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Development of the Route of Manufacture of an Oral H_1-H_3 Antagonist

Guillaume Bret,‡ Sandra J. Harling,† Karim Herbal,† Nathalie Langlade,† Mike Loft,‡ Alan Negus,‡ Mahesh Sanganee,† Steve Shanahan,‡ John B. Strachan,*,† Peter G. Turner,† and Matthew P. Whiting†

Synthetic Chemistry, GlaxoSmithKline Pharmaceuticals, Medicines Research Centre, Gunnels Wood Road, Stevenage SG1 2NY, U.K., and Synthetic Chemistry, GlaxoSmithKline Pharmaceuticals, Old Powder Mills, Leigh, nr Tonbridge TN11 9AN, U.K.

Abstract:

A new route to an H_1-H_3 antagonist was developed to address scalability and environmental and cost of goods issues associated with the initial route.

Introduction

Compound **10** is an H_1-H_3 antagonist which is being developed as an oral medicine for the treatment of allergic rhinitis. The initial route to this compound is shown in Scheme 1.

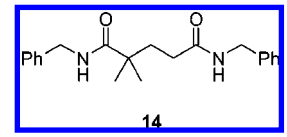
There were a number of issues associated with this synthesis which precluded its use as the long-term route of manufacture. Use of *p*-iodophenol generates iodine-containing waste streams and associated high disposal costs. The use of a BOC protecting group for the piperidone raises issues of thermal stability and the generation of isobutylene as a byproduct. The cryogenic temperature and low yield for the Grignard reaction was unsatisfactory and the resulting tetrahydropyridine **6** had limited stability. The use of expensive, thermally unstable TBTU as the final coupling agent was also of concern. Neither the piperidine (**3**) nor naphthalene (**7**) fragments were commercially available. Finally, the later stage intermediates were all non-crystalline, hindering the development of scalable isolations. Indeed the drug substance (**10**) itself was poorly crystalline, displaying a wide metastable zone width in potential crystallisation solvents. We therefore initiated a programme of work to improve the synthetic route in preparation for large-scale manufacture.

Results and Discussion

Preparation of 3,3-Dimethylpiperidine. 3,3-Dimethylpiperidine (**3**) was initially prepared by cyclisation of commercially available dimethylglutaric acid (**11**) with benzylamine followed by reduction with lithium aluminium hydride and then debenzylation (Scheme 2).

The cyclisation was conducted at 100-kg scale in *o*-xylene under Dean−Stark conditions in the presence of *p*-toluenesulphonic acid (pTSA) catalyst. Despite very good results in the laboratory, initial scale-up led to unexpected formation of around 10 mol % of diamide **14**.

The exact reason for the elevated levels of **14** are unclear; however, one could postulate that it could be directly related



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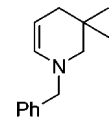
to degradation of the pTSA catalyst under the forcing conditions of the process (either by conversion to pTSA anhydride or by desulphonation). Laboratory studies showed that **14** would convert to **12** with a recharge of pTSA. This approach led to a 90% reduction of the diamide level with formation of more product.

Parallel studies showed that the impure plant batch could be reworked by selective crystallisation and filtration of **14**. In this way the contaminant could be reduced to <2%. These changes were successfully implemented, and yields of at least 84% were obtained for subsequent batches with <2% diamide impurity.

The original method for reduction of compound **12** with lithium aluminium hydride presented two main challenges: an unattractive filtration of the alumina byproduct through a Hyflow bed and a final distillation of 1-benzyl-3,3-dimethyl piperidine (**13**) under high vacuum at 150−200 °C. The first issue was resolved by quenching the reaction mixture with 40% w/w aqueous sodium hydroxide and separating the layers at 60 °C. Resolution of the second issue required significant capital investment, and so the decision was made to telescope this stage with the final debenzylation. This was reinforced by the fact that the reaction mixture was reasonably free of impurities with the exception of low level formation of enamine **15** (presumably from dehydration of the hemiaminal intermediate) which could be hydrogenated in the next stage.



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The process was conducted in pilot plant on a 38-kg scale with an overall yield of 72%. All reactions proceeded smoothly and were complete within two hours. Compound **13** was isolated as a THF solution after alkaline workup.

Debenzylation of **13** had previously been accomplished using 1-chloroethyl chloroformate (ACE-Cl) in 60% yield. This chemistry was considered undesirable for a pilot-plant campaign due to the moderate yield and environmental issues associated with handling the reagent and its byproducts, benzyl chloride and acetaldehyde.

* Author to whom correspondence may be sent. E-mail: john.b.strachan@gsk.com.

† GlaxoSmithKline Pharmaceuticals, Medicines Research Centre, Gunnels Wood Road.

‡ GlaxoSmithKline Pharmaceuticals, Old Powder Mills.

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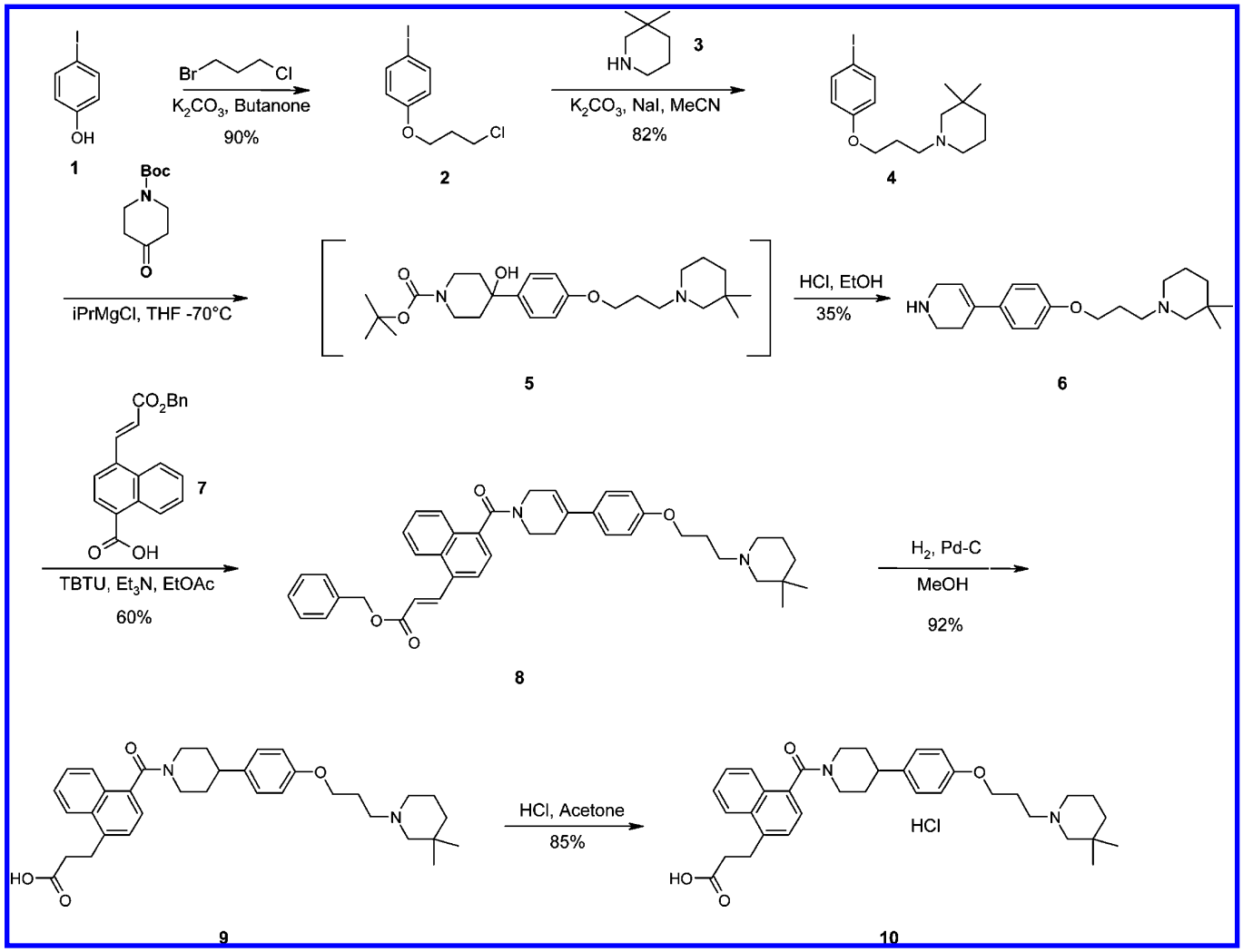
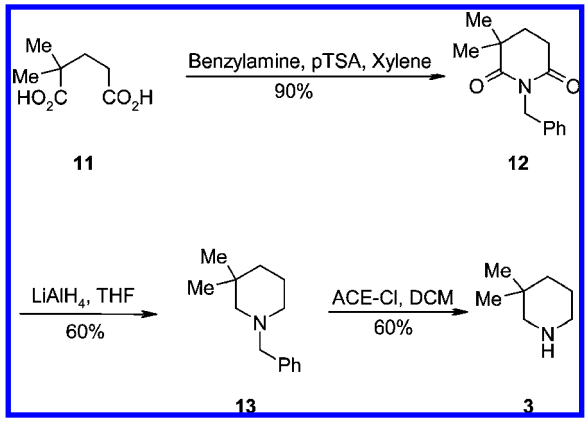
Scheme 1. **Initial synthesis of compound 10**



Scheme 2. **Initial supply route to 3,3-dimethylpiperidine**



Debenzylation of **13** by hydrogenation had previously been reported on small scale in the literature, offering the prospect of a clean and scalable transformation.[1] Initial results showed that the hydrogenation was stalling, probably due to catalyst poisoning by the amine product. This issue was easily overcome with the addition of acetic acid to the hydrogenation mixture. However, the enamine impurity generated in the lithium aluminium hydride reduction was not stable under acidic conditions. The hydrogenation was therefore carried out sequentially. First, the enamine was reduced (alkene reduction was rapid), and second, acetic acid was charged and the hydrogenation restarted to cleave the *N*-benzyl protecting group. Distillation was chosen as the preferred purification method for **3** over isolation by salt formation and crystallisation. The latter was investigated; however, the presence of basic impurities prevented a robust method from being developed.

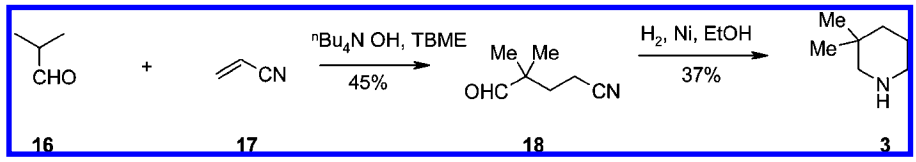
Although the above methodology successfully afforded 70 kg of **3**, a more efficient approach was sought. Michael addition of isobutyraldehyde (**16**) to acrylonitrile (**17**) produced 2,2-dimethyl-4-cyanobutyraldehyde (**18**) in an unoptimised yield of 45%. **18** was converted to compound **3** in an unoptimised, one-pot nitrile reduction−reductive amination sequence (Scheme 3).[2] This route was demonstrated on a 150-g scale in the laboratory. The cost of goods is significantly cheaper with this route, and with only two chemical steps, it also potentially offers considerable savings in processing time.

Phenol Alkylation and Grignard Reaction. *p*-Bromophenol is a cheaper alternative to *p*-iodophenol which would avoid the iodine waste issue and was expected to participate successfully in the desired chemistry. Sequential coupling with bro-

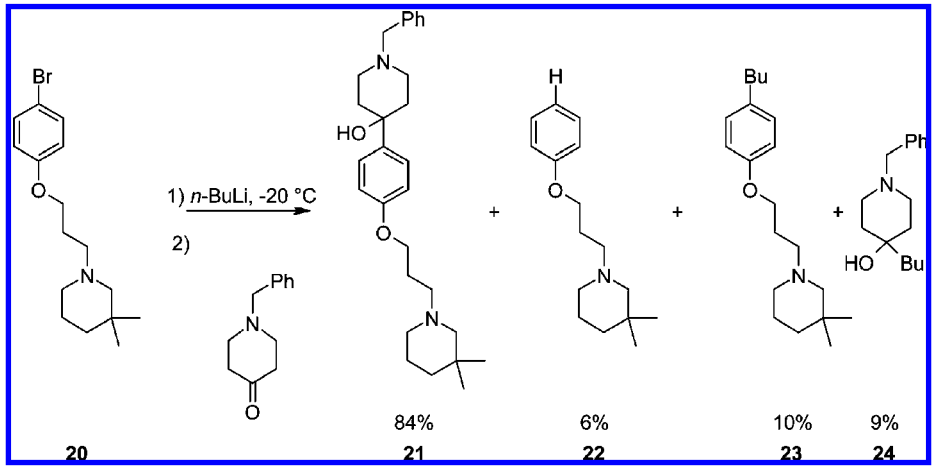
(1) See for example, Berardi, F.; Ferorelli, S.; Colabufo, N. A.; Leopoldo, M.; Perrone, R.; Tortorella, V. *Bioorg. Med. Chem.* **2001**, *9*, 1325.

(2) Schreyer, R. C. *J. Am. Chem. Soc.* **1952**, *74*, 3194.

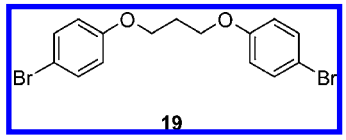
Scheme 3. **Concise route to 3,3-dimethylpiperidine**



Scheme 4. **Addition of aryl lithium reagent to *N*-benzyl piperidin-4-one, conversions determined by ^{1}H NMR analysis of the crude reaction product**



mochloropropane and 3,3-dimethylpiperidine yielded the desired bromide. In the initial process, potassium carbonate was used in two different solvents with an intermediate isolation. By using aqueous sodium hydroxide and MIBK under phase transfer conditions the two transformations could be effected without an intermediate workup. In addition, the reaction time was reduced from 24 to 5 h. The major byproduct was the diether **19** formed by over-reaction of bromophenol with bromochloropropane. No reaction conditions could be found which eliminated its formation; however, it was easily removed by acid−base extraction.



We were encouraged by literature examples suggesting that a high-yielding Grignard reaction could be achieved at non-cryogenic temperatures using a benzyl protecting group in place of a BOC group.[3] This would also avoid the associated thermal instability and isobutylene issues and provide a cheaper starting material.

As the aryl bromide intermediate **20** was not reactive enough to be metalated under Knochel conditions, we turned to bromine−lithium exchange using *n*-BuLi in hexanes (Scheme 4). This was successful; however, a significant amount of the butylated product **23** was obtained by reaction of the aryl lithium species with the bromobutane byproduct. This could be minimised by using two equivalents of *n*-BuLi and conducting the reaction at −20 °C. Under these conditions the majority of the bromobutane formed is consumed by reaction with the excess *n*-BuLi. Use of a larger excess was counterproductive as residual *n*-BuLi adds to the piperidone, giving rise to butyl piperidine derivative **24**. Low levels of the des-bromo compound **22** were also observed, presumably arising from competitive deprotonation of the piperidone.

As tertiary alcohol **21** was a gum, we decided to telescope the crude reaction mixture directly into the deprotection step (Scheme 5). We found we were able to remove the *N*-benzyl group and concomitantly reduce out the benzylic alcohol directly by hydrogenolysis over palladium on carbon in the presence of a strong acid. Specifically hydrogenolysis at 3 bar hydrogen pressure using 0.2 weights of 50% wet 10% Pd−C (∼3 mol % Pd) in 19:1 EtOH/water with 3 equiv of methanesulphonic acid gave clean conversion to the desired product in 8 h at 65 °C. In the absence of added acid or in the presence of weaker acids such as acetic only *N*-debenzylation was observed. Unlike the tetrahydropyridine **6**, this compound proved stable.

Unfortunately, neither the methanesulphonic acid salt nor the free base was suitable for isolation. We were, however, able to show that the benzoic acid salt could be readily crystallised from a number of solvents with TBME being shown to give a good cleanup of all the impurities. One minor issue with this crystallisation was that the product was obtained as a mixture of mono- and dibenzoate salts, due to the lower solubility of the monobenzoate. This was not considered to be a major issue at this stage, and the process was progressed to the plant.

The aryl bromide **20** was initially purified by acid base extraction to remove residual dimer **19**. The pure solution in TBME was azeotropically dried before being transferred into a solution of *n*-BuLi in THF and hexanes and then treated with benzyl piperidone. After quenching and aqueous workup, solvent exchange to ethanol for the hydrogenolysis was achieved by distillation. Aqueous workup under basic conditions enabled transfer of the free base to a TBME phase. This was again azeotropically dried

(3) See for example Sakamuri, S.; Enyedy, I.; Kozikowski, A.; Zaman, W.; Johnson, K.; Wang, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 495.

Scheme 5. **Telescoped alkylation−hydrogenolysis process**

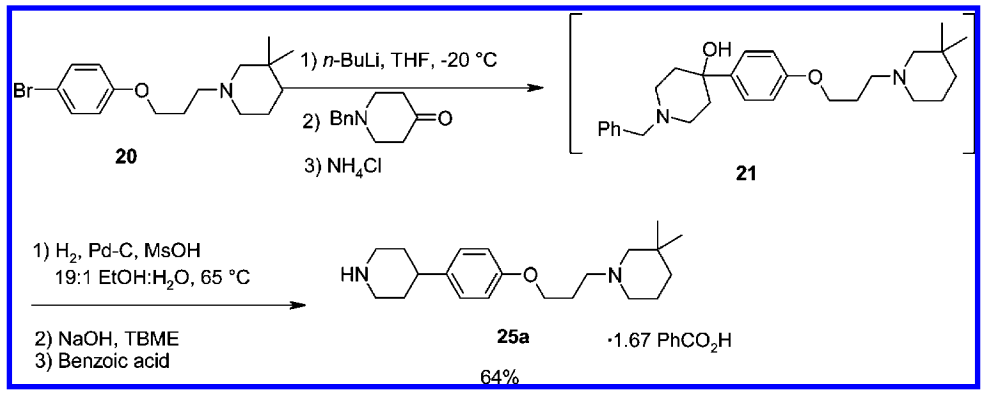


Table 1. **Alkylation selectivities for different ArM species, determined by ^{1}H NMR analysis of the crude reaction products**

entry	ArM	solvent	*T* (°C)	**21** (%)	**22** (%)	**23** (%)
1	ArLi	THF	−20	84	6	10
2	Ar_3MgLi	THF	0	69	26	4
3	ArMgBr	THF	20	76	23	0

before benzoic acid was added, and the product was isolated in 64% yield and >99% purity through a seeded cooling crystallisation.

Although this process worked very well on scale, there were several obvious areas which could potentially be improved for future campaigns. First, >15% of the material was lost in the initial alkylation as the butylated or des-bromo byproducts **23** and **22**, respectively. Second, the process was quite lengthy, with several solvent and salt swaps. We therefore decided to investigate both alternative metalation and alkylation procedures to try and improve the selectivity for the desired product, and also try to streamline the hydrogenation and isolation procedure, ideally removing the need for the salt and solvent swap.

Initially we looked into formation of less reactive aryl metal species. The electron-rich aryl bromide **20** did not undergo halogen−magnesium exchange (to give the Grignard reagent) under Knochel-type conditions.[4] However, the corresponding lithium triarylmagnesiate[5] was readily formed by addition of 0.66 equiv of *n*-BuLi to a solution of the aryl bromide and 0.33 equiv of *i*PrMgCl. This reagent exhibited much reduced reactivity towards bromobutane, forming only 4% of **23**, even in the absence of excess base and at the elevated temperature of 0 °C (Table 1). However, upon quenching with the piperidone, a large amount of protonated impurity **22** was formed. The bromomagnesium Grignard reagent itself was readily formed by direct insertion of Mg in THF at 40 °C. In this case formation of **23** was, of course, not a problem; however, upon quenching with the piperidone a significant amount of **22** was again observed. We assumed that this must arise from competitive deprotonation of the ketone (instead of the desired addition), and this was confirmed by quenching the Grignard reagent with α,α,α,α-d_4 deuterated *N*-benzylpiperidone, where we observed a large kinetic isotope effect for the deprotonation and also significant levels of deuterium incorporation into **22**.

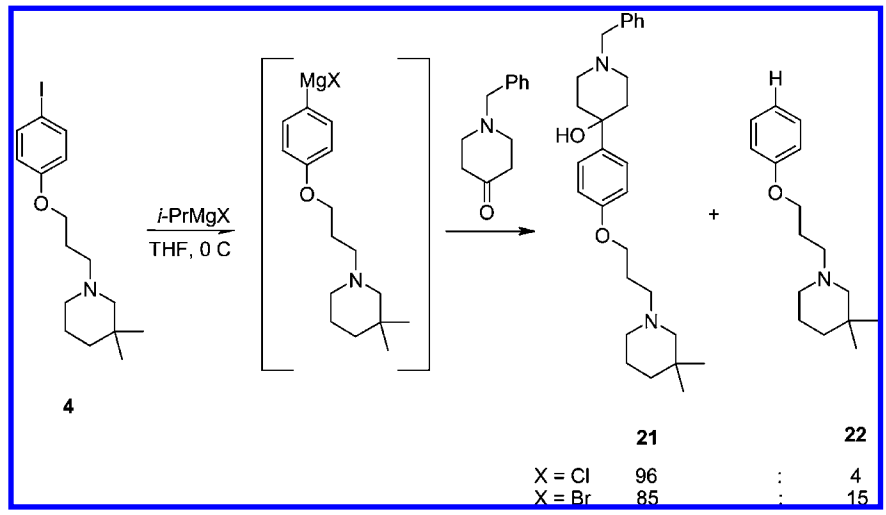
The ArMgCl reagent derived from aryl iodide **4** by iodine magnesium exchange using *i*PrMgCl had previously been shown to give highly selective addition, with only a trace of the deprotonation product **22** being observed. This implied that the halide ion has an effect on the reactivity of these Grignard reagents. Formation of the ArMgCl and ArMgBr species under otherwise identical reaction conditions showed that this was the case, with the ArMgBr reagent being significantly less selective (Scheme 6). It is in fact known that the rate of aryl Grignard addition to ketones can be highly dependent on the halide ion.[6]

Formation of the ArMgX reagent from the aryl iodide had been previously ruled out by cost and waste issues, and direct formation from the aryl chloride was not practical due to very slow Mg insertion. We therefore looked to optimise the ArMgBr reaction. It is well-known that solvent and concentration can play a large role in the reactivity of Grignard reagents thought to be due, in large part, to alteration of their aggregation states.[7] In order to carry out Mg insertion efficiently, THF was required as solvent. The effect of alternative solvents on the selectivity was therefore investigated by dilution of a concentrated THF solution of the Grignard reagent with a range of solvents prior to quenching with the piperidone. Of those used, only toluene gave a beneficial effect. Further experiments showed that increasing both the toluene/THF ratio and the reaction concentration further improved the selectivity for addition. An additional increase was gained by initiating the Mg insertion using *i*PrMgCl, instead of TMSCl,[8] which served to remove any residual water from the solvent and Mg surface prior to Grignard formation. Using the information gained, the selectivity for addition vs deprotonation could be increased from ∼3:1 to >10:1.

We reinvestigated the use of alternative solvents for the lithiation reaction, with the expectation that the ArLi would be more stable in less polar solvents. The initial

(4) Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed* **2004**, *43*, 3333, and references therein.
(5) Gallou, F.; Haenggi, R.; Hirt, H.; Marterer, W.; Schaefer, F.; Seeger-Weibel, M. *Tetrahedron Lett.* **2008**, *49*, 5024–5027, and references therein.
(6) Holm, T. *Acta Chem. Scand. B* **1983**, *37*, 567–584.
(7) Silverman, G. S.; Rakita, P. E., Eds. *Handbook of Grignard Reagents*; Marcel Dekker: New York, 1996.
(8) Ace, K. W.; Armitage, M. A.; Bellingham, R. K.; Blackler, P. D.; Ennis, D. S.; Hussain, N.; Lathbury, D. C.; Morgan, D. O.; O'Connor, N.; Oakes, G. H.; Passey, S. C.; Powling, L. C. *Org. Process Res. Dev.* **2001**, *5*, 479–490.

Scheme 6. **Differing reactivities of ArMgCl and ArMgBr species**



lithiation showed high solvent dependency. Addition of a solution of **20** in 4 volumes of TBME to *n*-BuLi in 8 volumes of THF gave immediate Br−Li exchange even at −50 °C. In contrast, addition of the bromide to *n*-BuLi in TBME or toluene only gave slow lithiation at −20 °C and required ∼1 h at 0 °C for complete reaction (Figure 1). The rate of formation of the butylated impurity (**23**) was also monitored in these reactions. In THF rapid reaction was observed with ∼50% formation of **23** over 1 h. In contrast, the reactions using TBME or toluene gave essentially no butylation at −20 °C with only 0.5% being formed even after 3 h at 0 °C (Figure 1 and Table 2).[9]

This vastly altered reactivity meant we were able to carry out the lithiation in TBME at 0 °C using only a small excess of *n*-BuLi without formation of significant levels of **23**. Disappointingly, upon addition of the piperidone we again observed significant levels of competitive deprotonation to form **22**. The product solution yield was, however, still slightly increased compared to that from the BuLi/THF process, and importantly the reaction appeared much more robust to time and temperature variations. The straightforward and robust nature of the process made this our favored option for further development.

Simplification of the hydrogenolysis/isolation process focused on finding a single acid that would both promote the desired reduction and also enable direct crystallisation of the product. The requirement of the reduction for a strong acid limited our choices but fortunately *p*-toluenesulphonic acid proved suitable. The reduction was slightly slower than using methanesulphonic acid but crucially after filtration to remove the catalyst, then dilution with TBME, the product could be directly crystallised as the ditosylate salt in good purity (Scheme 7).

Table 2. **Optimised alkylation selectivities determined by ^{1}H NMR analysis of the crude reaction products**

entry	ArM	solvent	*T* (°C)	**21** (%)	**22** (%)	**23** (%)	**20** (%)
1	ArLi	THF	−20	84	6	10	0
2	**ArLi**	**TBME**	**0**	**88**	**10**	**0**	**2**
3	ArMgBr	THF/toluene	20	91	9	0	0

The improved procedures could be readily telescoped and were demonstrated on laboratory scale, giving an unoptimised 67% isolated yield, only slightly higher than the initially scaled process. However, it is expected this could be improved with further development of the isolation, and importantly the new process is significantly shorter and expected to be more robust than that used initially.

Synthesis of Naphthalene Fragment. The naphthalene fragment (**7**) was prepared by monocarboxylation of dibromonaphthalene, followed by a Heck reaction with benzyl acrylate (Scheme 8). We decided to continue with the benzyl ester to avoid any problems in removing inorganic byproducts from hydrolysis of simple alkyl esters from the amphoteric drug substance in the downstream chemistry.

Isopropylmagnesium chloride and solid carbon dioxide were used in the original method and this led to the formation of high levels of desbromo **28**, monoacid **29**, and diacid **30** impurities in the product (see below). Using Turbo Grignard[10] (1.5 equiv) gave a quicker reaction time,

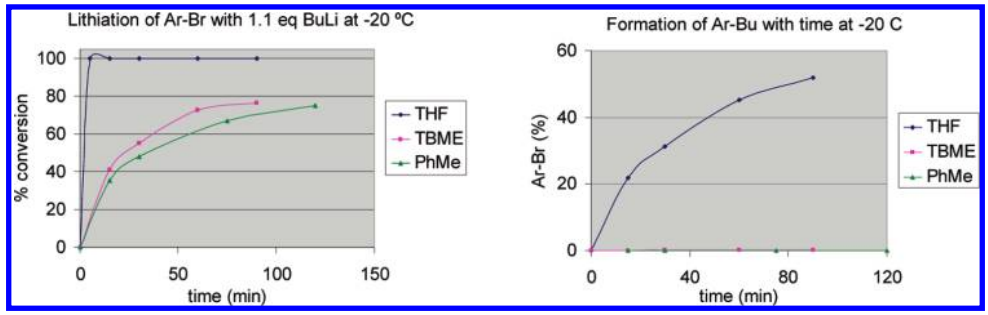
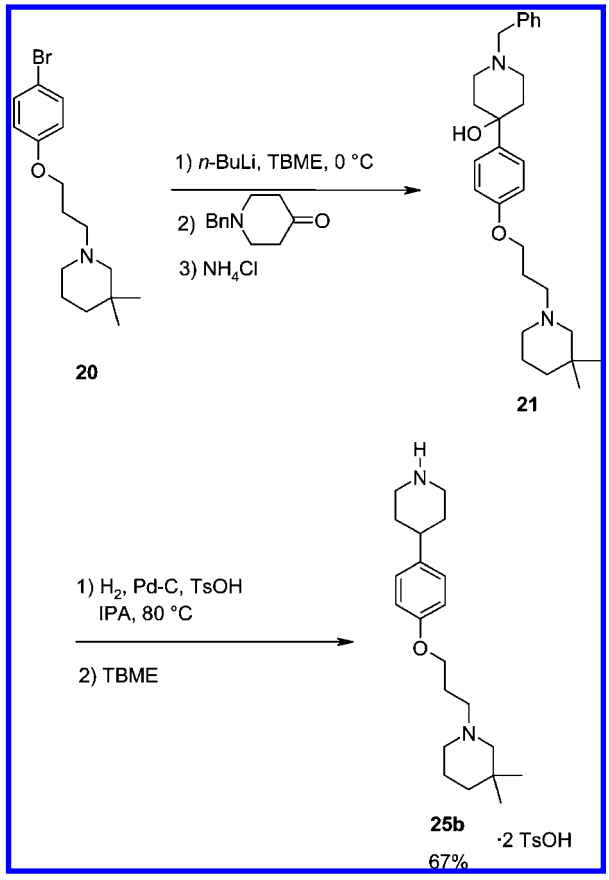
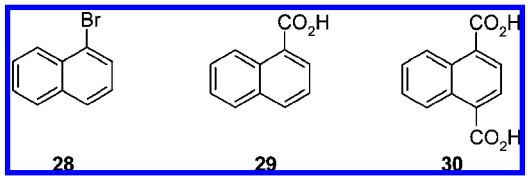


Figure 1. **Rate of lithiation and rate of reaction of ArLi with BuBr.**

Scheme 7. **Improved alkylation/hydrogenolysis telescope**



and use of dry carbon dioxide gas led to low levels of the three described impurities, consequently giving a better impurity profile in the product.



Previously the CO_2 sparging was carried out at 0 °C and took up to 12 h on scale. Looking at the solubility of CO_2 in THF (Figure 2) suggested working at a lower temperature, and the reaction was successfully repeated at −10 °C. At that temperature the rate of formation of the desbromo impurity is slower, allowing further control of its levels in solution and consequently in the product.

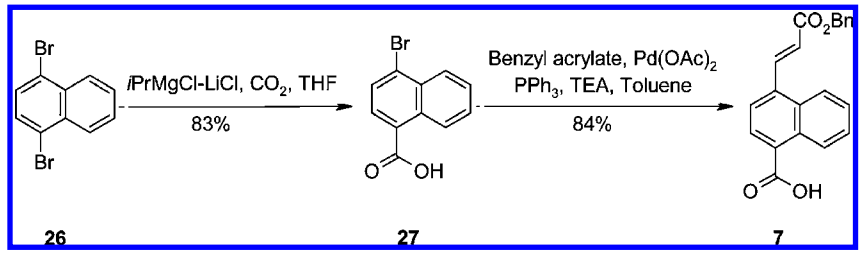
Initially the product was crystallised from water by acidification. However, in large-scale laboratory experiments the solid showed a tendency to form a gum. A solubility study was carried out to identify a potential organic solvent for crystallisation. Ethyl acetate gave the most promising results, and further investigations showed that a 1.7:1 mixture of ethyl acetate/heptane gave yield 74% on a 350-g scale.

For the Heck reaction, four solvents were screened (DMF, NMP, toluene and Me-THF). Toluene gave the cleanest purity profile and a complete reaction. Several catalysts ($Pd(OAc)_2$, $PdCl_2$, $Pd(PPh_3)_4$ and Pd−C) and ligands ($P(o\text{-tolyl})_3$, PPh_3 and beta-alanine) were screened but only the combination of $Pd(OAc)_2$ and PPh_3 gave complete reaction. It was demonstrated that only 3 mol % of palladium acetate and 5 mol % of triphenylphosphine were required to get complete reaction within 6 h.

The original workup process involved several solid isolations, loose charcoal treatments, and two crystallisations to remove palladium residues. Hence, we sought to simplify the workup and isolation. Once the reaction was complete, triethylamine hydrobromide precipitates upon cooling to room temperature. The reaction mixture was then filtered the cake washed with toluene, and the liquors were extracted with water. Hydrolysis of the product to the diacid was observed when leaving it in contact with basic aqueous solutions for too long. Other extractions were studied using an acidic aqueous solution which led to the precipitation of triethylamine hydrochloride as well as the product; basic extraction led to high levels of debenzylation. Once the product was extracted into the aqueous phase, an organic solvent was added to the solution and the aqueous phase acidified to pH < 3 to extract the product into the organic phase. Me-THF was chosen as the extractive solvent as it could also be used for the crystallisation when combined with an antisolvent such as heptane.

Final Coupling and Salt Formation. A screen of activating agents was conducted to find a replacement for TBTU, and it was found that thionyl chloride could be used to form the acid chloride of **7** in either toluene or ethyl acetate. Reacting **25** with the solution of the acid chloride, using either Hünig's base or Schotten−Baumann conditions, gave the desired amide. Schotten−Baumann conditions in ethyl acetate were chosen for further development to avoid issues with removing excess Hünig's base. On scale-up ethyl acetate was hydrolysed by the aqueous sodium hydroxide; this issue was resolved by switching the solvent to isopropyl acetate and changing the base to aqueous potassium carbonate. The product was a gum, and a salt screen revealed one isolable solid, the fumaric acid salt. Hence, the fumarate salt **33** was isolated after a solvent swap to isopropanol (Scheme 9). Two batches of this process were run in the pilot plant, delivering 75 kg with an average yield of 83%.

Scheme 8. **Synthesis of the naphthalene fragment**



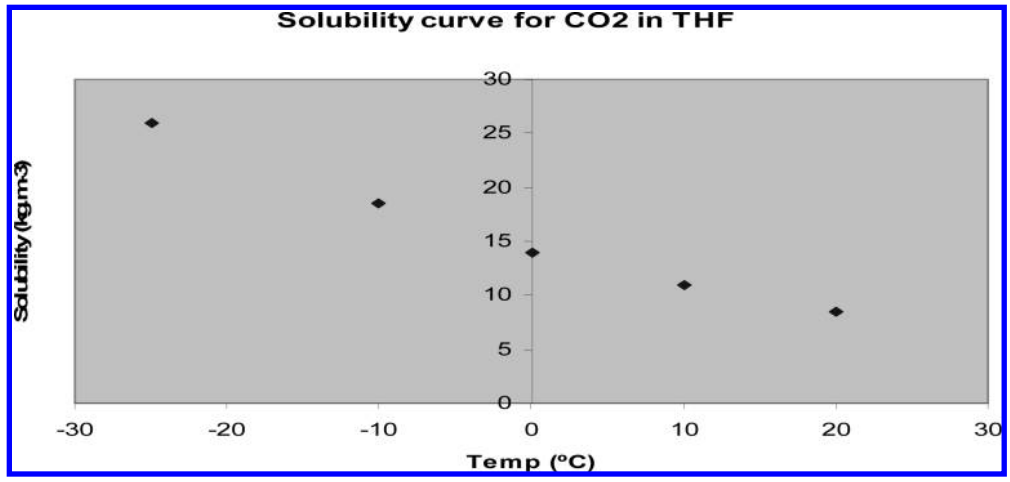
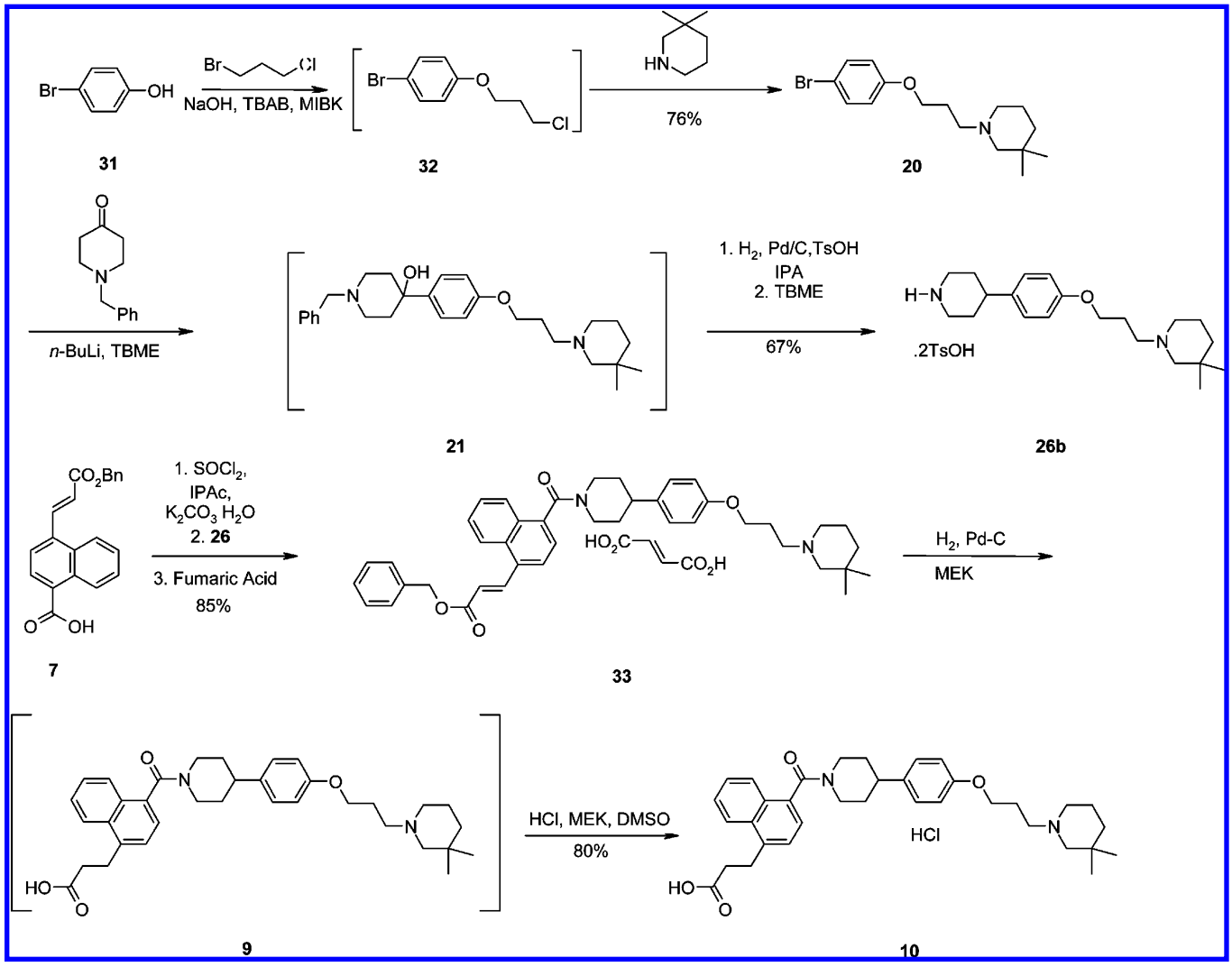


Figure 2. **Solubility of CO_2 in THF.**

Scheme 9. **Proposed manufacturing route for compound 10**



To convert **33** to **10** a reduction of the olefin and benzyl acrylate followed by hydrochloride salt formation was required. The API was poorly crystalline, had a wide metastable zone and a high tendency to gum. The free base was a glassy foam, and thus, the decision was taken to telescope the reduction and salt formation and not include a final recrystallisation stage. The reduction was achieved with 5% palladium on carbon, 3 bar hydrogen pressure at 50 °C in a range of solvents: TBME,

(9) For related observations: Boros, E. E.; Burova, S. A.; Erickson, G. A.; Johns, B. A.; Koble, C. S.; Kurose, N.; Sharp, M. J.; Tabet, E. A.; Thompson, J. B.; Toczko, M. A. *Org. Process Res. Dev.* **2007**, *11*, 899–902.

(10) Krasovskiy, A.; Straub, B.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 159.

IPA, IPAc, EtOAc, or MEK. The conditions were finalised once a suitable salt formation had been developed.

A solvent screen revealed that the final salt formation could only be conducted in acetone, 2-methyl tetrahydrofuran, or MEK. As the hydrogenation and salt formation were to be telescoped, acetone was not considered a viable solvent due to its miscibility with water. 2-Methyl tetrahydrofuran has the potential to generate genotoxic impurities under the acidic reaction conditions; thus, MEK was selected as the solvent. The free base of **33** was formed with aqueous potassium carbonate and the benzyl acrylate reduced with 5% palladium on carbon (50% aqueous paste, 0.1 wt) under 2 bar hydrogen pressure at 50 °C.

The hydrochloride salt formation showed a large degree of initial oiling. To avoid oiling, seeding was performed at lower supersaturation by increasing the acid addition temperature to 70 °C and adding DMSO (0.75 vol) as a cosolvent. To form the API, the solution was seeded followed by an MEK antisolvent addition and cooled to crystallise **10**. Three batches of this process were run on plant to deliver 30 kg of API, with an average yield of 79%.

Conclusions

The new route is shown in Scheme 9. Phase transfer catalysis simplified and accelerated the alkylation chemistry. Bromine−lithium exchange eliminated iodide waste, and use of a benzyl protecting group avoided cryogenic temperatures. Scalable isolations were achieved by careful salt selection of the intermediates, and use of the acid chloride under Schotten−Baumann conditions simplified the downstream chemistry. In addition to addressing all of the key sustainability and operability issues associated with the initial process, the cost of goods was reduced by 80%.

Experimental Section

Reagents and solvents were purchased from commercial suppliers and were used as received. ^{1}H NMR spectra were recorded at 400, 500, or 700 MHz. Chemical shifts are reported in ppm on the δ scale with the residual solvent peaks or tetramethylsilane as internal standard, respectively. Data are presented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant, J (Hz) and integration. HPLC−MS data were acquired either on a Waters ZQ or LCT mass spectrometer, both fitted with an electrospray (ESI) source and coupled to an Agilent 1100 HPLC. Mass spectra were obtained in positive ion mode. Analyses were performed using a capillary voltage of 3.5 kV and a cone voltage of 30 V.

Preparation of 3,3-Dimethyl-1-(phenylmethyl)-2,6-piperidinedione (12). 2,2-Dimethylglutaric acid (100 kg, 1 equiv) and *p*-toluenesulphonic acid monohydrate (2.3 kg, 0.02 equiv) were placed in a reactor under an inert atmosphere. *o*-Xylene (600 L) was charged and the resulting suspension heated to reflux under Dean−Stark conditions. A solution of benzylamine (67 kg, 1 equiv) in *o*-xylene (150 L) was added over 2−3 h, maintaining reflux and azeotropic removal of water. Following the addition, the reaction was maintained at reflux and water continuously removed for 18 h. The batch was cooled to 80−85 °C and *p*-toluenesulphonic acid monohydrate (2.3 kg, 0.02 equiv) added. The reaction mixture was heated to reflux for 10−12 h. The batch was cooled to 80−85 °C and the last portion of *p*-toluenesulphonic acid monohydrate (2.3 kg, 0.02 equiv) added. The batch was then refluxed for 5−10 h. The reaction was monitored by LC and mass of water evolved. The reaction was judged complete by GC and then cooled to 15−25 °C. The mixture was transferred to a second workup reactor and partitioned with 11%w/w aqueous potassium carbonate (300 L). After stirring for around 1 h at 15−25 °C, the layers were allowed to separate, and the lower aqueous layer was discarded. The remaining yellow *o*-xylene solution is repartitioned with 1 M HCl and stirred for 1 h at 15−25 °C before being allowed to separate. The lower aqueous layer was again run out to waste. The remaining *o*-xylene solution was then reduced in volume and dried by distilling off *o*-xylene (approximately 100 L) under reduced pressure to afford a yellow oil (140.9 kg total, 133.6 kg **12**, 93% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (s, 6 H), 1.78 (t, J = 7 Hz, 2 H), 2.71 (t, J = 7 Hz, 2 H), 4.93 (s, 2 H), 7.06−7.14 (m, 2 H), 7.20−7.32 (m, 3 H).

Preparation of 3,3-Dimethyl-1-(phenylmethyl)piperidine (13). The diketopiperidine **12** solution in *o*-xylene (37.7 kg pure **12**) was diluted with THF (360 L, 14 vol based on pure **12**) at 20−25 °C under a nitrogen atmosphere. The yellow solution obtained was heated to 60 °C ± 3 °C and a 1 M solution of $LiAlH_4$ in THF (295.2 kg, 2 equiv) added dropwise maintaining the temperature below 65 °C. The resulting white slurry was stirred for at least 2 h and analysed for completion of reaction using HPLC. Once complete, 32% w/w aqueous NaOH (0.95 vol, 35.8 L, 47.5 kg, 1.26 equiv) was added very slowly (hydrogen gas formation) followed by 40% w/w aqueous NaOH (530 L, 14 vol). The biphasic mixture was then stirred for 1 h at 60 °C ± 3 °C, and the layers separated leaving any emulsion with the organic layer. 32% w/w aq NaOH (200 L, 5.3 vol) was added and the biphasic mixture stirred at 60 °C ± 3 °C for 30 min. Layers were allowed to separate, and the aqueous layer was discarded. The THF layer was then concentrated to 4 vol at atmospheric pressure (155.5 kg total, 24.8 kg of **13**, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (s, 6 H), 1.15−1.25 (m, 2 H), 1.54−1.61 (m, 2 H), 1.99 (s, 2 H), 2.26−2.35 (m, 2 H), 3.41 (s, 2 H), 7.00−7.35 (m, 5 H).

Preparation of 3,3-Dimethylpiperidine (3) Plant Process. A solution of **13** in THF was filtered to remove NaOH particulates prior to distillation under reduced pressure. Solvent was removed to minimum stir volume. To the resulting oil was added IPA (180 L) and the solvent again removed by distillation under reduced pressure to minimum stir volume. To the resulting oil was added IPA (143 L). THF content was checked by ^{1}H NMR and shown to be <5% w/w. To palladium on carbon catalyst (3.58 kg, 0.1 wt) under an inert atmosphere was added the IPA solution of **12**. The stirred mixture was heated to ∼55 °C and pressurised to 2.5 bar H_2, and hydrogenation continued for ∼3 h to consume the enamine **18**. The vessel was depressurised and purged as required and sample taken (HPLC - to verify consumption of enamine). Acetic acid (∼1.1 mol equiv, 0.33 wt, 11.8 kg) was charged. The reaction mixture was reheated to ∼55 °C and repressurised to 2.5 bar H_2. Hydrogenation was continued for 10 h before depressurising and purging the vessel. A sample was taken (LC or GC to assess

chemical conversion). The reaction mixture was filtered and the catalyst cake washed with IPA (53.7 L, 1.18 wt). The resulting solution of **3** as its acetate salt was then concentrated under reduced pressure at 70 °C and −0.7 bar. Water was added (2 × 15 L), and further distillation removed the remaining isopropanol at 80 °C and −0.7 bar pressure (IPA level <0.5% w/w by ^{1}H NMR). The solution was basified with 16% w/w sodium hydroxide solution (87 L, pH > 12) and extracted into TBME (194 L). The layers were separated, and the TBME layer was washed with 40% sodium hydroxide (25 L) and concentrated at atmospheric pressure. The product **3** was isolated by vacuum distillation (boiling point 70−80 °C at −0.85 to −0.90 bar) to yield a colourless liquid (14.15 kg, 71% yield).^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.91 (s, 6 H), 1.32−1.35 (m, 2 H), 1.39 (br s, 1 H), 1.46−1.52 (m, 2 H), 2.47 (s, 2 H), 2.69−2.77 (m, 2 H).

Preparation of 4,4-Dimethyl-5-oxopentanenitrile (18). To a solution of tetrabutylammonium hydroxide (38.9 g of a 40 wt % solution in methanol, 0.032 equiv, 0.06 mol) in TBME (150 mL) was added a solution of isobutyraldehyde (150 g, 2.08 mol, 1.1equiv) and acrylonitrile (102 g, 1.89 mol, 1 equiv) in TBME (150 mL) over 2 h at 50 °C. After completion of reaction, acetic acid (4.7 mL, 81.7 mmol, 4.7 mol %) was added, and the solvents were removed at 150 mbar/45 °C. The desired product was then isolated and purified by distillation (20−10 mbar, 100−105 °C) to afford 106.85 g (45%) of a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.10 (s, 6 H), 1.84−1.88 (m, 2 H), 2.24−2.33 (m, 2 H), 9.41 (s, 1 H).

Preparation of 3,3-Dimethylpiperidine (3) by Alternative Route. 18. (63.1 g, 0.505 mol) was charged to a 1 L hydrogenator. Sponge Ni (21.45 g, Johnson Matthey type A-5000) and absolute ethanol (630 mL) were added. Finally, acetic acid (21 mL) was charged. The reaction was hydrogenated and stirred for 18 h at 1000 rpm at room temperature. The catalyst was filtered through Celite and the filter bed was washed with ethanol (250 mL). More acetic acid (1 equiv, 0.505 mol, 30.4 g) was added and the solution was concentrated at 70 °C/300 mbar until the distillation ceased. Water (63 mL, 1 vol) was added and the mixture was evaporated at 70 °C/200 mbar. The residue was diluted with TBME (250 mL). Water (125 mL and 32% w/w aqueous NaOH (125 mL) were charged. The layers were separated and the organics were washed with 40% w/w aqueous NaOH (125 mL). TBME was then evaporated at 250 mbar/40 °C and the desired product **3** was purified and isolated by distillation (62 °C/100 mbar) to yield 21.02 g (37%) as a colourless oil.

Preparation of 1-{3-[(4-Bromophenyl)Oxy]Propyl}-3,3-dimethylpiperidine (20). 4-Bromophenol (100 g, 0.58 mol) and tetrabutyl ammonium bromide (18.6 g, 0.058 mol) were charged to a vessel. MIBK (200 mL), water (127 mL), and 10 M NaOH solution (173 mL, 1.73 mol) were added followed by bromochloropropane (60 mL, 0.61 mol). The mixture was heated to 80 °C for 1 h and then cooled to 50 °C; 3,3-dimethylpiperidine (89 mL, 0.58 mol) was then charged to the vessel and the mixture heated at 80 °C for 4 h. The mixture was cooled to about 50 °C, TBME (800 mL) was added, and the aqueous layer was separated. The organic layer was washed with water (200 mL). The organic layer was extracted with 0.5 M HCl (2 × 700 mL and then 1 × 200 mL). TBME (800 mL) was added to the combined acid layers and heated to about 50 °C, and then 10 M NaOH (150 mL) was added. The aqueous layer was separated, and then the TBME layer was heated to reflux and 500 mL of solvent distilled out. IPA (1 L) was added and 1 L of solvent distilled out of the vessel. A second portion of IPA (500 mL) was added, and then the solution was concentrated to about 300 mL by distillation. The solution was then cooled to 0−5 °C and aged for 1 h. The solid was filtered off, washed with cold IPA (200 mL), and dried under vacuum at 40 °C to afford **20** as a white solid (142.5 g, 76% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92 (s, 6 H), 1.20−1.25 (m, 2 H), 1.54−1.61 (m, 2 H), 1.88−1.96 (m, 2 H), 2.01 (br s, 2 H), 2.25−2.33 (br s, 2 H), 2.38 (t, J = 7 Hz, 2 H), 3.99 (t, J = 6 Hz, 2 H), 6.78 (d, J = 9 Hz, 2 H), 7.35 (d, J = 9 Hz, 2 H); MS: MH^+ = 327.

Preparation of 3,3-Dimethyl-1-(3-{[4-(4-piperidinyl)-phenyl]oxy}propyl)piperidine Benzoate (25a). Bromide **20** (34 kg, 104 mol) was dissolved in 0.5 M hydrochloric acid (238 L, 119 mol) and washed with TBME (340 L). The aqueous solution was basified with aqueous sodium hydroxide (10 M, 20 L) and extracted with TBME (306 L). The TBME solution was washed with water (102 L) and then dried by Dean−Stark azeotropic distillation to give a solution of **20** in TBME. THF (272 L) at −20 °C was treated with 2.5 M *n*-butyl lithium (84.6 L, 212 mol); the TBME solution of **20** was then added over 3−6 h followed by *N*-benzylpiperidin-4-one (19.65 kg, 112 mol). The reaction mixture was warmed to 0 °C before being quenched with 18.5% w/w ammonium chloride solution (170 kg). The reaction was warmed to 22 °C, the aqueous phase separated; and the organic phase washed with water (170 L). The organic solution was concentrated by atmospheric distillation to 102 L, diluted with ethanol (306 L), and further concentrated to 187 L. Water (9.5 L), 10% Pd−C/50% wet (6.8 kg), and methanesulphonic acid (20.4 L, 314 mol) were added, and the reaction was hydrogenated under 3 bar H_2 pressure at 65 °C for 8 h. The reaction mixture was filtered to remove the catalyst before being concentrated to 102 L by atmospheric pressure distillation. Water (170 L) and TBME (340 L) followed by 10 M aqueous sodium hydroxide (34 L) were added, and the biphasic solution was filtered before the aqueous layer was separated. The organic layer was further washed with water (170 L) before being dried by Dean−Stark azeotropic distillation to give a 340 L solution in TBME. Benzoic acid (25.5 kg, 209 mol) was added and the mixture seeded and cooled to room temperature. The slurry was aged for 1 h before the product was collected by filtration, washing with TBME (2 × 68 L). Drying under vacuum afforded **25a** as a white solid (35.4 kg, 65%). ^{1}H NMR (MeOD, 400 MHz) δ 0.98 (s, 6 H), 1.28−1.34 (m, 2 H), 1.65−1.75 (m, 2 H), 1.78−1.89 (m, 2 H), 1.97−2.04 (m, 2 H), 2.33 (br s, 2 H), 2.53−2.60 (br s, 2 H), 2.63−2.68 (t, J = 8 Hz, 2 H), 2.76−2.84 (m, 1 H), 3.08 (td, 2 H), 3.45 (d, J = 13 Hz, 2 H), 4.01 (t, J = 6 Hz, 2 H), 6.86 (d, J = 8 Hz, 2 H), 7.15 (d, J = 8 Hz, 2 H), 7.32−7.42 (m, 3 H), 7.94 (d, J = 7 Hz, 2 H); MS: MH^+ = 331.

Preparation of 4-Bromo-1-naphthalenecarboxylic Acid (27). To a solution of 1,4-dibromonaphthalene (25 kg, 87 mol) at 0 °C in THF (175 L) was added a solution of *i*PrMgCl:LiCl (1.35 M in THF, 100 L, 135 mol) under a nitrogen atmosphere. The mixture was stirred at 0 °C for 30 min, warmed to 20 °C, and stirred at that temperature until complete formation of the Grignard intermediate (level of dibromonaphthalene <2% by HPLC). The mixture was cooled to −10 °C and sparged with CO_2 gas for ∼1 h until there was no more consumption of the Grignard intermediate (typical level of Grignard intermediate in solution at the end of the reaction is 7%). The reaction mixture was warmed to 20 °C and added to water (200 L), and then THF was distilled off at atmospheric pressure (65 °C). At the end of the distillation, the mixture was cooled to 45 °C; ethyl acetate (325 L) was added followed by aqueous HCl (5 M, 75 L). The biphasic mixture was stirred at 45 °C for 20 min and allowed to settle. The aqueous phase was removed. Water (175 L) was added, the biphasic mixture was stirred at 45 °C for 10 min, and the aqueous phase was removed. Heptane (175 L) was added and the mixture concentrated down to 175 L at atmospheric pressure. The mixture was then cooled to 55 °C, and heptane (75 L) added. The mixture was then seeded with an authentic sample of **27** (25 g) if required, cooled to 50 °C, and stirred for 1 h. It was then cooled to 20 °C over 2 h and stirred at 20 °C for 1 h. It was finally cooled to 5 °C over 30 min and stirred at that temperature for 1 h, and then the solid was filtered off and the cake washed with heptane (50 L) and dried at 50 °C under vacuum to give a white solid (18.15 kg, 83%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.73−7.80 (m, 2 H), 7.98−8.05 (m, 2 H), 8.25−8.32 (m, 1 H), 8.89−8.97 (m, 1 H), 13.40 (s, 1 H); MS: MH^+ = 251−253.

Preparation of 4-{(1*E*)-3-Oxo-3-[(phenylmethyl)oxy]-1-propen-1-yl}-1-naphthalenecarboxylic Acid (7). To a solution of **27** (29 kg, 116 mol) at 20 °C in toluene (174 L) and triethylamine (80 L, 574 mol) was added palladium acetate (0.78 kg, 3.5 mol), triphenylphosphine (1.5 kg, 5.7 mol), and benzyl acrylate (26 L) under a nitrogen atmosphere. The mixture was heated to 90 ± 3 °C and stirred for at least 11 h. The reaction mixture was cooled to 70 °C and then sampled and analysed by HPLC. The reaction was deemed complete when **25** was <2%. After completion of the reaction the solution was cooled to 20 ± 5 °C. The reaction mixture was filtered through a 5 μm cloth. The precipitate was washed with toluene (58 L), and the washes were combined with the previous filtrate. HCl (1 M, 57 L) was added to the toluene solution, and the mixture was stirred for at least 5 min and then allowed to settle. The organic phase was removed. 2-Methyltetrahydrofuran (435 L) was added to the aqueous phase followed by 1 M HCl (174 L) over at least 5 min. The mixture was stirred for at least 5 min and then allowed to settle. The pH of the aqueous phase was controlled to <3, and the aqueous phase was removed. The contents were concentrated to ∼145 L by atmospheric distillation. The solution was cooled to 20 ± 3 °C over at least 3 h, and *n*-heptane was (145 L) added over at least 2 h, maintaining the contents at 20 ± 3 °C. The slurry was aged at 20 ± 3 °C for at least 5 h before being filtered. The solid was then washed with *n*-heptane (58 L) and dried in a vacuum oven at 40 °C to constant probe temperature to give a white solid (32.1 kg, 84%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.30 (s, 2 H), 6.82 (d, J = 16 Hz, 1 H), 7.36 (t, J = 7 Hz, 1 H), 7.42 (t, J = 7 Hz, 2 H), 7.46−7.50 (m, 2 H), 7.67−7.74 (m, 2 H), 8.02 (d, J = 8 Hz, 1 H), 8.11 (d, J = 8 Hz, 1 H), 8.25−8.33 (m, 1 H), 8.51 (d, J = 16 Hz, 1 H), 8.85−8.92 (m, 1 H), 13.34 (s, 1 H); MS: MH^+ = 333.

Preparation of Phenylmethyl (2*E*)-3-(4-{[4-(4-{[3-(3,3-dimethyl-1-piperidinyl)propyl]oxy}phenyl)-1-piperidinyl]-carbonyl}-1-naphthalenyl)-2-propenoate fumarate (33). 7 (20 kg, 60 mol) was slurried in isopropyl acetate (200 L) and heated to 79 ± 3 °C. Thionyl chloride (5.26 L, 72 mol) was added; once a solution was obtained, the reaction was heated to reflux; heating continued until there was less than 5% a/a **7** by HPLC analysis (typically <1.0 h) and the solution cooled to 55 ± 3 °C. **25a** (32 kg, 51 mol) was slurried in isopropyl acetate (160 L) and aqueous potassium carbonate (20% w/w, 160 L) added. The biphasic solution was heated to 55 ± 3 °C. The biphasic mixture was stirred for 10 min, and the layers were separated, and the aqueous phase was discarded. Aqueous potassium carbonate (20% w/w, 160 L) was added to the isopropyl acetate layer, the biphasic mixture was stirred for 10 min at 55 ± 3 °C, and the layers were separated, the aqueous phase discarded. Aqueous potassium carbonate (20% w/w, 160 L) was added to the solution and the biphasic mixture heated to 55 ± 3 °C. The acid chloride solution was added, maintaining the internal temperature at 55 ± 5 °C; the biphasic mixture was heated until there was less than 0.25% a/a **25** by HPLC analysis (typically <0.25 h). The layers were separated, and the isopropyl acetate layer was washed with water (160 L) at 55 ± 3 °C. The isopropyl acetate layer was distilled to 320 L, isopropyl alcohol (320 L) was added and the solution distilled to 320 L. Further isopropyl alcohol (320 L) was added, and the solution was distilled to 480 L and cooled to 70 ± 3 °C. Fumaric acid (7 kg, 60 mol) was added, and the mixture was stirred at 70 ± 3 °C to obtain a solution and cooled to 50 °C over 1 h. The solution was aged for 4 h to form a slurry; the slurry was cooled to 25 °C over 2 h and aged for 15 min. The slurry was filtered, and the cake was washed with isopropyl acetate/isopropyl alcohol (3× 40 L) and dried in a vacuum oven at 65 °C to yield **33** as a white solid (36.6 kg, 81%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.91 (s, 6 H), 1.17−1.25 (m, 2 H), 1.51−1.60 (m, 2 H), 1.63−1.79 (m, 2 H), 1.84−1.92 (m, 4 H), 2.15 (br s, 2 H), 2.35−2.43 (m, 2 H), 2.70−2.79 (m, 1 H), 2.91−3.17 (m, 3 H), 3.26−3.30 (m, 1 H), 3.95−3.99 (m, 2 H), 4.79−4.85 (m, 2 H), 5.30 (s, 2 H), 6.61 (s, 2 H), 6.79−6.86 (m, 3 H), 7.13−7.20 (dd, J = 21 Hz, 9 Hz, 2 H), 7.35−7.97 (m, 9 H), 8.02−8.04 (m, 1 H), 8.29 (d, J = 5 Hz, 1 H), 8.51 (d, J = 15 Hz, 1 H); MS: MH^+ = 645.

Preparation of 3-(4-{[4-(4-{[3-(3,3-Dimethyl-1-piperidinyl)-propyl]oxy}phenyl)-1-piperidinyl]carbonyl}-1-naphthalenyl)-propanoic Acid Hydrochloride (10). 33 (23.5 kg) was slurried in butanone (235 L) and aqueous potassium carbonate (20% w/w, 118 L) added. The biphasic solution was stirred at 25 ± 3 °C for 15 min, the layers were separated, and the aqueous phase was discarded. Aqueous potassium carbonate (20% w/w, 118 L) was added to the butanone layer, the biphasic mixture was stirred for 15 min at 25 ± 3 °C, and the layers were separated, the aqueous phase discarded. The butanone layer was

distilled to 118 L, further butanone (118 L) was added and the solution distilled to 118 L. After cooling to room temperature the solution was filtered before acetone (47 L) and 5% palladium on carbon (50% aqueous paste, type 4530, 2.35 kg) were added to the filtrate. The vessel was purged with nitrogen. An atmosphere of 3 bar hydrogen was placed on the vessel and the mixture stirred vigorously at 40 ± 3 °C until there was less than 0.25% a/a **33** by HPLC analysis (typically 8 h). The mixture was filtered through an R55S carbon CUNO and the cake washed with butanone (70 L). The filtrate was distilled to 118 L, butanone (118 L) was added, and the solution was distilled to 118 L. Further butanone (118 L) was added and the solution distilled to 118 L and cooled to 70 ± 3 °C. Butanone (47 L) and DMSO (17.6 L) were added; the solution was stirred for 5 min, and concentrated hydrochloric acid (0.115 vol, 1.05 equiv) was added, maintaining the temperature at 70 ± 3 °C. The mixture was stirred for 10 min and clarified, the filtrate was heated to 70 ± 3 °C and seeded with **10** (0.12 kg slurried in butanone 0.1 vol) and the slurry aged for 15 min. Butanone (212 L) was added over 2 h, maintaining the temperature at 70 ± 3 °C, cooled to 20 ± 3 °C over 3 h and aged for 4 h. The slurry was filtered and the cake washed with butanone (2 × 94 L) and dried in a vacuum oven at 55 °C to yield **10** as a white solid (14.7 kg, 80%). ^{1}H NMR (700 MHz, DMSO-d_6) δ 0.95 (s, 3 H), 1.14 (s, 3 H), 1.25 (ddd, 0.5 H), 1.32 (t, 1 H), 1.44 (d, 1 H), 1.49−1.61 (m, 1.5 H), 1.64 (ddd, 0.5 H), 1.68−1.77 (m, 1.5 H), 1.81−1.95 (m, 2 H), 2.13−2.18 (m, 2 H), 2.63−2.79 (m, 5 H), 2.91 (t, 0.5 H), 2.96 (t, 0.5 H), 3.02 (t, 0.5 H), 3.08−3.17 (m, 2.5 H), 3.19 (d, 1 H), 3.26 −3.41 (m), 3.97−4.04 (m, 2 H), 4.80 (d, 0.5 H), 4.84 (d, 0.5 H), 6.85−6.90 (m, 2 H), 7.17 (d, 1H), 7.21 (d, 1H), 7.33 (d, 0.5 H), 7.43 (m, 1 H), 7.48 (d, 0.5 H), 7.57−7.66 (m, 2 H), 7.74 (d, 0.5 H), 7.90−7.94 (m, 0.5 H), 8.12−8.17 (m, 1 H), 9.76 (br s, 1 H), 12.25 (br s, 1 H); MS: $MH^+ = 557$.

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