases.

(26) Relative Aldrich catalogue prices are illustrative. Aryl halides: **14**, $1.7/g (25 g bottle); **19**, $0.13/g (100 g bottle). Boronic acids: **15**, $30/g (5 g bottle); **18**, $14/g (10 g bottle).

(27) For a lead reference on Pd/PCy_3-catalyzed SMC reactions, see: Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282.

(28) Alkylation reactions evaluated in THF, EtOAc or MTBE solvents resulted in slower reaction rates and incomplete conversions. The rate of the alkylation reaction in acetone (2−20 h for >99% conversion) was dependent on the particle size of the K_2CO_3 employed. Granular base was typically employed but faster reactions occurred with finer powder.

(29) The main degradation pathway is via oxidative cleavage of the alkyne moiety. A pure sample of the largest degradant was obtained by flash chromatography, and the structure proposed on the basis of 1D (^1H, ^{13}C) and 2D (HMBC) NMR experiments ($CDCl_3$) is a mixture of keto-ester (91%) and its enol tautomer (~9%) and is consistent with the measured LCMS M+ (428) value. For example, when a crude sample of neat **21** was allowed to stand open to air at room temperature for 17 h, 5.1% keto-ester was generated (HPLC assay).

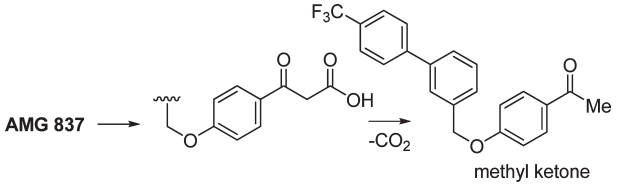


(30) The bromide **2** also has high solubility in many organic solvents including the subsequent crystallization solvents and was not detected in the API by HPLC assay.

(31) At least half of the initial ethanol charge was distilled to prevent formation of an emulsion during the isopropyl acetate extraction.

(32) Details and scope of this method have been reported elsewhere: Liu, P.; Huang, L.; Faul, M. M. *Tetrahedron Lett.* **2007**, *48*, 7380.

(33) Oxidative degradation (presumably via the intermediacy of a keto-acid) led to accumulation of a methyl ketone as the largest single impurity in aged samples of AMG 837. For example, when solid AMG 837 free acid was aged at 44 °C overnight (open air), ~1% methyl ketone was detected by HPLC analysis. A solution of AMG 837 in acetonitrile (5 vol) at room temperature for 1 week accumulated 4% methyl ketone.



(34) For a detailed discussion of salt screening for AMG 837, see: Morrison, H.; Jona, J.; Walker, S. D.; Woo, J. C. S.; Li, L.; Fang, J. *Org. Process Res. Dev.* **2011**, *15*, 104.

(35) Crystallization studies using focused beam reflectance measurements (FBRM, Lastentec) indicated significant particle attrition under high sheer agitation resulting in increased fines and poor filtration rates. To ensure good filtration on scale, the agitation should be reduced to maintain just-suspended solids after complete addition of NaOH and acetonitrile antisolvent.

(36) Upon oven drying, initial acetonitrile levels in the wet cakes (typically 20−30 wt %) rapidly decreased but remained steady at ~8 wt %, consistent with the theoretical monosolvate value.

(37) Analytical samples of the conjugated diene degradation products were isolated by HPLC and their structures determined by 1D and 2D NMR analyses and HRMS. Related thermal and base-mediated prototropic rearrangements of acetylenic compounds to conjugated dienes have been reported: Jones, E. R. H.; Mansfield, E. H.; Whiting, M. C. *J. Chem. Soc.* **1954**, 3208. For a review see:Iwai, I. *Mechanisms of Molecular Migrations*; Interscience: New York, 1969; Vol. 2.

(38) The sodium salt is hygroscopic above 55% relative humidity (RH) with >30 wt% gain up to 95% RH by vapor sorption analysis. Static drying times on an Aurora filter varied from 2 days to >1 week depending on the batch and filter size. Bench-top modeling of unit operations (50−500 g scale pilots), indicated drying cycle times could be reduced using a rotary (<50 h) or fluid bed dryer (<5 h).

(39) LCAP = liquid chromatography area percent.

(40) For a report describing online humidity analysis during factory drying of a hydrate, see: Cypes, S. H.; Wenslow, R. M.; Thomas, S. M.; Chen, A. M.; Dorwart, J. G.; Corte, J. R.; Kaba, M. *Org. Process Res. Dev.* **2004**, *8*, 576.

(41) Typically, the hemicalcium salt wet cake contained ~14 wt% water (by KF titration) before drying.

(42) A multivariate curve resolution (MCR) method based on second derivative Raman measurements of the pure crystalline and amorphous forms was used. For full details, see: Xie, Y.; Tao, W.; Morrison, H.; Chiu, R.; Jona, J.; Fang, J.; Cauchon, N. *Int. J. Pharm.* **2008**, *362*, 29.