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Development of a Scaleable Synthesis of a Geminal Dimethyl Tertiary Amine as an Inhaled Muscarinic Antagonist for the Treatment of COPD

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Supporting Information

ABSTRACT: An efficient and scalable process for the synthesis of muscarinic antagonist, PF-3635659 **1**, is described, illustrating redesign of an analogue-targeted synthesis which contained a scale-limiting rhodium-activated C−H amination step. The final route includes a reproducible modified Bouveault reaction which has not previously been reported on a substrate of this complexity, or on such a scale with over 5 kg of the requisite *gem*-dimethylamine prepared via this methodology.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by airflow limitation that is both progressive and not fully reversible, resulting in chronic deterioration of lung function.[1] COPD is currently the fourth largest cause of death in the U.S. and is projected to become the third leading cause of death worldwide by 2020.[1] Bronchodilator drugs are commonly used to manage the symptoms of COPD, and one class of these prescribed for symptom control are inhaled muscarinic receptor antagonists. Five distinct muscarinic receptors (M_1−M_5) are known in humans, three of which are present in the human lung (M_1−M_3). The M_3 receptor is located on airway smooth muscle cells where it mediates contractile responses.[2] PF-3635659 **1** is a potent antagonist of the M_3 receptor and, as such, is a suitable, once-daily, inhaled treatment for COPD that has advanced to phase II clinical studies. Herein we describe the process development which led to a synthetic route amenable for large-scale preparation.

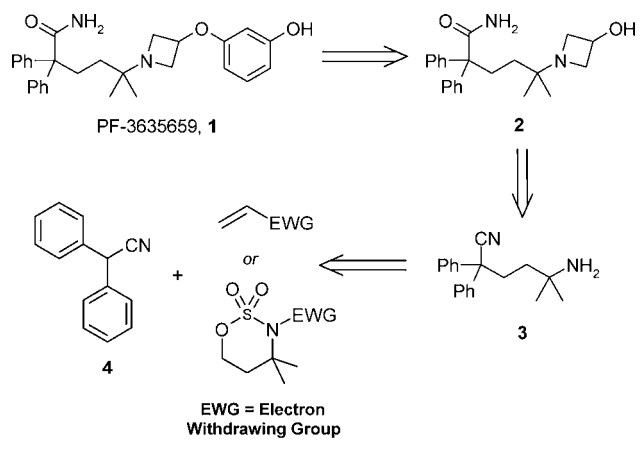

Figure 1. Retrosynthetic analysis of PF-3635659 **1**.

Retrosynthesis of target **1** was first performed with analogue generation in mind; as such, a late-stage intermediate such as alcohol **2** (Figure 1) was desirable.

Literature precedents suggested that azetidinols could be conveniently formed by reaction of primary amines with epihalohydrins,[3] and hence, it was introduction of the sterically encumbered *gem*-dimethyl moiety that was envisaged to present the greatest challenge. Under basic conditions phenylacetonitriles are known to be excellent nucleophiles which can react with Michael acceptors such as acrylonitrile or alkyl acrylates.[4] This knowledge might lead to supposition that Ritter chemistry,[5] similar to that performed in our laboratories previously,[6] would be a suitable way to access the primary *gem*-dimethylamine (Figure 2); however, for this particular series such chemistry

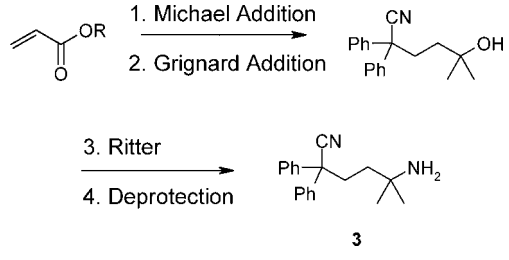

Figure 2. Suggested Ritter chemistry.

proved to be far less reliable with complex mixtures produced in the key amination step. Instead, an alternative electrophile was sought and identified in the form of protected cyclic sulphamidate **6** (Scheme 1).[7]

RESULTS AND DISCUSSION

Synthesis began with Boc protection of cyclic sulphamidate **5** under standard conditions. Diphenylacetonitrile **4** was then

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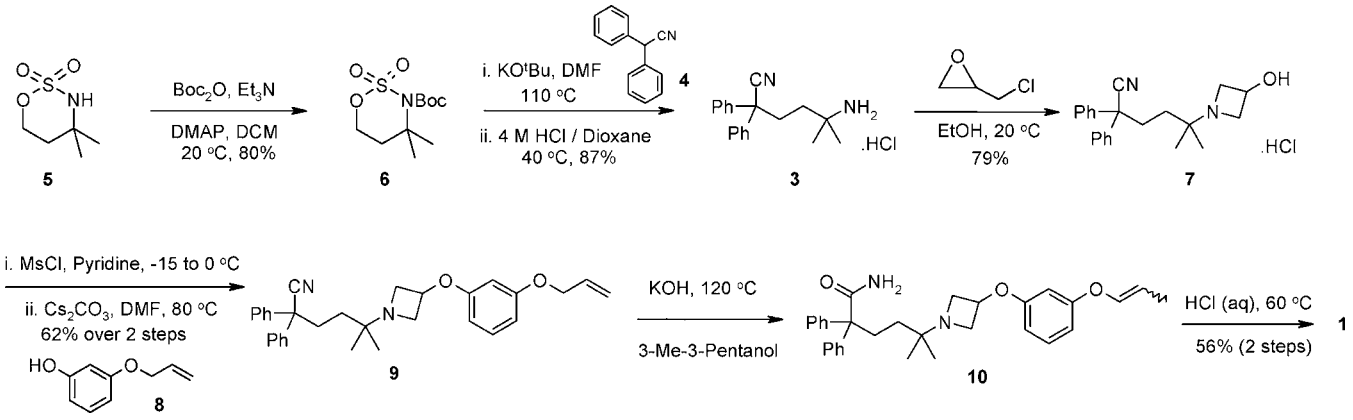
Scheme 1. First-generation discovery route

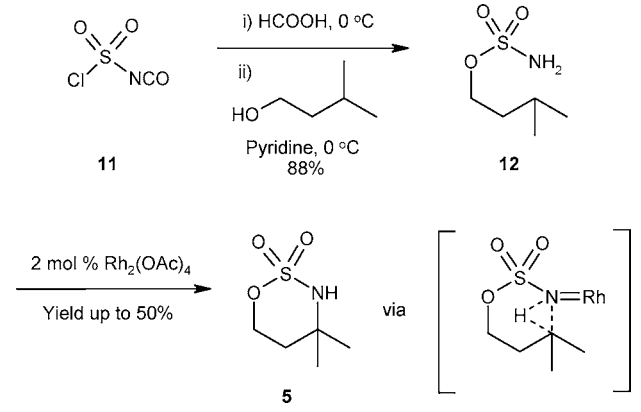


deprotonated and offered to protected compound **6** as a nucleophile. This reaction proceeded with gratifyingly high conversion and the subsequent ring-opened intermediate was deprotected with acid in situ to afford key *gem*-dimethylamine **3** as its hydrochloride salt. Following a salt break, further reaction of **3** with epichlorohydrin provided late-stage intermediate **7**, also as its hydrochloride salt, which concurrently enabled an array of analogue syntheses.

For the purposes of the lead target, alcohol **7** could be mesylated under standard conditions followed by displacement with allyl protected resorcinol **8**.[8] Allylation was the preferred protection strategy over methylation as it would allow us to avoid the use of toxic demethylating agents such as boron tribromide. The original intent from this point was to unmask the primary amide through nitrile hydrolysis and then to finally unveil the phenol by palladium-mediated deallylation. On exposure of protected compound **9** to the preferred basic hydrolysis conditions, however, enol ether **10** was unexpectedly obtained. This isomerisation negated the need for late-stage use of palladium and meant we were instead able to perform a mild acidic cleavage which provided us with first access, after basic workup, to target **1** in its parent form on 100-mg scale.

In general terms this strategy looked very promising for large scale, with good yields and well-documented reagents throughout. Our attention now shifted to the long-term provision of cyclic sulphamidate **5** which had previously been obtained from an in-house bulk supply by the method depicted in Scheme 2.

Scheme 2. Synthesis of cyclic sulphamidate 5



Problems unfortunately arose at this stage for two distinct reasons. The first was the exothermic tendency when hydrolyzing isocyanate **11**; however, this could be managed by careful cooling and controlled addition of formic acid. The second was regrettably more detrimental when it was found that the rhodium-activated C−H amination, as described by Du Bois et al.,[9] demonstrated poor reproducibility in our hands. Isolated yields of **5** fluctuated, and this outcome appeared to worsen with increasing scale with only a maximum of 50% achieved on greater than 10 g. Various attempts at optimisation were made, including a screen of alternative rhodium catalysts, but no reliable improvement was secured. Hence, an alternative approach became necessary.

This led us to reevaluate how we might utilise Michael addition as a means to construct our four-carbon skeleton; however, we would need a robust alternative to the aforementioned Ritter chemistry.[5] Ultimately the option we settled upon was a modified Bouveault reaction. The Bouveault reaction[10] was originally reported in 1904 and involves reaction of an alkyl Grignard with a tertiary amide to give an aldehyde or ketone, plus a secondary amine. In addition, there is commonly a side product identified in these reactions which corresponds to the geminal dialkylamine, and it was noted by our colleagues some 17 years previous to our endeavours that addition of an oxophilic Lewis acid species (such as titanium or zirconium tetrachloride) to these reactions can promote this side product as the major outcome (Figure 3).[11] This approach showed huge potential for

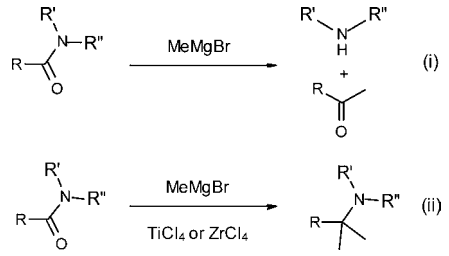


Figure 3. Bouveault (i) and modified Bouveault (ii) reactions.

installation of the *gem*-dimethyl functionality in our lead compound, and so we proceeded along this course to generate the required amide starting material (Scheme 3).

Diphenylacetonitrile **4** was again employed as the nucleophile, this time partnered with *tert*-butyl acrylate **13**. Michael addition proceeded smoothly with subsequent deprotection affording crystalline acid **14** in good yield. This could then be

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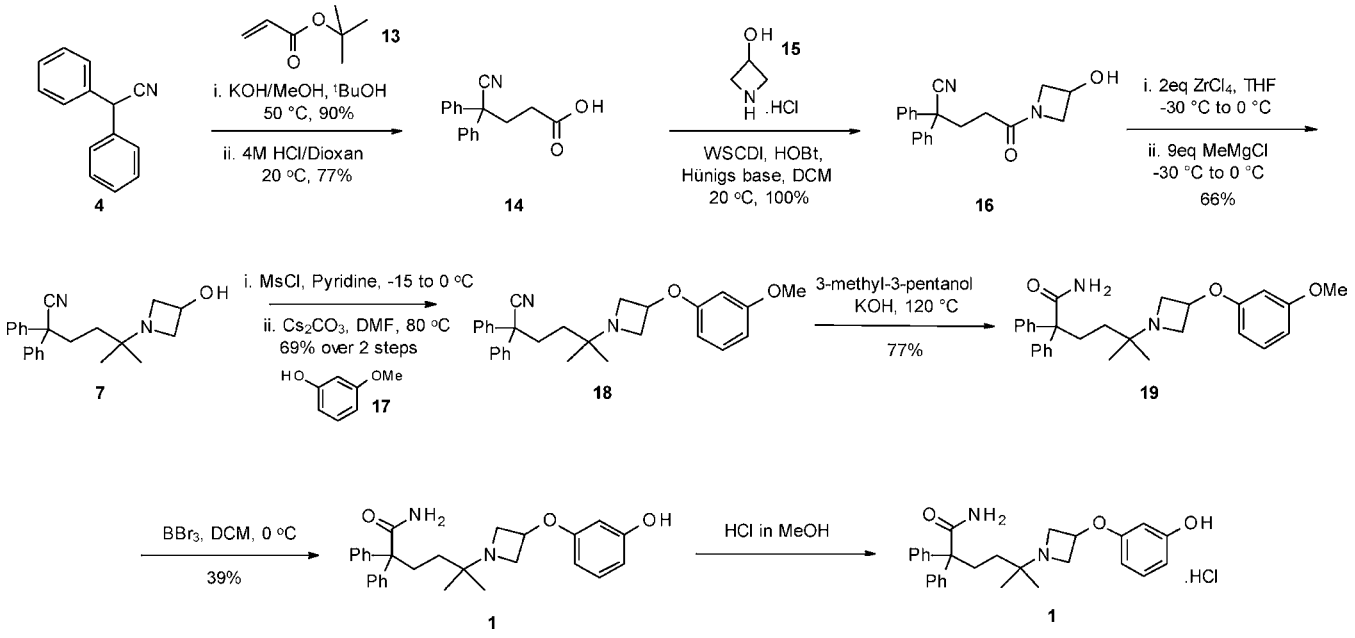
Scheme 3. Second-generation discovery route



coupled with azetidinol **15**, available commercially as the hydrochloride salt, to provide key amide **16**, which was found to crystallise from ethyl acetate.

We were now ready to attempt the decisive modified Bouveault step. For our Lewis acid we chose to use zirconium tetrachloride, which can be purchased as a weighable solid and demonstrates superior handling properties over its fuming, liquid titanium counterpart. Initial trials were promising, providing desired tertiary amine **7** in 30−40% yields when using a single equivalent of zirconium tetrachloride and 4 equiv of methylmagnesium chloride. It seemed, however, that reagent stoichiometry was critical to optimising yield and that this needed to be considered on a substrate-specific basis. It was found to be optimal in this case to use 2 equiv of Lewis acid and 9 equiv of Grignard reagent in order to achieve quantitative conversion and reproducibly high isolated yields. Gratifyingly, common intermediate **7** was also seen to be crystalline on milligram scale, presenting another useful optimisation handle for scale-up.

With key amine **7** in hand, the route previously outlined in Scheme 1 could be mirrored using allyl-protected resorcinol **8**. Alternatively the end game could be altered to incorporate 3-methoxyphenol **17** (Scheme 3). This proved advantageous mainly due to the commercial availability of **17** versus literature precedented preparation of allyl ether **8**.[8] This did of course bring back into play the issue of late-stage use of boron tribromide for the final deprotection, and this would need to be further addressed as we proceeded. The final compound **1** could be cleanly isolated and converted to its hydrochloride salt; however, thermal analysis and single-crystal X-ray data of preliminary samples suggested that the material in this salt form had a propensity towards either solvation or solvent occlusion, depending on the solvent. A solvated form would not be suitable to progress,[12] in particular due to this being an inhalation candidate with a requirement for lactose stability.[13]

As we now homed in on nomination of compound **1** as a potential candidate, we began to undertake a thorough review of the route, with a view to facilitating scale-up towards multikilogram manufacture. Although the existing process had thus far been robust for its purpose, further opportunities for improvement could be identified. These were triaged to highlight the two highest priority transformations as being the demethylation (in which the avoidance of boron tribromide was strongly desirable) and the modified Bouveault reaction. For the latter, it was felt that the modified Bouveault reaction was a suitable method to quickly scale to fund early-phase studies; however, it was realized that the current process could be difficult to scale in terms of both practical and safety considerations. Additional areas for improvement involved the avoidance of all column chromatography, identification of stable isolable intermediates, and a final recrystallisation that avoided solvation.

Whilst the current route offered convenient divergence for analogue screening, it was felt that a more targeted disconnection strategy could be applied. Disconnection at the amide bond (Figure 4) offered increased convergence. Additionally it allowed the replacement of unprotected azetidinol **15**, which had proven difficult to source on scale, with the more readily available and cost-effective benzhydryl-protected mesylated azetidinol **24**.

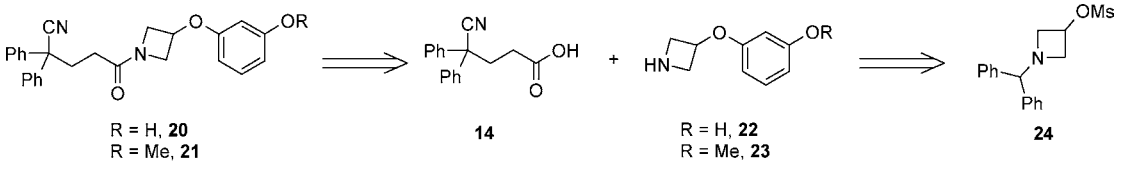


Figure 4. Amide disconnection strategy.

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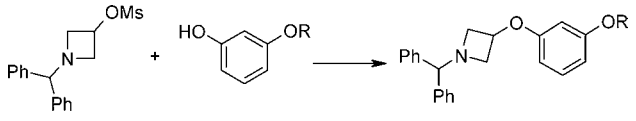
Ideally this route would be compatible with application of the modified Bouveault reaction to amide **20**, in which protection of the phenol could be avoided (and thus save a deprotection step). Thus, opening investigations into this alternative route focused on the direct coupling of resorcinol **25** with mesylated azetidinol **24** (Scheme 4).

Scheme 4. Phenol displacement of mesyl-azetidinol



24

R = H, **25**
R = Ac, **26**
R = Me, **17**

R = H, **27**
R = Ac, **28**
R = Me, **29**

Initial attempts at ether formation proved unsuccessful with complex reaction profiles including over-reaction to dimeric byproduct. A range of bases, solvents, and reagent equivalents were screened; however, in each instance a clean reaction profile could not be obtained. To accelerate progress we thus moved at this point to adopt a phenol protection strategy. As anisole deprotections generally require harsh conditions and form alkylating byproduct, it was felt that pursuing more labile alternatives may offer some advantages. Hence, acetate-protected analogue **26** was trialled in coupling with mesylated azetidine **24**; however, this proved unstable to various reaction conditions producing reaction profiles analogous to that observed with resorcinol **25**. Benzoyl-protected resorcinol was also attempted, but limited success led us to revert to 3-methoxyphenol **17** with a view to enable the anisole deprotection at a later stage. The mesylate displacement with this partner progressed cleanly with potassium carbonate in propionitrile with the solvent also facilitating a separative workup, with subsequent isolation of aryl ether **29** directly by filtration from methanol in a yield of 71% (11.2 kg). Acetonitrile also afforded clean conversion, but an extensive workup procedure made this option less desirable.

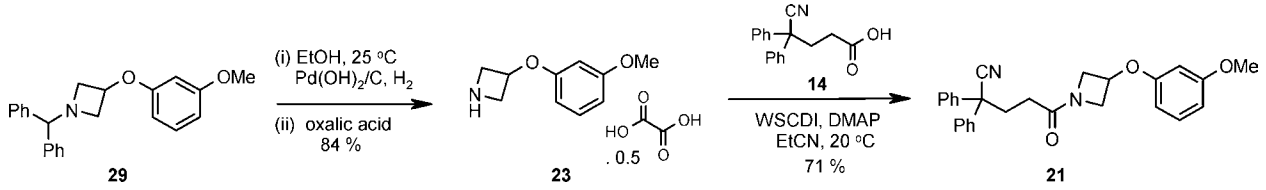
With aryl ether **29** in hand, a method was sought for benzhydryl deprotection to afford amine **23**. A range of Lewis acid and catalytic hydrogenation conditions were attempted with the benzhydryl group proving relatively inert. Our only positive result was obtained with 20% weight Pearlman's catalyst ($Pd(OH)_2/C$) in ethanol at 60 psi and 25 °C which provided clean conversion (Scheme 5). The amine product **23**, however, proved unstable to heat which presented some difficulties in isolation. Telescoping amine **23** into the amide coupling directly after catalyst filtration was attempted and found to give high conversion with clean reaction profiles. Unfortunately, subsequent crystallization of amide **21** was not robust, and even when crystal growth was achieved, the isolated yields of **21** were poor (<40%). It is postulated that the diphenylmethylene byproduct liberated by the benzhydryl protecting group under hydrogenation conditions inhibited crystallization. Attempts to exchange solvent to improve isolation were untenable due to instability with even mild warming. Direct drop of the amine product **23** as a salt eventually offered a way forward with amine **23** being isolated as a hemi-oxalate salt in 84% yield (5.4 kg over two batches) and excellent purity, with palladium levels detected at only 1 ppm (progressing to none detected after subsequent steps).

Acid **14** was prepared by Michael Addition, as previously described (Scheme 3), followed by deprotection with lithium hydroxide in 87% yield over two steps (12.1 kg). Coupling with amine-oxalate salt **23** was carried out with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSCDI) and catalytic 4-dimethylaminopyridine (DMAP) in propionitrile (EtCN). Alternative coupling agents of carbonyldiimidazole (CDI) or boronic acid/trimethoxyborane under thermal conditions failed to offer good conversion. Both DMAP and 1-hydroxy-benxotriazole (HOBt) proved beneficial additives in combination with WSCDI, with DMAP chosen on scale in consideration of sourcing and safety. Propionitrile offered linearity between reaction and workup washes before solvent exchange into methanol facilitated crystallisation of amide **21** in good yield 71% (7.1 kg). Interestingly salt break of amine-oxalate salt **23** was not required prior to coupling. It was found that addition of an extra 0.5 equiv of WSCDI allowed for decomposition of the oxalic acid prior to reaction and thus conferred a simplified process.

With **21** in hand our focus shifted to the modified Bouveault reaction of this more extensively functionalised amide. Pleasingly, following the previous procedure of treatment with 2 equiv of zirconium tetrachloride and 9 equiv of methylmagnesium chloride, amide **21** converted to desired *gem*-dimethylamine **18** in encouraging yields (50−65%). Limitations to the procedure included cryogenic conditions, requirement to decant due to significant inorganic precipitation, excessive volumes upon workup (~100 mL/g), and the requirement for column chromatography.

Initially we looked at order of addition; we were interested in previous investigations which suggested that combining methyl Grignard and zirconium tetrachloride formed an in situ tetramethylzirconium species.[14] Experimentation showed that, in line with our current process, best results were obtained when undertaking this pre-preparation, as opposed to adding all reagents simultaneously; hence, we believe the active species for this transformation is tetramethylzirconium. The report also suggests instability of this species upon exposure to elevated temperatures which again was reflected in poorer yields when the reaction temperaure exceeded 0 °C and also when using a preprepared solution which was stored for an extended period of time at 0 °C (>8 h). Pleasingly, when tetramethylzirconium was prepared fresh, we found that the reaction profile was stable and consistent up to 0 °C, and thus, we could avoid cryogenic conditions. Safety studies of this reagent reassured us of its stability with a TSU of the zirconium tetrachloride/methylmagnesium chloride mixture showing no significant

Scheme 5. Preparation of amide 21



29 **23** **21**

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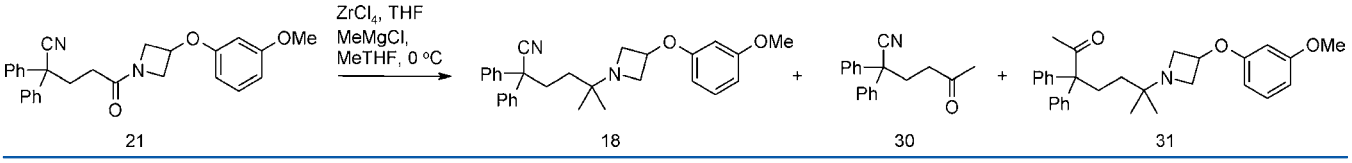
Scheme 6. Modified Bouveault reaction



exotherm or gas evolution upon heating to 200 °C at a rate of 2 °C per minute. The addition of the Grignard reagent to zirconium tetrachloride was highly exothermic with an RC1 measurement of −942.7 kJ/mol and an associated adiabatic temperature rise of 80 K. This would be sufficient to boil the solvent if added as a single dose without additional controls; hence, the process was made plausible via slow addition and full reactor cooling. The gas flow was also measured during this process with the flow of evolved gas below the limit of detection during the Grignard addition.

Our attentions were next drawn to the reaction stochiometry. Previous investigations on less complex substrates could be carried out with 1 equiv zirconium tetrachloride and 4 equiv methyl Grignard;[11] however, a screen for our substrate showed a steep decline in conversion to desired product below 1.5 equiv of zirconium tetrachloride and 7 equiv of methyl Grignard with 2.1 and 9 equiv, respectively, offering the best conversion. Key byproducts for this step were methyl ketones **30** and **31** (Scheme 6) arising respectively from breakdown of the complex after monomethyl addition or from nucleophilic attack at the nitrile position of the desired product.

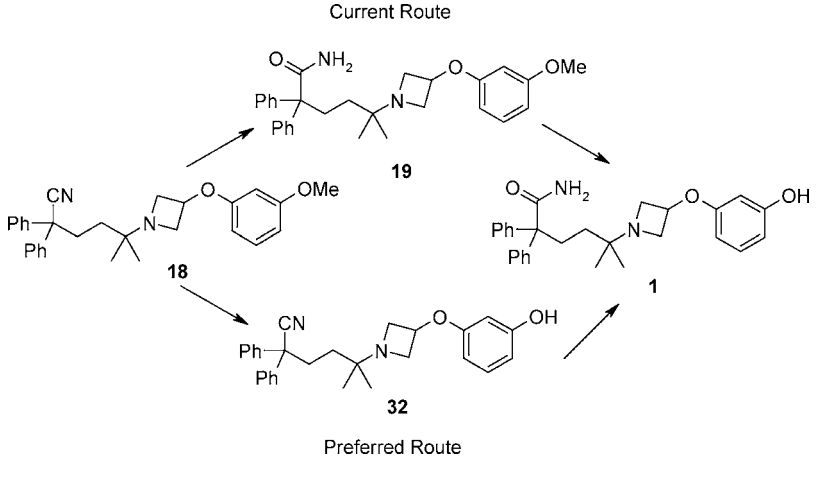
With respect to reaction workup it was noted that a water quench was highly exothermic and off-gassed. Head-space analysis showed the gas to be methane, and gas flow monitoring showed that its liberation could be dose controlled. In addition, the water quench resulted in excessive precipitation which led to the initial decanting procedure. Acetic acid diluted in 2-methyltetrahydrofuran (MeTHF) was found to give control of the exotherm and afforded a much more manageable suspension. The associated gas evolution during this addition was measured as −1018.9 kJ/mol of amide **21** over a 45 min addition at −5 °C and the associated adiabatic temp rise as 45 K. Gas evolution was detected during this addition with the rate measured as 3.9 L/min/mol of amide **21**, and the total amount of gas evolved measured as 90 L/mol. The safety studies showed a controlled quench offered a manageable exotherm and gas evolution within the acceptable limits of the pilot plant for safety and environment. Alternative quenches were attempted to minimize gas evolution and exothermic events, notably by the use of acetone or ethyl acetate; however, the profile and isolated yield through the original acetic acid quench were far superior in both respects. Subsequent addition of aqueous ammonium chloride resulted in a biphasic solution that could now be manipulated by a standard workup. Whilst the maximum workup volume was still high at ∼41 volumes, this approach offered significant improvement to throughput over the original procedure. Ultimately, solvent exchange into ethanol provided a suspension with product obtained by filtration in good yield and purity (average yield of 66% on 5.1-kg scale).

gem-Dimethylamine intermediate **18** offered a common intermediate to the early-phase route (Scheme 3) from which we could directly seek to enable the remaining demethylation and hydrolysis steps. The two procedures could potentially be undertaken in either order (Scheme 7).

Whilst the original sequence in early phase had been hydrolysis followed by demethylation, we now noted that the hydrolysis was generally a cleaner transformation. In addition, most common demethylation procedures result in alkylating byproduct with strict control required. Hence, our preference was to first undertake the demethylation of **18** to afford phenol **32** and then nitrile hydrolysis to primary amide **1**.

Screening a range of demethylation conditions found no alternative hits for conversion of ether **18** to phenol **32** other than boron tribromide which was undesired due to safety and toxicity issues. We were encouraged, however, by a report from Merck[15] in which DL-methionine had been employed as a demethylating agent with the advantage that the methylated-methionine byproduct (colloquially referred to as vitamin U) is not highlighted as an alkylating agent/genotoxic alert.[16] Whilst the reaction proved very specific to variations in solvent, temperature, and acid, conditions of 30 °C for 2−3 days in neat methanesulfonic acid (MsOH) and 3 equiv of DL-methionine afforded clean demethylation of **18**. To avoid an extensive basic quench of the neat acid upon workup, which would require

Scheme 7. Alternative end game approaches to target molecule 1



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strict control of exothermic events, the reaction was first diluted with isopropyl acetate/MeTHF. The methanesulfonic acid could then be largely washed out with water before quenching any residual acid and exchanging solvent to enable crystallization from toluene of phenol **32** in 68% yield (3.4 kg). It was noted at this stage that the level of zirconium in isolated phenol **32** was 13 ppm. This was significantly lower than the level of 228 ppm identified in the previous *gem*-dimethyl intermediate **18** and now complied with all the requisite specifications.

The final step involving hydrolysis of nitrile **32** to primary amide **1** was undertaken using potassium hydroxide in *tert*-amyl alcohol. Optimal conditions were found to be 18 equiv of potassium hydroxide at 100 °C from which only two impurities were observed, carboxylic acid **33** and decarboxylated byproduct **34** (Figure 5).

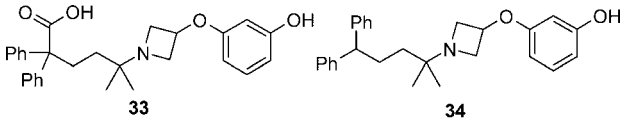


Figure 5. Impurities from nitrile hydrolysis of **32**.

Both impurities could be minimised by controlling reaction time and temperature. It was found that the level of decarboxylation increased significantly above 110 °C; therefore, the boiling point of *tert*-amyl alcohol (bp 102 °C) offered convenient control when compared to the initially utilised 3-methyl-3-pentanol (bp 123 °C). With the level of impurities minimised, both **33** and **34** could be purged upon isolation of target molecule **1** as the crude hydrochloride salt in 83% yield (2.85 kg).

Whilst this crude hydrochloride salt met HPLC purity specification, it was found to have occluded *tert*-amyl alcohol up to 6 wt %, which, given its non-ICH classification, presented complications and a desire to limit. A reslurry in aqueous methylethyl ketone (MEK) purged the alcohol to acceptable levels of <1 wt % in 76% yield over the two steps, providing 2.6 kg of target molecule **1** as a hydrochloride salt for toxicological and clinical trials.

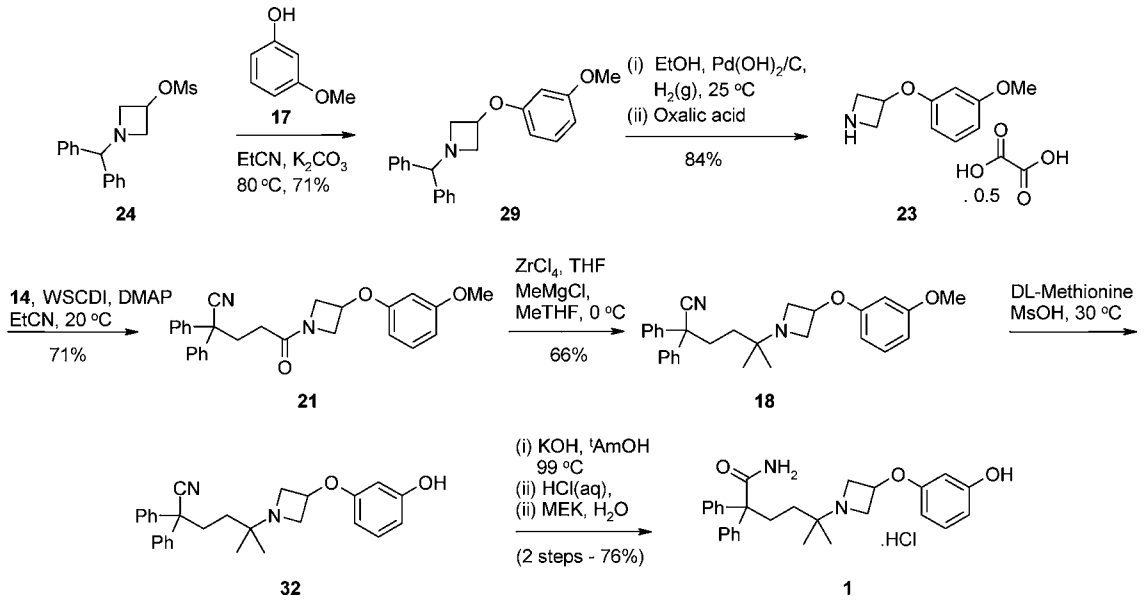
In summary we have presented a concise and scalable synthesis of PF-3635659 **1** as its hydrochloride salt which can support the required clinical studies toward the advancement of this phase II candidate (Scheme 8).[17] We have demonstrated two diverse alternatives for incorporation of a nontrivial, sterically encumbered geminal dimethyl amine moiety which encompass a broad functional group compatibility. The modified Bouveault reaction in particular has been performed on a synthetically advanced intermediate and on a scale which, to our knowledge, has never previously been attempted. We have also implemented a mild and technically uncomplicated method of unmasking a methylated phenol at a late stage in the synthesis, avoiding the notorious genetic toxicty problems of the more commonly used boron tribromide. The final route is now chromatography free, aided in no small part by continuous reappraisal of potential crystalline intermediates throughout the entire process from first synthesis to clinical preparation, with all steps developed to be suitable for safe and standard processing.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer. HPLC analyses were performed using a reverse phase technique. LC/MS analysis was performed using the following system; Hewlett-Packard 1100 with SB C18 3.0 mm ×50 mm, 1.8 μm particles; mobile phase consisting of solvent A, 0.05% TFA in water, solvent B, 0.05% TFA in acetonitrile. 0 min = 5% solvent B; 3.5 min = 100% solvent B; 4.5 min = 100% solvent B; 4.6 min = 5% solvent B; run time 5 min; column temperature 50 °C; 225 nm; with Waters Micromass ZQ 2000/4000 mass detector. Combustion analyses were performed by Warwick Analytical Service, University of Warwick Science Park, The Venture Centre, Sir William Lyons Road, Coventry CV4 7EZ, U.K. Experimental data is provided for the largest batch produced.

Preparation 1: 1-Benzhydryl-3-(3-methoxyphenoxy)-azetidine 29. To propionitrile (130.5 L) at 20 °C (±5 °C) was added methanesulfonic acid 1-benzhydrylazetidin-3-yl ester **24** (14.5 kg, 45.7 mol, 1 equiv) resulting in a solution. Potassium carbonate (7.6 kg, 54.8 mol, 1.2 equiv) was added in single portion and to the resulting slurry was added a

Scheme 8. Enabled route to deliver initial toxicity and clinical batches of PF-3635659·HCl salt



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preformed solution of 3-methoxyphenol (6.8 kg, 54.8 mol, 1.2 equiv) in propionitrile (14.5 L) maintaining a temperature of 20 °C (±5 °C). The mixture was heated to 80 °C (±5 °C) for 18 h, whereupon the reaction was deemed to have reached completion with <5% area starting material by HPLC.

The reaction was cooled to 20 °C (±5 °C) then 1 M NaOH (72.5 L) was added, maintaining a temperature of 20 °C (±5 °C) by controlled addition. The resulting solution was stirred for 15 min before being allowed to separate. The layers were partitioned, and the organic layer was washed with 1 M NaOH (2 × 43.5 L) and aqueous brine (24.0 kg NaCl in 72.5 L water) at 20 °C (±5 °C). The organic layer was placed under atmospheric distillation conditions and concentrated to low volume with a distillate temperature of 97 °C before solvent exchange into methanol (2 × 362.5 L), resulting in a final volume of ∼60 L and a distillate temperature of 65 °C. The resulting suspension is cooled to 0 °C (±5 °C) for 5 h and then filtered through a pressure filter. The cake was washed with methanol (87.0 L) and then dried under vacuum at 50 °C (±5 °C) for 10 h to give 1-benzhydryl-3-(3-methoxyphenoxy)azetidine **29** as a white solid (11.2 kg, 71%).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.94−3.02 (m, 2H), 3.58−3.66 (m, 2H), 3.70 (s, 3H), 4.51 (s, 1H), 4.79−4.87 (m, 1H), 6.36−6.42 (m, 2H), 6.49−6.55 (m, 1H), 7.16−7.22 (m, 3H), 7.29 (t, J = 7.52 Hz, 4H), 7.40−7.49 (m, 4H); ^{13}CNMR (100 MHz, DMSO-d_6) δ: 55.0, 59.6, 65.6, 76.9, 100.8, 106.5, 106.8, 127.0, 127.1, 128.4, 130.1, 142.3, 157.9, 160.6. Anal. Calcd for $C_{23}H_{23}NO_2$: C 79.97; H 6.71; N 4.05. Found: C 80.15; H 6.76; N 4.02.

Preparation 2: 3-(3-Methoxyphenoxy)azetidine Hemioxalate 23. To ethanol (102 L) were added 1-benzhydryl-3-(3-methoxyphenoxy)azetidine **29** (5.1 kg, 14.7 mol, 1 equiv) and $Pd(OH)_2$/C (20 wt % on carbon) (1.02 kg, 20 wt %), and the vessel was placed under hydrogenation conditions of 60 psi H_2 and 20 °C (±5 °C) for 72 h whereupon the hydrogen uptake had significantly decreased and HPLC reported <5% starting material. The reaction mixture was filtered through filter aid and concentrated to ∼22 L under vacuum distillation using full vacuum whilst maintaining the temperature below 35 °C. To the resulting solution at 20 °C (±5 °C) was added oxalic acid (0.66 kg, 7.4 mol, 0.5 equiv) resulting in a thick suspension and a temperature rise of 4 °C. The mixture was left to stir for 5 h at 20 °C (±5 °C) then 3 h at 0 °C (±5 °C) before filtering through a pressure filter and washing the cake with ethanol (20 L) and then drying under vacuum at 50 °C (±5 °C) for 16 h to give 3-(3-methoxyphenoxy)azetidine hemioxalate **23** as a white solid (2.68 kg, 81%).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.73 (s, 3H), 3.76−3.85 (m, 2H), 4.11−4.23 (m, 2H), 4.97−5.09 (m, 1H), 6.34−6.44 (m, 2H), 6.52−6.61 (m, 1H), 7.15−7.23 (m, 1H); ^{13}CNMR (100 MHz, DMSO-d_6) δ: 52.6, 55.1, 66.4, 101.0, 106.7, 107.1, 130.3, 157.3, 160.6.

Preparation 3: 4-Cyano-4,4-diphenylbutyric Acid 14. Diphenylacetonitrile (5.1 kg, 26.4 mol, 1 equiv) and *tert*-butanol (26 L) were heated to 45 °C (±5 °C). To the resulting solution were added a suspension of KOH (145 g, 2.64 mol, 0.1 equiv) in methanol (0.55 L) and then *tert*-butyl acrylate (4.16 kg, 31.7 mol, 1.2 equiv) over 30 min. The reaction was heated at 60 °C (±5 °C) for 5 h, whereupon the reaction was complete with HPLC indicating <5% starting material. Upon cooling to 20 °C (±5 °C) a solution of lithium hydroxide hydrate (2.88 kg, 68.6 mol, 2.6 equiv) in water (26 L) was added and the batch heated at reflux (89 °C) for 5 h. The reaction was then placed under vacuum distillation at 50 °C (±5 °C) and the *tert*-butanol removed, leaving an aqueous concentrate of ∼22 L. Water (128 L) was added and the reaction warmed to 40 °C (±5 °C) to achieve dissolution. The solution was then cooled to 30 °C (±5 °C) before extracting with dichloromethane (3 × 20 L). The dichloromethane layers were discarded, and the aqueous layer was distilled under vacuum at 45 °C (±5 °C) to remove ∼5 L of distillate (all traces of dichloromethane). The mixture was then cooled to 25 °C (±5 °C) and acidified to pH 2 by addition of 37% conc. HCl (6.9 L), resulting in a suspension. After stirring at 25 °C (±5 °C) for 1 h the suspension was filtered under vacuum and the cake washed with water (10 L) and dried under vacuum at 40 °C (±5 °C) to give 4-cyano-4,4-diphenylbutyric acid **14** as a white solid (6.1 kg, 87%).

^{1}HNMR (400 MHz, DMSO-d_6) δ: 2.21−2.32 (m, 2H), 2.71−2.83 (m, 2H), 7.29−7.38 (m, 2H), 7.38−7.50 (m, 8H), 12.30−12.51 (br s, 1H); ^{13}CNMR (100 MHz, DMSO-d_6) δ: 30.6, 33.5, 50.8, 121.8, 126.5, 128.0, 129.1, 139.4, 172.8.

Preparation 4: 5-[3-(3-Methoxyphenoxy)azetidin-1-yl]-5-oxo-2,2-diphenylpentanenitrile 21. To a suspension of 4-Cyano-4,4-diphenyl-butyric acid **14** (3.15 kg, 11.9 mol, 1 equiv) in propionitrile (31.5 L) at 20 °C (±5 °C) were added 3-(3-methoxyphenoxy)azetidine hemioxalate **23** (2.66 kg, 11.9 mol, 1 equiv) and 4-dimethylaminopyridine (145 g, 1.2 mol, 0.1 equiv). The reaction was stirred for 10 min before adding WSCDI (3.42 kg, 17.8 mol, 1.5 equiv) resulting in slight effervescence, a 10 °C exotherm and dissolution to a solution. The reaction was recooled to 20 °C (±5 °C) and after 3 h the reaction was deemed complete by HPLC with <3% area of starting material **23**. Aqueous 2 M HCl (13.0 L) was added, maintaining a temperature of 25 °C (±5 °C); then the biphasic mixture was stirred for 10 min at 20 °C (±5 °C) before separating and washing the organic layer with aqueous 2 M NaOH (15.8 L) and water (2 × 15.8 L). The organic layer was placed under atmospheric distillation conditions, initially collecting the distillate at 84 °C and ending at 99 °C and low volume before solvent exchange into methanol (2 × 50 L), resulting in a final volume of ∼25 L and a distillate temperature of 65 °C. The resulting suspension is cooled to 20 °C (±5 °C) and stirred for 5 h and then 0 °C (±5 °C) for 2 h before filtering in a pressure filter, washing the cake with methanol (12.6 L), and then drying under vacuum at 45 °C (±5 °C) for 12 h to afford 5-[3-(3-methoxyphenoxy)-azetidin-1-yl]-5-oxo-2,2-diphenylpentanenitrile **21** as a white solid (3.6 kg, 71%).

^{1}HNMR (400 MHz, DMSO-d_6) δ: 2.04−2.23 (m, 2H), 2.65−2.83 (m, 2H), 3.73 (s, 3H), 3.74−3.79 (m, 1H), 3.92−4.01 (m, 1H), 4.21−4.32 (m, 1H), 4.38−4.48 (m, 1H), 4.90−5.01 (m, 1H), 6.34−6.44 (m, 2H), 6.52−6.62 (m, 1H), 7.16−7.24 (m, 1H), 7.31−7.37 (m, 2H), 7.38−7.49 (m, 8H); ^{13}CNMR (100 MHz, DMSO-d_6) δ: 27.6, 33.4, 51.0, 54.5, 55.1, 56.5, 65.2, 101.0, 106.6, 107.1, 121.9, 126.4, 128.0, 128.4, 128.6, 129.1, 130.2, 139.5, 139.6, 157.4, 160.6, 170.4. Anal. Calcd for $C_{27}H_{26}N_2O_3$: C 76.03; H 6.14; N 6.57. Found: C 76.12; H 6.19; N 6.38.

Preparation 5: 5-[3-(3-Methoxyphenoxy)azetidin-1-yl]-5-methyl-2,2-diphenylhexanenitrile 18. All vessels were rinsed and boiled out with tetrahydrofuran and then analysed to ensure <0.1 wt % water before commencing with the reaction. The $ZrCl_4$ was freshly weighed into dry CTC immediately before use, due to its hygroscopic nature.

To tetrahydrofuran (35.0 L) at −15 °C to −10 °C under a N_2 atmosphere was carefully added $ZrCl_4$ (4.4 kg, 18.9 mol,

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2.3 equiv) over three equal portions, maintaining a temperature below 0 °C. The potential exotherm from a single addition of the full 4.4 kg of $ZrCl_4$ was estimated to be 44 °C, and the observed exotherm for each portion of 1.5 kg of $ZrCl_4$ was 8.2 °C. The resulting brown suspension was cooled to −5 °C (±5 °C) before the addition of a solution of methylmagnesium chloride (3 M in tetrahydrofuran, 24.6 L, 73.9 mol, 9 equiv) over 1 h, maintaining the temperature below 0 °C. The potential heat rise from the Grignard addition was estimated as 88 °C; however, this was readily controlled by addition rate. A line wash of tetrahydrofuran (20 L) was applied. The resulting black slurry was stirred at −5 °C (±5 °C) for 30 min before adding a preformed solution of 5-[3-(3-methoxyphenoxy)azetidin-1-yl]-5-oxo-2,2-diphenylpentanenitrile **21** (3.5 kg, 8.21 mol, 1 equiv) in tetrahydrofuran (10.5 L) maintaining the temperature below 0 °C (±5 °C) (potential for 20 °C rise controlled by addition rate). An additional line wash with tetrahydrofuran (17.0 L) was carried out before the mixture was stirred for 4 h at −5 °C (±5 °C) resulting in reaction completion which was noted by >80% area of desired product by HPLC and <8% methylketone **30**. The reaction was quenched with a preformed solution of 2-methyltetrahydrofuran (35.0 L) and glacial acetic acid (4.2 L, 73.9 mol, 9.0 equiv) maintaining the temperature below −5 °C and venting the methane off-gas through a hydrogen vent. The reaction was set to 10 °C and water (50 L) was added to the reaction followed by a solution of aqueous ammonium chloride (3.5 kg) in water (35.0 L) to ensure full quench maintaining the temperature below 10 °C. The mixture was then stirred for 16 h at 15 °C (±5 °C) then allowed to separate and the bottom layer discarded. At 15 °C (±5 °C) the organic layer was washed with a solution of dilute aqueous sodium hydroxide prepared from 40% NaOH (2.4 L) and water (32.6 L) and then with a solution of brine (3.5 kg NaCl in 35.0 L water). The resulting organic layer was concentrated to low volume under atmospheric distillation conditions with a final distillate temperature of 70 °C and then was solvent exchanged into ethanol (3 × 50.0 L portions), resulting in a final suspension of ∼18 L in volume and a consistent boiling point of 80 °C. The mixture was cooled to 20 °C (±5 °C) for 5 h and then to 0 °C (±5 °C) for 2 h before the resulting thick suspension was filtered through a pressure filter and the cake washed with ethanol (14 L). The solid was dried in a vacuum oven at 50 °C (±5 °C) under vacuum for 12 h to give 5-[3-(3-methoxyphenoxy)azetidin-1-yl]-5-methyl-2,2-diphenylhexanenitrile **18** as a white, crystalline solid (2.65 kg, 74%).

^{1}HNMR (400 MHz, DMSO-d_6) δ: 0.89 (s, 6H), 1.23 (dt, J = 8.21, 4.10 Hz, 2H), 2.49−2.53 (m, 2H), 2.98−3.08 (m, 2H), 3.38−3.47 (m, 2H), 3.72 (s, 3H), 4.69 (t, J = 5.57 Hz, 1H), 6.31−6.44 (m, 2H), 6.48−6.59 (m, 1H), 7.09−7.22 (m, 1H), 7.28−7.36 (m, 2H), 7.37−7.50 (m, 8H); ^{13}CNMR (100 MHz, DMSO-d_6) δ: 20.5, 33.1, 34.8, 51.4, 52.8, 53.3, 55.0, 65.1, 100.7, 106.6, 106.6, 122.2, 126.5, 127.6, 129.0, 130.1, 140.1, 158.0, 160.5; LRMS ESI m/z 441 $[M + H]^+$. Anal. Calcd for $C_{29}H_{32}N_2O_2$ (contains 0.3 mol water): C 79.06; H 7.32; N 6.36. Found: C 78.13; H 7.25; N 6.11.

Preparation 6: 5-[3-(3-Hydroxyphenoxy)azetidin-1-yl]-5-methyl-2,2-diphenylhexanenitrile 32. 5-[3-(3-Methoxyphenoxy)azetidin-1-yl]-5-methyl-2,2-diphenylhexanenitrile **18** (2.65 kg, 6.01 mol, 1 equiv) was added to methanesulfonic acid (13.3 L), resulting in an 18 °C exotherm. The mixture was stirred at 20 °C (±5 °C) for 30 min, resulting in a viscous solution. DL-methionine (2.69 kg, 18.03 mol, 3 equiv) was added resulting in an 8 °C exotherm, the mixture was heated to 30 °C (±5 °C) for 72 h whereupon the reaction had reached completion identified by <3% area starting material by HPLC. The mixture was cooled to 10 °C (±5 °C) then isopropyl acetate (26.5 L) added followed by the slow addition of water (26.5 L). (Note − there is a theoretical 27 °C exotherm, though the solution temperature is controlled to <25 °C by addition rate). 2-Methyltetrahydrofuran (5.3 L) was then added and the layers were mixed for 15 min at 20 °C (±5 °C) then separated. The aqueous layer is back-washed with isopropyl acetate (13.3 L). The organic layers were combined and washed at 20 °C (±5 °C) with 1 M NaOH (26.5 L), water (13.3 L), and brine (2.65 kg NaCl in 13.3 L water). The organic layer was placed under atmospheric distillation conditions (reflux = 86 °C) and solvent exchange conducted into toluene. Completion was noted by boiling point (target distillate temperature of >105 °C was targeted from small scale, although a distillate temperature of 112 °C was achieved on scale using a total of 155.8 kg of toluene over two portions) and a final reaction volume of ∼4 L/kg. The mixture was cooled to 20 °C (±5 °C) at a rate of 1 °C/min and granulated for 5 h before cooling to 5 °C (±5 °C) and granulating for a further 2 h. The suspension was filtered through a pressure filter and the cake washed with cold toluene (10.6 L) and dried at 50 °C (±5 °C) under reduced pressure to afford 5-[3-(3-hydroxyphenoxy)azetidin-1-yl]-5-methyl-2,2-diphenylhexanenitrile **32** as a white crystalline solid (1.65 kg, 64%).

^{1}HNMR (400 MHz, DMSO-d_6) δ: 0.98 (s, 6H), 1.22 (dt, J = 4.2, 8.3 Hz, 2H), 2.46−2.54 (m, 2H), 2.99−3.05 (m, 2H), 3.38−3.45 (m, 2H), 4.62 (t, J = 5.7 Hz, 1H), 6.20−6.25 (m, 2H), 6.34−6.38 (m, 1H), 7.03 (t, J = 8.1 Hz, 1H), 7.29−7.35 (m, 2H), 7.38−7.47 (m, 8H), 9.4 (s, 1H); ^{13}CNMR (100 MHz, DMSO-d_6) δ: 20.6, 33.2, 34.9, 51.4, 52.9, 53.3, 65.0, 101.8, 105.1, 108.1, 122.2, 126.5, 127.8, 129.0, 130.0, 140.1, 158.0, 158.6. Anal. Calcd for $C_{28}H_{30}N_2O_2$: C 78.84; H 7.09; N 6.57. Found: C 78.72; H 7.12; N 6.51.

Preparation 7: 5-[3-(3-Hydroxyphenoxy)azetidin-1-yl]-5-methyl-2,2-diphenylhexanamide 1 (Hydrochloride Salt). To a suspension of 5-[3-(3-hydroxyphenoxy)azetidin-1-yl]-5-methyl-2,2-diphenylhexanenitrile **32** (3.05 kg, 7.15 mol, 1 equiv) and *tert*-amyl alcohol (30.5 L) at 22 °C was added flake-KOH (7.42 kg, 132.3 mol, 18.5 equiv) and the mixture heated to 80 °C (±5 °C) for 2.5 h (note a change of morphology occurs, resulting in a thick suspension). The suspension was then heated to 99 °C (±5 °C) at a rate of 0.5 °C/min and then held at this temperature for 24 h, whereupon the reaction was deemed complete with <5% starting material remaining by HPLC. The reaction was cooled to 20 °C (±5 °C) and quenched slowly with water (30.5 L), maintaining the temperature below 25 °C. The layers were mixed for 1 h and separated; the upper organic layer was washed with water (30.5 L). The organic layer was adjusted to a pH range of 6.8−8 with 37% hydrochloric acid (0.66 L, 1.1 equiv), maintaining a temperature below 25 °C, before the layers were separated. The upper layer was passed through a 2 μm filter to spec-free the solution, and all additional solvent and reagents from this point were passed through 2 μm filters (as were reactors and equipment cleaned and verified to spec-free prior to use). To the clarified upper organic layer was added *tert*-butylmethyl ether (9.3 L) and 37% hydrochloric acid (0.63 L, 1.05 equiv) maintaining a temperature below 25 °C (±5 °C) and the mixture stirred for 19 h at 20 °C (±5 °C) resulting in a thick suspension. The suspension was filtered through a pressure filter and the cake washed with *tert*-butylmethyl ether (22.3 L) and dried at 70 °C (±5 °C) under reduced pressure in a tray drier for 12 h to afford crude the hydrochloride salt of 5-[3-(3-hydroxyphenoxy)azetidin-1-yl]-5-methyl-2,2-diphenylhexanamide

1 (PF-3635659·HCl) as a white crystalline solid with 6 wt % occluded *tert*-amyl alcohol (2.85 kg, 83%).

A stirred suspension of the hydrochloride salt of **1** (2.85 kg) in methylethylketone (27.0 L) and water (1.5 L) was heated to reflux (73 °C) and the resulting suspension stirred for 16 h before cooling to 20 °C (±5 °C) at a rate of 1 °C per min and then stirring for 5 h. The suspension was filtered on a pressure filter and the cake washed with methylethylketone (19.9 L) before drying at 70 °C (±5 °C) in a tray drier under reduced pressure for 12 h to afford the purified hydrochloride salt of 5-[3-(3-hydroxyphenoxy)azetidin-1-yl]-5-methyl-2,2-diphenylhexanamide **1** (PF-3635659·HCl) as a white crystalline solid (2.60 kg, 91%). Combined yield over both steps is 76%.

^{1}HNMR (400 MHz, DMSO-d_6) δ: 1.10 (s, 6H), 1.22−1.34 (m, 2H), 2.42−2.55 (m, 2H), 3.28−3.40 (m, 2H), 3.65−3.88 (m, 2H), 4.70−4.80 (m, 1H), 5.55−5.70 (br s, 2H), 6.23−6.36 (m, 2H), 6.45−6.53 (m, 1H), 7.03−7.12 (m, 1H), 7.19−7.39 (m, 10H); ^{13}CNMR (100 MHz, DMSO-d_6) δ: 19.8, 19.9, 31.7, 53.0, 53.9, 59.5, 61.0, 62.5, 64.1, 102.2, 105.1, 109.2, 126.4, 127.8, 128.8, 128.9, 130.1, 130.2, 143.6, 156.7, 156.9, 158.9, 174.7; LRMS ESI m/z 445 $[M + H]^+$. Anal. Calcd for $C_{28}H_{32}N_2O_3$·HCl: C 69.91; H 6.91; N 5.82; Cl 7.37. Found: C 69.75; H 7.05; N 5.66; Cl 7.16.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all early-stage synthetic routes. This material is available free of charge via the Internet at http://pubs.acs.org.

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