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Technical Note

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Sequential Acetic Acid–Sodium Chloride Treatment to Control Salt Stoichiometry of a Hydrochloride Salt

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Supporting Information

ABSTRACT: The sequential treatment of an intermediate in the synthesis of GSK159797 with a protic acid and sodium chloride was developed to control the stoichiometry of the hydrochloric acid salt of the API. This offered significant advantages over addition of hydrochloric acid, thus avoiding decomposition of an acid-sensitive formamide group. A range of acids were investigated to determine the optimum pK_a range in which to use the acid. The optimum process, using acetic acid, was performed on >100 kg input scale.

INTRODUCTION

The choice of the salt for an active pharmaceutical ingredient (API) can be a critical decision for a medicine.[1] The salt plays a critical role in the biological effect of the medicine since it determines the solubility in biologically relevant fluids. It also contributes to the ability to isolate and purify the API and lends to the stability profile of the parent molecule. Depending upon the salt, the API may exhibit multiple polymorphic forms,[2] and the choice of salt can lead to a simplification of the development process through minimization of polymorphic forms.

Hydrochloric acid salts are the most common for basic pharmaceutical molecules.[3] Hydrochloride salts are most typically formed through the addition of the requisite amount of hydrochloric acid to the free base of the API molecule. This can be carried out under a range of conditions to suit the maximization of yield, purity, and operational simplicity. On a few occasions, hydrochloric acid salts have been generated by the treatment of bases with buffered sources of hydrochloric acid. This is most typically ammonium chloride,[4] but any protonated ammonium chloride may be capable of transfer of the hydrochloric acid to the API, where good correlation of basicities occurs.

Where the stoichiometry of a salt can be variable due to multiple acidic or basic sites in the API molecule, it is necessary to control the ratio closely such that a mixture of salts is not likely to be produced. Where a molecule displays instability in the presence of extremes of acid or base, great care is required in the salt-forming step, and conditions must be controlled to limit decomposition while maintaining the correct stoichiometry of desired salt.

GSK159797 (Figure 1, **1**) is a long acting β-agonist which was in early development for the treatment of COPD and asthma.[5] After extensive screening, two salt forms were identified which were considered for further development. These were the *mono*-hydrochloride and the *bis*-hydrochloride. The formation of the *bis*-hydrochloride was complicated since (a) the weakly basic aniline site required more than two equivalents of hydrochloric acid to enable robust and consistent stoichiometric control of the salt, and (b) the formamide group

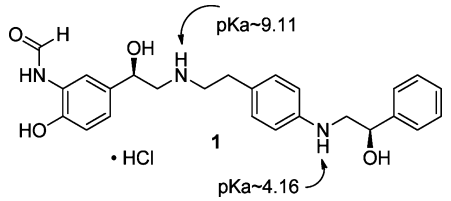

Figure 1. GSK159797 **1**; structure and calculated[6] pK_a of conjugate acids.

was unstable in the presence of more than one equivalent of hydrochloric acid. As a consequence, the process to make the *bis*-hydrochloride was difficult to render under control, and a decision was taken to target the *mono*-hydrochloride. However, the instability of **1** in the presence of more than one equivalent of hydrochloric acid was an unwanted complication.

Herein, we report a conceptually novel approach to the generation of the *mono*-hydrochloride salt of GSK159797 whereby the hydrochloric acid is not added directly or as a buffered source of hydrochloric acid but is generated from a protic acid and sodium chloride washing of an intermediate in the synthetic sequence. The suitable choice of protic acid allows us to generate the *mono*-hydrochloric acid salt without risking generation of the *bis*-hydrochloride and also minimizing decomposition of the formamide group.

RESULTS AND DISCUSSION

The final step of the synthesis of GSK159797 is a hydrogenolytic debenzylation of benzyl ether **2**. Compound **2**, in turn is synthesized by a highly telescoped stage that starts with the coupling of amine **3** and alkyl bromide **4** (Scheme 1). The coupling provides intermediate silyl ether **5** which is desilylated to provide compound **2**. At the start of our development program, the entire process to obtain **1** existed as a single telescoped set of reactions with no isolations of intermediates by crystallization. We decided to target the isolation of compound **2** as the opportunity to develop our novel approach

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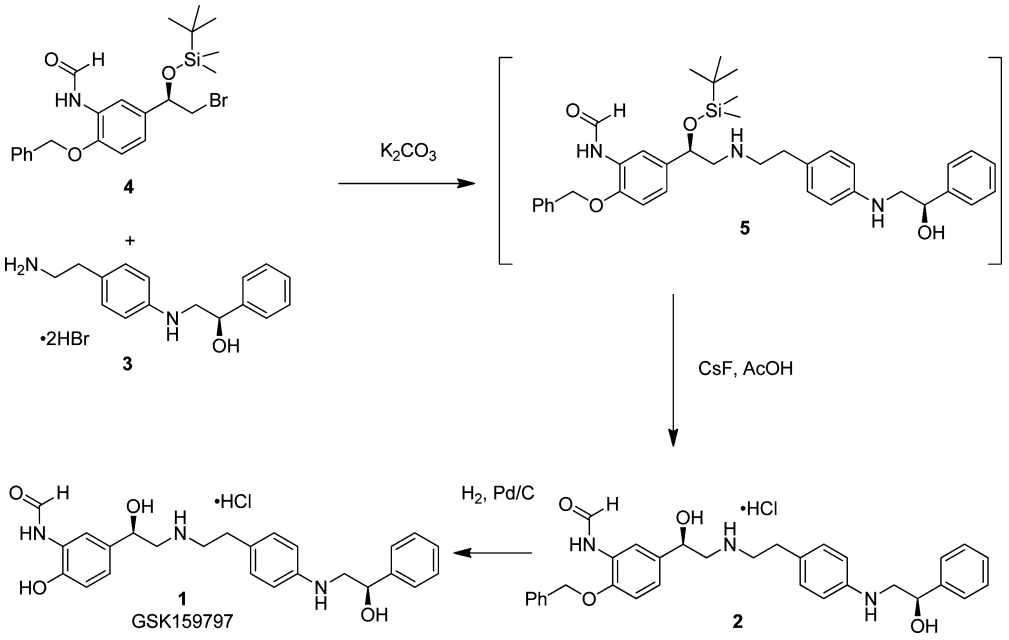
Scheme 1. Synthetic sequence to prepare GSK159797



to the generation of a hydrochloride salt. This was driven by the desire to effect a purification of **2** after a number of steps of chemistry. In particular, a high level of a deformylated compound (typically >5% peak area by HPLC) was present in isolated **2**. It was thought that the hydrochloride salt would be tolerated in the debenzylation conditions to provide **1** without complication. The free base of **2** is not crystalline, and it was felt that the generation of the hydrochloride salt would enable isolation and purification from the numerous impurities that are generated during the complex telescoped chemistry.

Similar to **1**, compound **2** contains an acid-sensitive formamide group; thus, we were well aware of the need to control the exposure to acid during any salt-forming step at the end of the telescoped sequence to **2**.

During early simplification of the chemistry to **2** it was found that very small amounts of crystalline material precipitated from dichloromethane solutions upon transfer between vessels, but only under certain processing conditions. The key condition which led to this precipitation was the omission of a basic wash to remove any acetic acid at the end of the desilylation step prior to washing with aqueous sodium chloride. Further analysis of the crystalline material indicated that it was the *mono*-hydrochloride[7] **2** of high purity, despite the fact that no hydrochloric acid had been used in the processing. It was postulated that the hydrochloride salt was formed by a combination of the acetic acid providing the proton and the sodium chloride providing the chloride anion. Clearly, on the basis of the acidities of the respective acids (hydrochloric acid and acetic acid)[8] this result is counterintuitive, but we felt that it was deserving of further investigation.

In order to ensure that the process was starting from a point of control at the end of the desilylation step, we reintroduced the potassium carbonate wash to ensure that no trace of acetic acid, from the desilylation step, was present. To this 2-butanone solution of the free base of crude **2** was added a small excess of acetic acid. This solution of (presumed) acetate salt was washed with an aqueous solution of sodium chloride. Analysis of the aqueous layer indicated minimal losses of **2** from the organic (2-butanone) layer to the aqueous wash. The resultant wet 2-butanone solution was distilled to remove any dissolved water, and the dried solution was seeded with the material obtained from the small-scale precipitations. Pleasingly, this resulted in a moderate, 71% yield of the *mono*-hydrochloride of **2** over the two stages of chemistry and salt formation. The isolated material was obtained with good purity (typically >98% peak area by HPLC), and the majority of the more than 40 impurities generated during the telescoped chemistry had been removed to the liquors.[9] ^{1}H NMR analysis of **2** indicated that no 2-butanone remained.

The recovery of the hydrochloride salt was maximized by ensuring that the 2-butanone slurry was completely dry, as determined by Karl Fisher analysis, prior to isolation of the solids. However, this was found to give considerable levels of inorganic contamination, determined by residue on ignition testing, when saturated solutions of sodium chloride were used.

It was found that the level of acetic acid was unimportant and could be charged between 1.5 and 10 mol equiv. From a cost perspective, the level of 1.5 equiv was chosen for further work. The number of washes of saturated sodium chloride solution also had no impact upon the isolated yield and purity of the hydrochloride salt. There was also no advantage in yield to be gained upon performing further iterations of the sequence of acetic acid treatment and sodium chloride washing.

In order to minimize the inorganic burden, sodium chloride solutions of varying strength were prepared and examined in the salt formation, using a stock solution of crude material to minimize the impact of variation in composition upon the crystallization (Table 1). All of the reactions gave satisfactory recovery of product, indicating that a lower concentration of sodium chloride was well tolerated and minimized the inorganic content of the solids.

It should be noted that treatment with acetic acid alone or washing with sodium chloride solution alone resulted in failure to isolate any product.

The difference in the calculated pK_a for the conjugate acids of the amine centres (9.11 and 4.16) in **2** indicated a considerable window for choice of acid to provide the proton in this approach to formation of the hydrochloride salt without

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Table 1. Impact of volume and composition of NaCl wash upon yield and inorganic content

entry[a]	NaCl (wt %); volume	isolated yield (%)	yield in liquors (%)[b]	total yield (%)	inorganic content (%w/w)[c]
1	6%; 5 vols	63.8	16.8	80.6	0.99
2	6%; 10 vols	59.8	13.8	73.6	1.76
3	10%; 5 vols	66.9	14.4	81.3	0.87
4	10%; 10 vols	71.6	9.1	80.7	1.41
5	29%; 5 vols	68.5	5.4	73.9	2.47
6	29%; 10 vols	57.0	22.5	79.5	15.89

[a]Reactions were run in Radley's carousel tubes, splitting one 2-butanone reaction such that each salt formation was based on an input of 5 g. Solutions of the free base of **2** were treated with acid for 30 min, washed with 29% w/v NaCl (5 vols) and then three times with 6% w/v NaCl (5 vols), diluted with 2-butanone (5 vols) and distilled (to remove 4 vols), diluted with 2-butanone (4 vols), seeded, and distilled (to remove 4 vols) prior to being isolated by filtration. [b]Determined by HPLC assay. [c]Determined by residue on ignition (ROI) analysis.

risking formation of the *bis*-hydrochloride. We examined a range of acids within this window, and a couple that were more acidic than the aniline nitrogen position, to define the scope of acids and a failure mode of the new salt formation. All of the acids were examined using a single stock batch of material to minimize the impact of different impurity profiles. All of the isolated solids were analyzed by ion chromatography to determine the salt stoichiometry. The results are shown in Table 2 and indicate that strong acids that can protonate the

Table 2. Variation of proton source and impact on yield and stoichiometry of 2

entry[a]	acid	pK_a	yield (%)	mono·/bis·HCl
1	acetic acid	4.75	76	mono
2	ammonium chloride[b]	9.24	55.5	mono
3	dichloroacetic acid	1.29	25.3	mixture
4	chloroacetic acid	2.86	63.3	mixture
5	*p*-methoxybenzoic acid	4.47	67.3	mono
6	*o*-methoxybenzoic acid	4.08	48.6	mono
7	pentafluorophenol[c]	~7	9.1	mono

[a]Reactions were run in Radley's carousel tubes, splitting one 2-butanone reaction such that each salt formation was based on an input of 5 g. Solutions of the free base of **2** were treated with acid for 30 min, washed with 29% w/v NaCl (5 vols) and then three times with 6% w/v NaCl (5 vols), diluted with 2-butanone (5 vols) and distilled (to remove 4 vols), diluted with 2-butanone (4 vols), seeded, and distilled (to remove 4 vols) prior to being isolated by filtration. [b]2-Butanone solution washed with 29% w/v NH_4Cl (5 vols) and then three times with 6% w/v NH_4Cl (5 vols), diluted with 2-butanone (5 vols) and distilled (to remove 4 vols), diluted with 2-butanone (4 vols), seeded, and distilled (to remove 4 vols) prior to being isolated by filtration. [c]Low yield potentially caused by omission of the final distillation.

aniline nitrogen lead to mixtures of *mono*- and *bis*-hydrochlorides and poor control of salt stoichiometry. All of the acids which fell within the range bordered by the acidities of the two nitrogens led to good stoichiometric control generating the monohydrochloride, although the yields were somewhat variable. The optimum acid was acetic acid in terms of yield, availability, and cost. In addition ammonium chloride also fared well as a source of hydrochloric acid for the salt formation. In this instance, no acetic acid was used, but the sodium chloride washes were retained to ensure similar control of water levels in the 2-butanone during the washing sequence.

The requirement for complete water removal from the 2-butanone solution of **2** was troublesome. 2-Butanone partitions with aqueous solutions, but considerable mixing of the organic and aqueous contents for each layer is observed. This meant that a significant volume of solvent was required to be removed by distillation and replaced with fresh solvent to ensure that the Karl Fisher analysis indicated that an acceptable yield would be achieved. Any alternative solvent would have to meet a number of criteria: it would need to enable an aqueous work up after the alkylation step, be a competent cosolvent in the cesium fluoride mediated desilylation, enable efficient salt formation through sequential treatment with acetic acid and aqueous sodium chloride washing, and enable clean phase separations in the washing regime.

Eight potential solvents were examined on the basis of their lower solubility in water (Table 3).[10] Of these, the pentanols

Table 3. Solubility of potential alternative solvents in water.[10]

entry	solvent	solubility in water (mass %)[a]
1	2-butanone	25.6
2	2-pentanone	5.5
3	3-pentanone	4.9
4	2-hexanone	1.49
5	2-heptanone	0.435
6	methyl isobutyl ketone	1.85
7	1-pentanol	2.14
8	2-pentanol	4.3
9	3-pentanol	5.6

[a]All figures for 25 °C.

and 2-pentanone were found to give the desired hydrochloride **2**. Some of the longer-chain and bulkier ketones resulted in deposition of the intermediate acetate salt or desired hydrochloride salt as gums during the washing regime. Further scale-up and comparison of isolated yields and purity indicated that 1-pentanol was the optimal solvent to replace 2-butanone and resulted in much reduced solvent use. Indeed, the water content of the 1-pentanol layer was sufficiently low immediately after the sodium chloride wash that seeding of product was possible without distillation. A single, small distillation was subsequently performed to increase the isolated yield. ^{1}H NMR analysis of **2** indicated that no 1-pentanol was retained.

With an optimized protocol in hand we ran a comparison between our new process, using acetic acid and sodium chloride washes and the traditional use of aqueous hydrochloric acid. A telescoped alkylation and desilylation was split into two portions. One half was submitted to our new protocol, and the other was treated with 1.2 equiv of concentrated aqueous hydrochloric acid and distilled as the new protocol. The lower molar equivalent of concentrated aqueous hydrochloric acid (relative to acetic acid in the new process) was deliberately targeted to reduce the risk of deformylation. Although the yields were highly consistent between the two, the new protocol produced the product with lower levels (typically <2% peak area by HPLC) of the deformylated compound and less colouration of the isolated material.

With a new process to **2** in hand it was necessary to verify that material could be processed to provide the API (GSK159797, **1**) in an appropriate yield and purity. Submission

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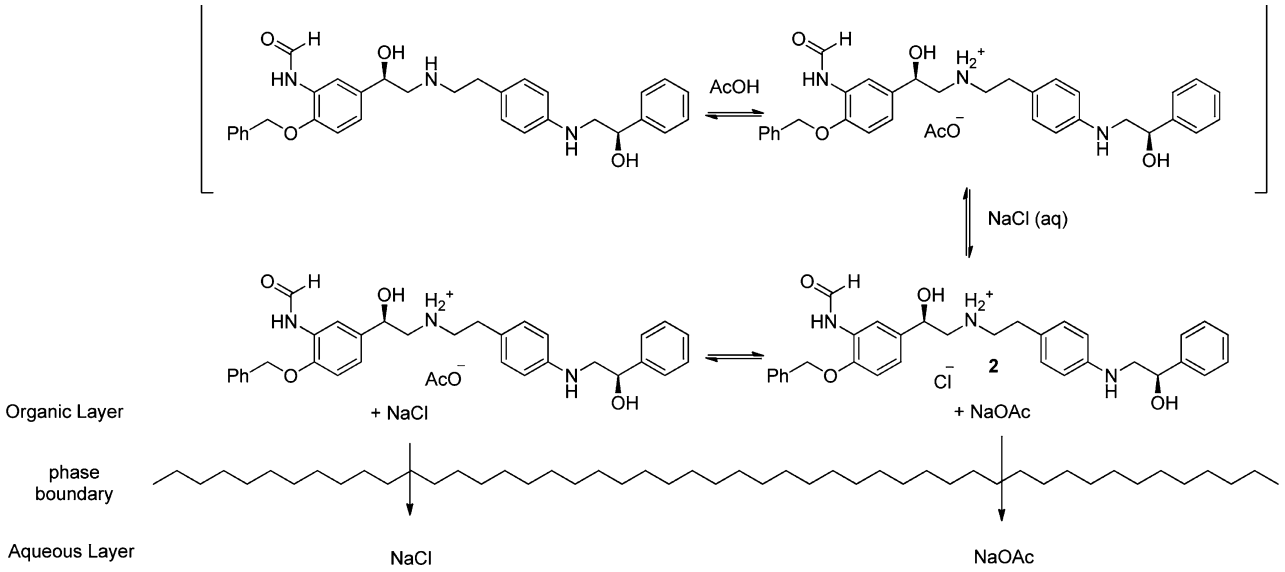

Figure 2. Equilibria and partitions set up during sodium chloride washing of acetic acid treated free base of **2**.

of the hydrochloride salt of **2** to palladium-catalyzed hydrogenolysis conditions using *N*-methylpyrrolidinone and 2-propanol as solvents enabled clean hydrogenolysis of the benzyl protecting group to give **1** in good yield and purity. Ion chromatography analysis of the output **1** showed that retention of the hydrochloride salt stoichiometry had been achieved. No additional hydrochloric acid was required to provide stoichiometric control of the *mono*-hydrochloride salt **1**. Application of the new protocol for formation of the hydrochloride of **2** enabled clean production of the API with stoichiometric control of the salt and also purification at an intermediate stage allowing control of the overall purity of the API.

Acetic acid ($pK_a \approx 4.75$ in water; 12.3 in DMSO)[8] is not acidic enough to protonate a chloride ion as it is far less acidic than hydrochloric acid ($pK_a \approx -8$ in water; 1.8 in DMSO).[8] When the free base of **2** is treated with excess acetic acid, a *mono*-acetate salt will be the major species formed (Figure 2). Acetic acid is not anticipated to be acidic enough to generate any appreciable levels of the *bis*-acetate salt. The free base of **2** and all of these salt forms are evidently soluble in wet organic solvents which possess a solubility of >2 mass % in water. When the solutions of acetate salt are washed with aqueous sodium chloride, a complex series of equilibria and partition events are set up. In the organic phase, the free base of **2** enters into equilibrium between the formed acetate salt and the hydrochloride salt. Partitioning of the various species present between the aqueous and organic phases upon phase separation is also an important factor in determining the outcome.

In order to gain clarity on the specifics of the salt formation, we examined a hydrochloride salt formation from purified free base of **2** in 1-pentanol. The free base was formed by base washing a typical product derived from this process. By using purer material we were able to trace the loss of acetate ions to the aqueous layers during the phase separations. The first wash contained 70% and the second contained 15% of the available acetate, which correlated well with the isolated yield of 86% for this reaction. The salt metathesis apparently occurs during the phase separations to leave hydrochloride salt **2** in the wet organic layer prior to distillations. At the point of phase separation, the organic soluble ammonium salt requires a counterion, and the most prevalent species, chloride, is preferentially incorporated into the salt. The acetate counterion, not utilized, is rejected into the aqueous layer. Subsequent washing enhances the chloride content of the organic layer. In the limiting extreme investigated, the acetate salt was subjected to only 2.4 mol equiv of chloride which represents an impressive incorporation of available chloride. It is important to note that an alternative mechanistic scenario can be discounted. The level of acetate removed to the aqueous washes is inconsistent with a scenario in which the freebase of **2** forms an acetate salt, which is retained in the organic layer along with sodium chloride, after the aqueous washes. Crystallization would then induce a shift of the equilibrium through phase separation, leading to isolation of hydrochloride salt **2**.

■ SUMMARY

A new protocol for the isolation of **2** was developed through the sequential treatment of the free base with acetic acid and aqueous sodium chloride washes. This protocol enabled isolation of the hydrochloride salt in good yield and purity after a lengthy telescoped process while avoiding complications of *bis*-hydrochloride formation and additional undesired deformylation. Yields of the telescoped process depended slightly upon the events of the earlier chemistry steps and impurity profile, yet the successful isolation of purified **2** proved to be highly robust and independent of the impurity profile of crude mixture. The telescoped process was scaled up to 109 kg input (of **4**) and generated **2** in 70−75% yield. Subsequent processing through the debenzylation to form **1** proceeded without incident on 60 kg input scale. The application of this approach rendered complete control of stoichiometry of the *mono*-hydrochloride salt **1** to fund toxicological and early clinical studies.

While the full kinetic and mechanistic details of the salt formation have not been elucidated, there is sufficient flexibility demonstrated through the range of acids and range of solvents to make this approach worth considering for similar lipophilic amine free bases.

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EXPERIMENTAL SECTION

Preparation of 2 Using 2-Butanone..[11] 2-[4-((*R*)-2-Hydroxy-2-phenylethylamino)phenyl]ethylamine *bis*-hydrochloride (107.9 kg) was dissolved in water (440 L). Isopropyl acetate (550 L) was added. A 32% w/v aqueous sodium hydroxide solution (95 L) was added over at least 30 min. The organic layer was washed with water (550 L) and then was distilled at atmospheric pressure to a volume of ~380 L.

To this solution was added *N*,*N*-dimethyl acetamide (DMAc, 275 L) followed by 2-bromo-(*R*)-1-*tert*-butyldimethylsiloxy-1-(3-formamido-4-benzyloxyphenyl)ethane (109 kg) and potassium carbonate[12] (40.5 kg). The mixture was heated at 90 °C for 17 h and then cooled to 50 °C. Water (820 L) was added, and the mixture was cooled further to room temperature. 2-Butanone (820 L) was added, and the layers were separated. The organic layer was washed with 17:40:340 (v/w/v) acetic acid/sodium acetate/water (550 L) followed by 29% w/v aqueous sodium chloride (550 L). The organic layer was diluted with 2-butanone (270 L) and then was distilled at atmospheric pressure to a volume of approximately 820 L, followed by addition of more 2-butanone (270 L). The mixture was heated to 37 °C, and a solution of cesium fluoride (44.1 kg) in methanol (550 L) was added. Heating at 37 °C was continued for 7.5 h, and then the mixture was cooled to 30 °C. The reaction was quenched with 44% w/v aqueous potassium carbonate solution (550 L), and water (110 L) was added. The organic layer was washed with 29% w/v aqueous sodium chloride solution (550 L) and then treated with acetic acid (20.2 L). The mixture was washed with 29% w/v aqueous sodium chloride solution (550 L) and then 6% w/v aqueous sodium chloride solution (3 × 550 L).

The solution was diluted with 2-butanone (550 L) and then distilled at atmospheric pressure to a volume of about 660 L. 2-Butanone (440 L) was added, and the mixture was seeded with **2**. The mixture was further distilled to a volume of about 770 L. More 2-butanone (330 L) was added, and the mixture was cooled to room temperature. The solids were collected by filtration, washed with 2-butanone (3 × 110 L), and dried in vacuo to give **2** as a colourless solid (99 kg, 75% yield). ^{1}H NMR in accord of structure (400 MHz, DMSO-d_6) δ (ppm): 2.70−2.89 (m, 2H); 2.95 (m, 1H); 3.01−3.14 (m, 4H); 3.14−3.23 (m, 1H); 4.71 (m, 1H); 4.81 (m, 1H); 5.17* (s, 1H); 5.23 (s, 1H); 5.46 (d, J = 4.4 Hz, 1H); 5.50 (m, 1H); 6.10 (d, J = 3.2 Hz, 1H); 6.59 (d, J = 8.3 Hz, 2H); 6.94 (d, J = 8.3 Hz, 2H); 7.03 (d of d, J = 8.6, 2.0 Hz, 1H); 7.12 (d, J = 8.6 Hz, 1H); 7.25 (m, 1H); 7.30−7.36 (m, 3H); 7.36−7.42 (m, 4H); 7.50 (d, J = 7.3 Hz, 2H); 8.26 (d, J = 2.0 Hz, 1H); 8.35 (d, J = 1.7 Hz, 1H); 8.45* (d, J = 11.0 Hz, 1H); 8.63 (br, 2H); 9.64* (m, 1H); 9.67 (s, 1H). HRMS (ES +ve) calcd for $C_{32}H_{35}N_3O_4$ 526.2700, found 526.2694.

*Peaks are due to ~11.5 mol % of the minor rotamer due to the presence of the formamide group.

Preparation of 2 in 1-Pentanol..[11] 2-Bromo-(*R*)-1-*tert*-butyldimethylsiloxy-1-(3-formamido-4-benzyloxyphenyl)ethane (**4**, 100 g, 215 mmol), 2-[4-((*R*)-2-Hydroxy-2-phenylethylamino)phenyl]ethylamine *bis*-hydrobromide salt[13] (**3**, 99 g, 237 mmol), and potassium carbonate[12] (119 g, 861 mmol) were charged to a reactor. *N*-Methylpyrrolidinone (NMP, 500 mL) was added, and the mixture was heated at 110−115 °C for 5 h and then cooled to 50 °C. Water (900 mL) was added followed by 1-pentanol (500 mL), the mixture was cooled further to room temperature, and the layers were separated. The organic layer was washed with water (500 mL) followed by 2% w/v aqueous sodium chloride (500 mL).

To the organic layer was added acetic acid (20 mL, 350 mmol) followed by a solution of cesium fluoride (39 g, 257 mmol) in methanol (500 mL). The mixture was heated at 55 °C for 4 h. The reaction was quenched with 37% w/v aqueous potassium carbonate solution (500 mL) and cooled to 30 °C. The organic layer was washed with 10% w/v aqueous sodium chloride solution (500 mL) and then treated with acetic acid (18.5 mL, 324 mmol). The mixture was washed with 10% w/v aqueous sodium chloride solution (2 × 500 mL).

The solution was diluted with 1-pentanol (1 L), seeded with **2** (0.2 g), and aged for 30 min. The mixture was distilled under reduced pressure (100 mbar) to a volume of about 1.4 L and then cooled to room temperature. The solids were collected by filtration, washed with 1-pentanol (2 × 300 mL) followed by ethyl acetate (300 mL), and dried in vacuo to give **2** as a colourless solid (86.09 g, 71% yield). ^{1}H NMR in accord of structure (400 MHz, DMSO-d_6) δ (ppm): 2.70−2.89 (m, 2H); 2.95 (m, 1H); 3.01−3.14 (m, 4H); 3.14−3.23 (m,, 1H); 4.71 (m, 1H); 4.81 (m, 1H); 5.17* (s, 1H); 5.23 (s, 1H); 5.46 (d, J = 4.4 Hz, 1H); 5.50 (m, 1H); 6.10 (d, J = 3.2 Hz, 1H); 6.59 (d, J = 8.3 Hz, 2H); 6.94 (d, J = 8.3 Hz, 2H); 7.03 (d of d, J = 8.6, 2.0 Hz, 1H); 7.12 (d, J = 8.6 Hz, 1H); 7.25 (m, 1H); 7.30−7.36 (m, 3H); 7.36−7.42 (m, 4H); 7.50 (d, J = 7.3 Hz, 2H); 8.26 (d, J = 2.0 Hz, 1H); 8.35 (d, J = 1.7 Hz, 1H); 8.45* (d, J = 11.0 Hz, 1H); 8.63 (br, 2H); 9.64* (m, 1H); 9.67 (s, 1H). ^{13}C (100 MHz, DMSO-d_6) δ (ppm):30.6, 48.5, 51.5, 53.5, 68.0, 69.7, 70.7, 112.4, 118.4, 121.5, 124.0, 126.0, 126.9, 127.1, 127.6, 127.8, 128.0, 128.4, 129.1, 134.0, 136.7, 144.2, 146.9, 147.5, 160.3. HRMS (ES +ve) calcd for $C_{32}H_{35}N_3O_4$: 526.2700, found: 526.2694.

*Peaks are due to ~11.5 mol % of the minor rotamer due to the presence of the formamide group.

Preparation of 1. A mixture of *N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-benzyloxyphenyl)ethylamine monohydrochloride (**2**, 60 kg), *N*-methylmorpholine (3.6 L), and 5% Pd/C catalyst (Engelhard 167, 50% wet with water; 0.6 kg) in *N*-methylpyrrolidinone (NMP, 150 L) was stirred under 1.5 atm of hydrogen at 22 ± 2 °C until the reaction was judged complete by HPLC analysis. The mixture was filtered through a Eurofiltec filter to remove the catalyst and then through a Cuno Zeta carbon filter to remove dissolved palladium followed by a polishing filter. The filter system was washed successively with NMP (60 L), followed by 2-propanol (90 L).

The combined filtrates were stirred and heated to 69 ± 3 °C. Water (30 L) was added followed by 2-propanol (180 L) added at a rate to ensure the temperature remained at 69 ± 3 °C. Seed crystals of **1** (0.06 kg) were added. The mixture was aged for 60 min before 2-propanol (390 L) was added over 1.5 to 2 h at 69 ± 3 °C. The resulting slurry was stirred at 69 ± 3 °C for 1 h and then cooled to room temperature over 4 h and aged at 20 °C for 4 h.

The solids were collected by filtration and washed successively with 10:1 v/v 2-propanol/water (120 L) and then 2-propanol (180 L). The solids were dried in vacuo at 50 °C to give **1** as colourless crystals (39.9 kg, 79%) yield. ^{1}H NMR in accord of structure (400 MHz, DMSO-d_6) δ (ppm): 2.73−2.89 (m, 2H); 2.95 (m, 1H); 3.01−3.14 (m, 4H); 3.15−3.24 (m, 1H); 4.72 (m, 1H); 4.82 (m, 1H); 5.46 (d, J = 4.7 Hz, 1H); 5.48 (m, 1H); 6.03 (d, J = 3.4 Hz, 1H); 6.59 (d, J = 8.6 Hz, 2H); 6.89 (d, J = 8.1 Hz, 1H); 6.91−6.98 (m, 3H); 7.01*

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(d, J = 8.6 Hz, 1H); 7.14* (s, 1H); 7.25 (t, J = 7.3 Hz, 1H); 7.33 (d of d, J = 7.3, 7.6 Hz, 2H); 7.39 (d, J = 7.6 Hz, 2H); 8.13 (d, J = 1.5 Hz, 1H); 8.29 (d, J = 1.7 Hz, 1H); 8.53* (d, J = 11.0 Hz, 1H); 8.57−9.08 (br, 2H); 9.36* (d, J = 11.0 Hz, 1H); 9.60 (s, 1H); 9.92* (s, 1H); 10.10 (s, 1H). ^{13}C (100 MHz, DMSO-d_6) δ (ppm): 30.6, 48.5, 51.5, 53.3*, 53.5, 67.7*, 68.1, 70.7, 112.4, 114.8, 116.0*, 118.4, 119.4*, 121.5, 123.0, 124.0, 125.9, 126.0, 126.9, 128.0, 129.1, 132.2, 132.7*, 144.2, 146.3, 147.5, 160.0, 163.4*. Anal. Calcd for **1**: C, 63.8; H, 6.2; N, 8.9; Cl, 7.5; found: C, 63.7; H, 6.4; N, 8.9; Cl, 7.4. HRMS (ES +ve) calcd for $C_{25}H_{29}N_3O_4$: 436.2231, found: 436.2241.

*Peaks are due to ∼11 mol % of the minor rotamer due to the presence of the formamide group.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR, LC/MS, accurate mass and HPLC data of **1** and **2**. This information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) Two processes for the preparation of **2** are provided. The first, using 2-butanone, was used on the largest scale. The second, using 1-pentanol, was the preferred process for further scale-up yet was not implemented due to cessation of development activities.

(12) The use of finely divided "325 mesh" potassium carbonate is important for the success of the alkylation. The use of "granular" potassium carbonate resulted in a slower, incomplete reaction with greater levels of impurities.

(13) During development work, **3** was changed from the *bis*-hydrochloride salt to the *bis*-hydrobromide salt. This avoided the formation of the chloro-analogue of **4**, which was substantially less reactive and led to lower conversions in the alkylation step.