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Development of a Multikilogram Synthesis of a Chiral Epoxide Precursor to a CCR1 Antagonist. Use of in Situ Monitoring for Informed Optimisation via Fragile Intermediates

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Abstract:

The optimisation and scale up of a manufacturing route to a key intermediate, acetic acid 4-acetylamino-3-(2-methyl-oxiranylmethoxy)phenyl ester (2), utilising a S_NAr coupling, the hydrogenation of a nitro moiety and the conversion of a chiral acetonide into a chiral epoxide is described along with other routes to access intermediate 2 including the chemoselective reduction of a nitro moiety in the presence of an epoxide.

Introduction

Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as pathologies such as rheumatoid arthritis and atherosclerosis. Studies have demonstrated that the action of chemokines is mediated by subfamilies of G protein-coupled receptors including CCR1 receptors.[1] We have previously disclosed[2] that *N*-{2-[((2*S*)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide (**1**) had shown antagonistic CCR1 activity. Scheme 1 illustrates our retrosynthetic approach to **1** which relies on the alkylation of 1-(4-chlorobenzyl)piperidin-4-ylamine (**3**) by acetic acid 4-acetylamino-3-(2-methyl-oxiranylmethoxy)phenyl ester (**2**).

Compound **3** was available by the selective alkylation of 4-aminopiperidine utilising a method described by Laduron et al.[3] Improvement on this method[4] enabled easy access to **3** at multikilogram scale. This improved procedure was utilised to supply 43 and 120 kg of **3** as its acetic acid salt for two pilot-plant campaigns.

Many approaches were considered to access the challenging epoxide intermediate **2**,[5] but the route described here looked the most attractive for further scale up. A manufacturing route to **2** capable of supplying mutikilogram quantities was therefore required, and our efforts to secure such a route are described herein.

Results and Discussion

Route 1: Modified Medicinal Chemistry Route. Compound **2** had previously been synthesised by Medicinal Chemistry as detailed in Scheme 2 utilising ((2*S*)-2-methyloxiranyl)-methyl 3-nitrobenzenesulfonate (**4**) and 4-(acetylamino)-3-hydroxyphenyl acetate (**7**).[6,7]

The Sharpless asymmetric epoxidation[8] of 2-methyl-2-propen-1-ol (**6**) afforded enantiomerically enriched (*2R*)-methylglycidol (**5**). Treatment of **5** with 3-nitrobenzenesulfonyl chloride in the presence of base afforded, after chromatography, ((2*S*)-methyloxiranyl)methyl 3-nitrobenzene sulfonate (**4**) in 93.2−94.3% enantiomeric purity.[9] Initial investigations carried out by the Process Safety Group demonstrated that **4** was a high energy material[10] that decomposed in an autocatalytic manner at relatively low temperatures. It became apparent that **4** could not be used neat and it was recommended to handle this intermediate as a 50% w/w solution in toluene for safety reasons.

Treatment of 1-(2,4-dihydroxyphenyl)ethanone (**10**) with hydroxylamine hydrochloride in pyridine, followed by reaction of the intermediate oxime with phosphorous oxychloride in acetonitrile and DMA afforded 2-methyl-1,3-benzoxazol-6-ol (**9**). Intermediate **9** was acylated with acetyl chloride in THF in the presence of triethylamine to give 2-methyl-1,3-benzoxazol-6-yl acetate (**8**), which upon treatment with TFA in THF afforded 4-(acetylamino)-3-hydroxyphenyl acetate (**7**).[6,11]

The syntheses of intermediates **4** and **7** were successfully scaled up in collaboration with contract manufacturers and provided a total 9.9 kg of nosylate **4** (as a toluene solution) and 8.7 kg of phenol **7**.

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(10) Neat material: exothermic activity from 125−130 °C, energy 2000−2400 J g^{-1} - toluene solution: exothermic activity from 170 °C, energy 950−1150 J g^{-1}.

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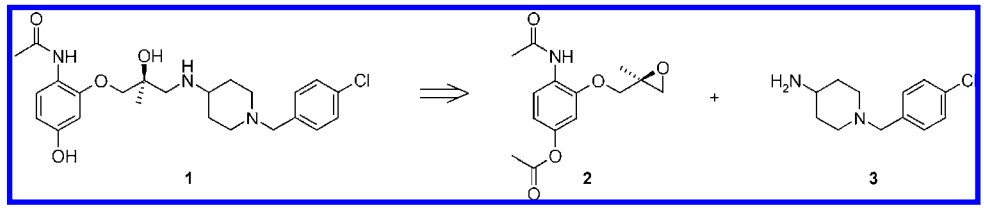
Scheme 1. **Retrosynthetic analysis of 1**



Scheme 2. **Medicinal chemistry route**

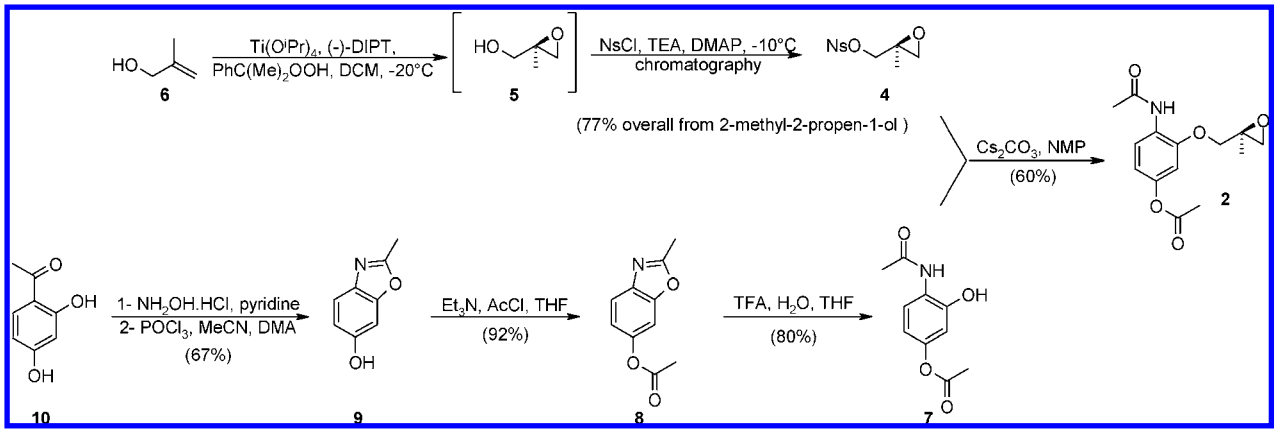


Table 1. **Solvent and base screen for the formation of intermediate 2**[a]

solvent	base	reaction temperature (°C)	reaction time (h)	comments
NMP	Cs_2CO_3	20	24	Reference experiment. Complete conversion after 24 h at 20 °C but difficult workup.
NMP/toluene (10/1 or 1/1 ratio)	Cs_2CO_3	20	24	Similar conversion to that in reference experiment, but isolation is difficult.
NMP/toluene (1/5 or 1/10 ratio)	Cs_2CO_3	20	24	Very slow conversion.
2-MeTHF	Cs_2CO_3	20	24	Slower reaction than reference experiment and poor product partition.
2-MeTHF	^{t}BuOK	20	24	Slower reaction than reference experiment or experiment in butyronitrile.
toluene	Cs_2CO_3 or K_2CO_3 or AcOK or Et_3N or ^{t}BuOK or ^{t}BuONa	20	24	Slow conversion to product and/or decomposition of starting material.
acetonitrile	Cs_2CO_3	20	5	Slower reaction than reference experiment and poor product partition.
^{i}Pr$_2$O or ^{i}PrOAc	Cs_2CO_3	50	5	Slower reaction than reference experiment or experiment in butyronitrile.
butyronitrile	Cs_2CO_3	50−80	5	Complete conversion to product and good product partition.
butyronitrile	Et_3N	20	24	Slow conversion.
butyronitrile	^{t}BuOK	20 or 50	24	Slow conversion.

[a] **7** (1.0 mol equiv), **4** (1.0 mol equiv) and base (1.25 mol equiv) were slurried in solvent (10 volumes) at the appropriate temperature.

The early development work was limited to improving the Medicinal Chemistry route to deliver **2** in a timely manner for the planned safety studies.[12] A solvent/base screen was carried out to find suitable replacements for NMP as there are environmental issues associated with its use and for Cs_2CO_3 which can be unreliable on scale due to mass transfer problems. NMP/Cs_2CO_3 were replaced with butyronitrile/Cs_2CO_3. The conditions investigated are reported in Table 1.

Using these conditions, the maximum process volume was reduced from 150 volumes to 15 volumes. The isolation of **2** as a white solid was achieved by concentration of the butyronitrile solution from 10 volumes to 3 volumes, followed by the addition of two apolar antisolvents xylene (2 volumes) and heptane (6 volumes) at a temperature above 50 °C. As the material partially oiled out during this precipitation, it was necessary to include a ripening step to improve the filtration properties of the solid. The ripening step consisted of a controlled cooling to 20 °C, reheating of the reaction mixture to 50 °C and cooling to 20 °C post crystallisation. The ripening would enable small particles of **2** to redissolve upon heating and other particles to grow further during cooling. The modified route was successfully scaled up to deliver a total 4.5 kg of **2** in the Large-Scale Laboratory. The analyses carried out on these batches are reported in Table 2.

(12) Toxicology and safety studies, SAD and MAD study.

Table 2. **Analysis of the large scale laboratory batches of epoxide 2**

batch	assay by HPLC % w/w	organic purity by HPLC % area	chiral purity by HPLC % w/w	% yield in solution from **7**
1	*a*	93.46	97.6	55
2		92.38	97.5	

[a] As the samples were found to be non-homogeneous, the assay could not be accurately determined. The combined batches were assayed as a solution prior to use in the next stage.

The desired compound **1**, as its benzoic acid salt, was obtained by reacting a solution of **3** in isopropyl acetate with a solution of epoxide **2** in methanol and isopropyl acetate at 55 °C, as described in Scheme 3. The reaction was regioselective and **1** was formed in high solution yield (80% w/w by HPLC). The isolated yield was lower (50%) due to the solubility of **1** in the reaction solvent but the overall purity was good as described in Table 11.

Closer inspection of the overall route highlighted several potential problems for further scale up associated with the synthesis of intermediate **2**. These were associated with the robustness of the Sharpless asymmetric epoxidation on scale[13] and the manufacture, handling and transport of high energy intermediate **4**. With this in mind, other potential routes were investigated for the formation of intermediate **2**.

Route 2: Process R and D Route. Retrosynthetic analysis, as described in Scheme 4, suggested that an aromatic nucleophilic substitution (S_NAr) reaction would be a potentially useful disconnection to access intermediate **2** from commercially available 3-fluoro-4-nitrophenol or 2,4-difluoronitrobenzene. The preferred starting material appeared to be 3-fluoro-4-nitrophenol as it would avoid regioselectivity issues during the S_NAr reaction and negate the need for an extra step to convert the residual fluoride moiety into the hydroxyl functionality. Furthermore, the conversion of the (protected) diol into the desired epoxide seemed a practical alternative for the formation of intermediate **2**.[14]

In practice, consideration of the synthesis in the forward direction led to the design, development and scale up of the route and processes detailed in Scheme 5, after initial synthetic proof of principle on small scale in the laboratory. This route utilised 3-fluoro-4-nitrophenol (**11**) and ((*R*)-2,2,4-trimethyl-1,3-dioxolan-4-yl)methanol (**12**)[4] as starting materials. We were able to source **11** on scale from a commercial supplier, but acetonide **12**[15] was not commercially available on scale and we required a practical manufacturing process for this material. Our approach was based on the resolution of the racemic acetonide using an enzyme-mediated hydrolysis of a derived ester, as detailed below.

*Synthesis of Chiral Acetonide **12.*** The route employed to obtain **12** is described in Scheme 6.

The dihydroxylation of 2-methyl-2-propen-1-ol (**6**) was achieved by treatment with H_2O_2 in water, in the presence of a catalytic amount of Na_2WO_4. 2-Methylglycerol (**15**) was treated with acetone in the presence of catalytic *p*-toluenesulfonic acid to afford (*R*,*S*)-2,2,4-trimethyl-1,3-dioxolane-4-methanol (**16**).[16] Racemate **16** was subsequently esterified using succinic anhydride in TBME, and an enzymatic resolution was subsequently achieved *via* hydrolysis catalysed by *Pseudomonas cepacia* lipase on Celite (Amano PS-D) giving **12** and the undesired (*R*)-succinate half ester (**17**) which was removed by extraction into the aqueous phase. Enantiomerically enriched acetonide **12** was purified by distillation. This process afforded **12** in 22% yield from **6** in >98% enantiomeric purity.

The synthesis of **12** was successfully optimised and scaled up in collaboration with a contract manufacturer and provided a total 174.9 kg of **12** in three batches. The analyses carried out on these batches are reported in Table 3.

S_NAr Reaction. We developed the synthesis of **13** by S_NAr reaction between 3-fluoro-4-nitrophenol (**11**) and the alkoxide derived from **12**. Initial screening conditions, reported in Table 4, identified ^{t}BuOK/NMP or ^{t}BuOK/acetonitrile as suitable systems to perform the S_NAr reaction. The conversion to **13** was clean in highly polar solvents such as acetonitrile or NMP; this was believed to be linked to the solubility of **11** and the alkoxide derived from **12**. However, it was recognised that the stability of acetonitrile in the presence of strong base would be an issue during the scale up, and the use of a relatively apolar solvent such as toluene in this reaction would allow an easier and more efficient workup.

A solvent and temperature screen, reported in Table 5, demonstrated that the formation of **13** was optimal when **11** (1 mol equiv) and **12** (1.15 mol equiv) were reacted in the presence of ^{t}BuOK (2.25 mol equiv) in 10 volumes of NMP/toluene (1:3) at 65 °C. These conditions ensured complete conversion to **13** in good purity (96% area by HPLC) in less than 1 h. Upon completion of the S_NAr, the phenolate derivative of **13** was extracted into water,[17] and **13** was isolated in solution after acidification with glacial acetic acid (1.9 mol equiv) and extraction into isopropyl acetate.[18]

During the development work, the attempted isolation of intermediate **13** as a solid was unsuccessful. We therefore decided to 'telescope' this intermediate as a solution in isopropyl acetate into the hydrogenation reaction. Although it did not interfere in the subsequent reaction, controlling the residual amount of NMP in the final isopropyl acetate solution of **13** was critical to ensure robust isolation of the subsequent intermediate **14**. The presence of elevated amount of NMP compromised the reproducibility of the crystallisation of **14**.

(13) Ten mol % of di-isopropyl tartrate and 10 mol % of titanium tetra-isopropoxide were needed on scale-up to 25 L scale to achieve good enantiomeric purity.

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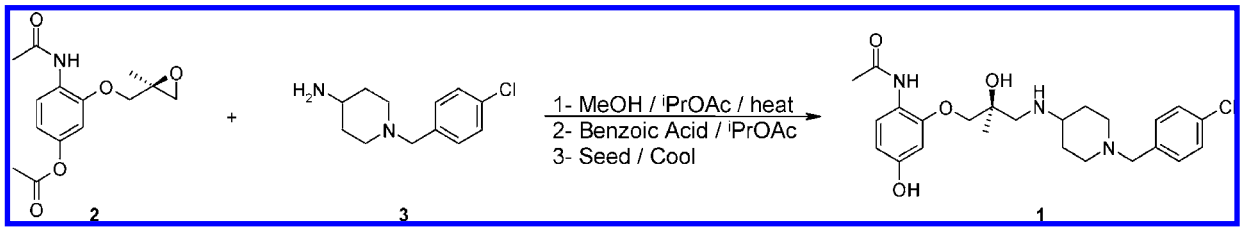
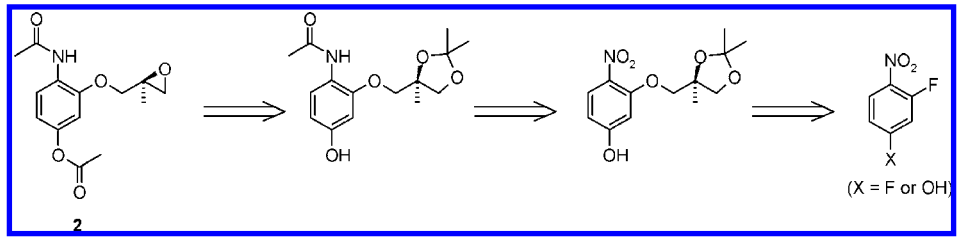
(17) The excess of **12** remained in the toluene layer.

(18) Glacial acetic acid was preferred to concentrated HCl, as the solution was buffered at pH 6 and would not lead to the formation of HF which would be detrimental on glass-lined reactors in the plant.

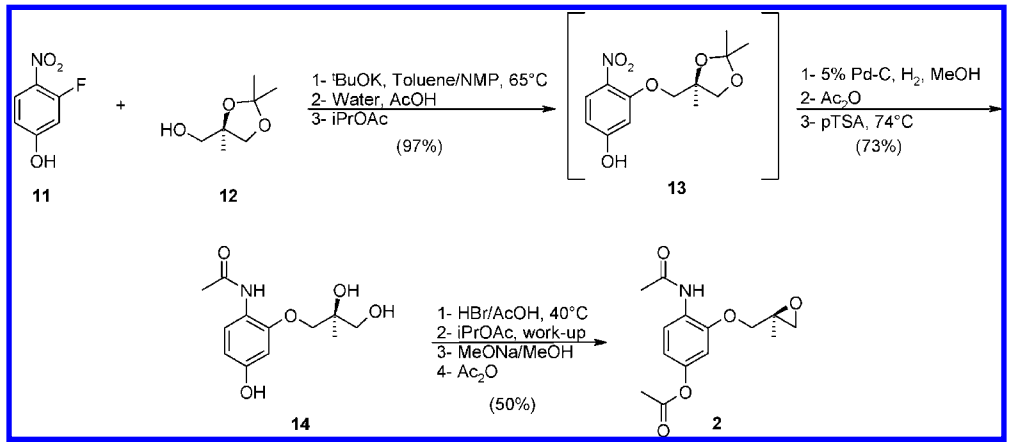
Scheme 3. **Formation of 1**



Scheme 4. **Retrosynthetic analysis of 2**



Scheme 5. **Process R&D route**



Scheme 6. **Access to chiral acetonide 12**

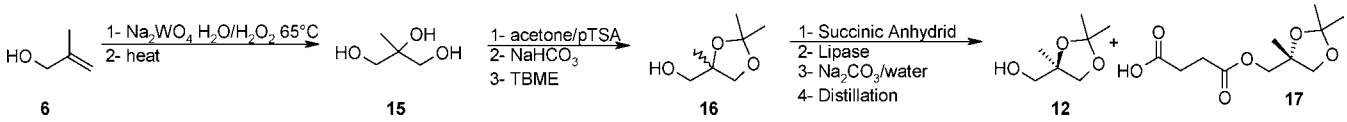


Table 3. **Analyses of pilot-plant batches of acetonide 12**

batch	assay by NMR % w/w	organic purity by GC % area	enantiomeric purity by GC % area	% yield from **6**
1	93	93.4	98.4	22
2	94	94.6	99.0	22
3	94	95.0	99.5	20

Note: The main impurity is 2,2,5-trimethyl-[1,3]dioxan-5-ol or 1,3-acetonide (3.3%area).

Table 4. **Initial screening conditions**[a]

solvent	base	reaction temperature (°C)	reaction time (h)	conversion by HPLC % area
THF	KOH + phase transfer catalyst	20	5−6	starting material recovered
2-MeTHF	tBuOK	65−70	5−6	84.8
NMP	tBuOK	75−80	2−2.5	97.1
acetonitrile	tBuOK	60−65	2−2.5	98.2

[a] **11** (1.0 mol equiv), solvent (10 volumes), base (4.0 mol equiv) and **12** (1.1 mol equiv) were heated to the appropriate temperature.

The removal of residual NMP to acceptable levels (<1.5% w/w) was achieved by the introduction of water washes of the isopropyl acetate solution of **13**.

The S_NAr reaction was successfully optimised and scaled up to deliver a total 156.5 kg of **13** (as a solution in isopropyl acetate) in two batches in the pilot plant. The analyses carried out on these batches are reported in Table 6.

Hydrogenation/Acetamidation. The reduction of the nitro moiety of intermediate **13** was investigated using hydrogenation conditions as shown in Scheme 7.

Since *p*-aminophenols **18** are unstable[19] and known to undergo oxidative coupling producing highly mutagenic *bis*-phenylanilines, our original aim was to avoid the formation of **18** by adding acetic anhydride to the reaction mixture prior to the hydrogenation. However, the amount of acetic anhydride influenced the outcome of the reaction, and mixtures of **18**, **19**

(19) Analysis for the end of reaction was an issue on large scale. Multiple analyses of the same analytical samples were not reproducible. The samples in solution would discolour and degrade upon storage.

Table 5. **Solvent and temperature screening conditions**[a]

solvent (volumes)	co-solvent (volumes)	reaction temperature (°C)	reaction time (h)	comments
toluene (10)	none	70	>16	very slow reaction.
toluene (10)	^{t}BuOH (2)	70	>16	very slow reaction.
toluene (7.5)	2-MeTHF (2.5)	70	>16	very slow reaction.
toluene (7.5)	THF (2.5)	70	>16	very slow reaction.
toluene (3)	THF (7)	70	3	faster reaction but isolation is difficult.
toluene (7.5)	acetonitrile (2.5)	70	3	faster reaction but isolation is difficult.
toluene (9)	NMP (1)	40	>16	very slow reaction.
toluene (9)	NMP (1)	50	>6	reaction time is improved.
toluene (7.5)	NMP (2.5)	65	<1	complete conversion to **13**.

[a] **11** (1.0 mol equiv), solvent, ^{t}BuOK (2.25 mol equiv) and **12** (1.15 mol equiv) were heated to the appropriate temperature.

Table 6. **Analyses of pilot-plant batches of nitro 13**

batch	assay by HPLC% w/w	organic purity by HPLC % area	chiral purity by HPLC % area	% yield in solution from **11**
1	16.4	94.1	98.0	98
2	16.6	94.2	98.4	96

and overacylated derivatives were generated. Experiments carried out in the laboratory indicated that the stepwise conversion of **13** to **19** in solution was the best way forward.

The only catalyst investigated for the conversion of **13** to **18** was 5% Pd/C used as a wet paste. The reaction was carried out at 20 °C and under 4 bar of hydrogen. The addition of methanol as a cosolvent was necessary to prevent the agglomeration of the catalyst and to ensure complete conversion to **18**.[20]

Safety investigations showed that the total adiabatic temperature rise for the entire hydrogenation was 120 °C (−566.3 kJ/mol of **13**); the peak power output (445.7 W/mol of **13**) occurred at the very start of the hydrogenation and rapidly subsided. Complete conversion was achieved after 1 h 45 min (Figure 1). Heat dissipation on scale was achieved by stirring the reaction mixture during the charge of hydrogen. As the hydrogen was consumed during pressurisation, the total hydrogen uptake was not available to indicate the end of formation of **18**.

The robustness of the hydrogenation was demonstrated by carrying out the reaction under chemical control[21] and under mass transfer conditions.[22] In these two extreme experiments, the reaction times were extended to 11−15 h without any effect on the quality of **19**. The progress of the hydrogenation was assessed using UV−vis in-line monitoring. The initial data set represented in Figure 2 as its first derivative exhibits significant variations at 268, 290, 316, and 353 nm. All the profiles have the same characteristic shape corresponding to the decrease in concentration of **13** (peaks at 290 and 353 nm) and the increase in concentration of intermediate **18** (peaks at 268 and 316 nm) (Figure 3). The initial examination of the UV data suggested that both species of interest could be detected and reaction profiles could be extracted from the data using univariate and multivariate approaches. The sensitivity of the method to the amount of **13** remaining was tested by running the hydrogenation to completion and then charging the equivalent of 10 mol % and 1 mol % intermediate **13**. The method could detect an addition of 1 mol % of **13** and would be suitable for determining the reaction end-point.

The addition of acetic anhydride (1.05 mol equiv) to the solution of **18** afforded **19**. In spite of multiple attempts, it was not possible to crystallise intermediate **19**; however, we knew that diol **14** was a highly crystalline intermediate, and so efforts were focused on isolation at the subsequent stage.

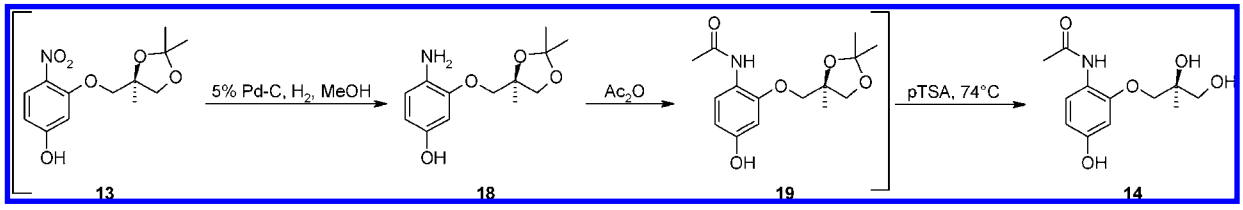
Deprotection. Deprotection of **19** in isopropyl acetate was achieved using catalytic amounts of *p*-toluenesulfonic acid (4.5 mol %). After 1 h at 74 °C, the conversion to **14** was >97%. The removal of solvent under reduced pressure was necessary to improve recovery, and diol **14** crystallised during the distillation.

The hydrogenation/acetamidation/deprotection sequence was successfully optimised and scaled up to deliver a total 107 kg of **14** in three batches in the pilot plant. The analyses carried out on these batches are reported in Table 7.

Epoxide Formation. The sequence used to transform diol **14** into the final intermediate **2** is described in Scheme 8 and relies upon the known conversion of diols into epoxides *via* bromo acetate intermediates.[14]

Acetic acid (2 volumes) was identified as the best solvent for the formation of **20**. A minimum of 3 equiv of HBr was necessary to achieve good conversion in less than 2 h. The reaction was carried out at 40 °C as it maximised the formation of **20** in a short reaction time; however, this could also lead to the degradation of **20** to **21** and **22** (Figure 4). The instability of bromide **20** and its facile degradation led to the investigation of *in situ* monitoring techniques to follow the formation of **20** on large scale.

Scheme 7. **Hydrogenation/acetamidation/deprotection of 13**



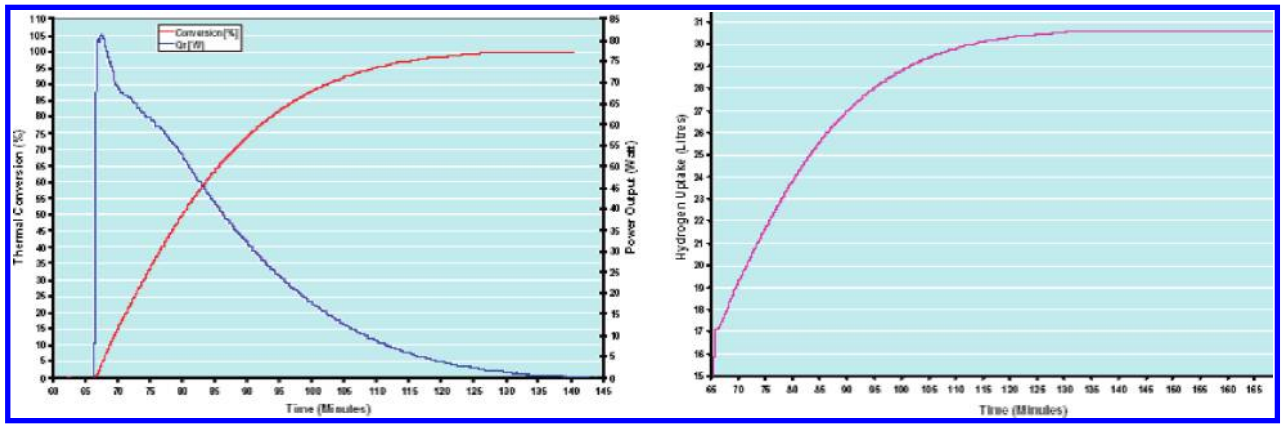


Figure 1. **Thermal conversion, power output and hydrogen uptake.**

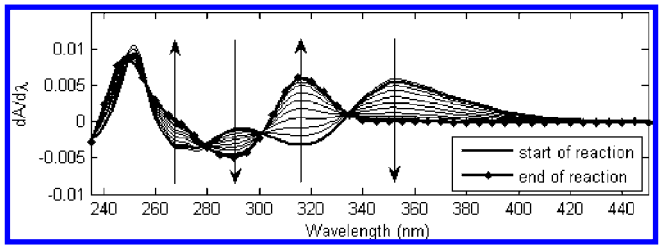


Figure 2. **UV−vis monitoring - overlaid first derivative of UV spectra.**

The conversion of **14** to **20** was followed using the in-line techniques ReactIR (Figure 5), Near-IR (Figure 6) and also ^{1}H NMR (Figure 7). All these techniques showed the same trend for the formation of **20** and concorded with the HPLC profile reported in Figure 4. Near-IR was used on scale up to identify the end of conversion of diol **14** to bromide **20**.

It was necessary to wash bromide **20** after formation and extraction into isopropyl acetate to reduce the amount of acid carried through and therefore limit the amount of base needed in the subsequent conversion to **23**. A wash sequence was designed to ensure quick phase separation on large scale and an increased stability of the solution of **20**. The initial water wash (10 volumes) would remove the bulk of the acid (pH of wash = 0−1); then a wash with 1 M ammonium hydroxide (20 volumes) was carried out (pH of wash = 5−6), and a final wash with aqueous sodium sulfite 12.5% w/v (20 volumes) gave a final aqueous wash with pH = 7−8. The resulting isopropyl acetate solution of **20** could be stored without degradation at −5 °C for at least 24 h.

The conversion of **20** to **23** was achieved by the addition of base to promote transesterification of the acetate moiety followed by the ring closure to give the epoxide. A solvent and base screen, summarised in Table 8, quickly demonstrated that methanol in combination with a strong base (sodium hydroxide or sodium methoxide) was the only suitable solvent for the conversion to **23**. Unfortunately, this phenolate intermediate was not stable in solution at temperatures above 0 °C, with the main degradation pathways being the formation of methanol adducts and oligomers of **23** detected by LCMS. A compromise between an acceptable rate of decomposition of **23** and a practical processing temperature was achieved by carrying out the formation of **23** at −5 °C. The attempted isolation of the free phenol derived from the protonation of **23** as a solid was unsuccesful due to the poor crystallinity of the compound and its tendency to form gum during isolation.

The addition of acetic anhydride (1.35 mol equiv) to the cold solution of **23** afforded the desired epoxide **2**. Initial investigations showed that **2** formed rapidly at −5 °C but was not stable for a prolonged time in the reaction mixture. Sequential water and saturated sodium bicarbonate washes were carried out to remove the residual acidity and improve the stability of **2** in solution.

Although the solubility of **2** in pure isopropyl acetate was low (0.06 mg/mL), isolation from the reaction mixture proved difficult because of the tendency of **2** to oil out during isolation. The complicated mixture of solvents present at the end of the formation of **2** combined with its poor crystallinity meant that finding a robust isolation procedure became a challenge.

The removal of a third of the reaction mixture by distillation, followed by seeding of the mixture at various temperatures, resulted in no precipitation since the seed dissolved due to the presence of methyl acetate[23] in which **2** was highly soluble (>200 mg/mL). We demonstrated that a molar ratio of isopropyl acetate to methyl acetate of 1:<0.07 would prevent the oiling out of **2** and that this could be achieved by removing methyl acetate by careful distillation. Concentration of the reaction mixture by half and removal of methyl acetate by distillation led to a 30% isolated yield. The addition of heptane (2 volumes) as an antisolvent improved recovery further. This procedure was utilised on scale and led to the uncontrolled but reproducible crystallisation of **2** as an heterogeneous pink solid of relatively poor purity which required a solution assay prior to combination with **3** in the key alkylation stage to give **1**.

The epoxide formation was successfully optimised and scaled up to deliver a total 50.4 kg of **2** in three batches in the pilot plant. The analyses carried out on these batches are reported in Table 9.

Although **Route 2** enabled delivery of **2** in acceptable quality, we had some concerns about further scale up of the chemistry due to the relative instability of several intermediates (particularly bromide **20**) and the robustness of the process for the isolation of epoxide **2**. Therefore, we considered alternatives to **Route 2** that might offer advantages, in particular, the

(20) This agglomeration was attributed to the low solubility of **18** in isopropyl acetate, leading to partial precipitation.
(21) Four bars pressure, 0.0025 equiv Pd, 11% vessel fill, 600 rpm.
(22) One bar pressure, 0.025 equiv Pd, 66% vessel fill, 400 rpm.

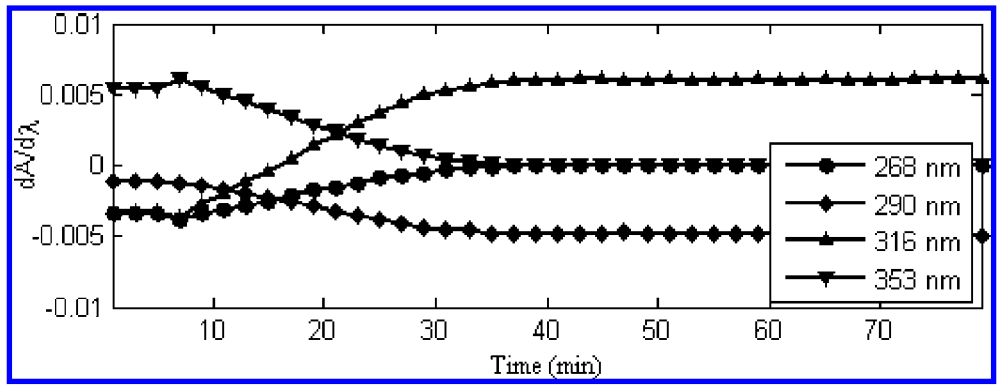
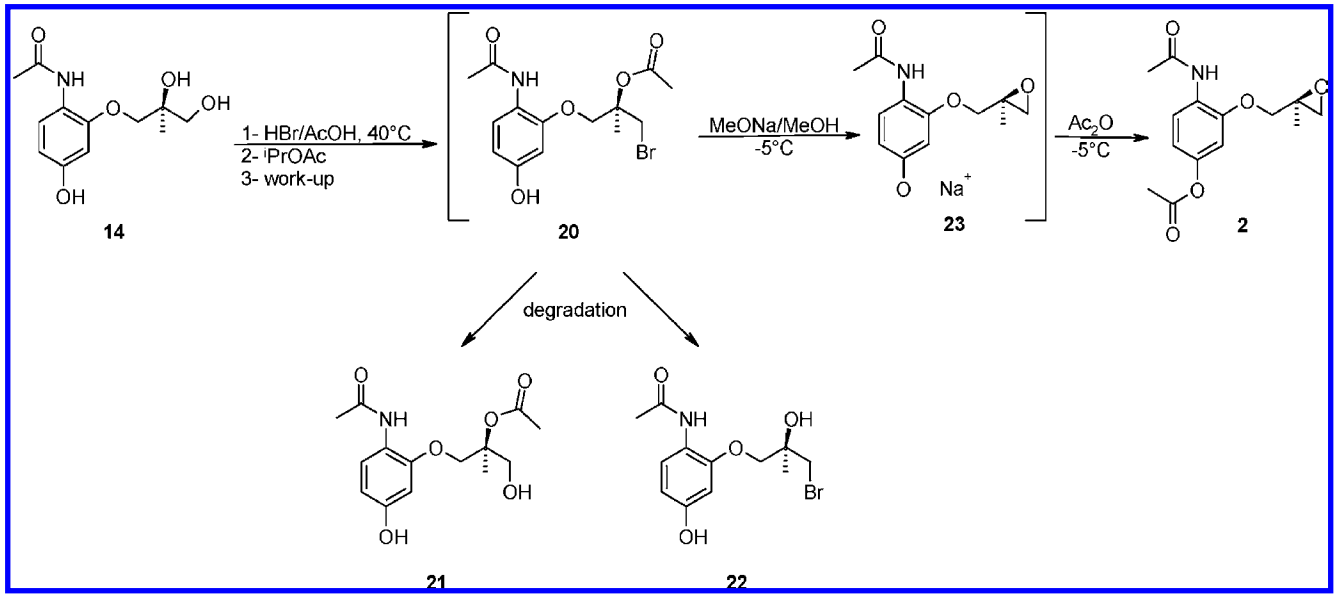


Figure 3. **UV−vis monitoring - first derivative absorbance values vs time.**

Table 7. **Analyses of pilot-plant batches of diol 14**

batch	assay by NMR % w/w	organic purity by HPLC % area	chiral purity by HPLC % area	residual Pd by HPLC ppm	% yield from **13**
1	96	99.2	97.9	<1	75
2	96	99.4	98.1	<1	74
3	96	99.5	98.3	1.3	70

Scheme 8. **Formation of epoxide 2**



possibility of transposing the nitro reduction and the epoxide formation in the synthetic sequence.

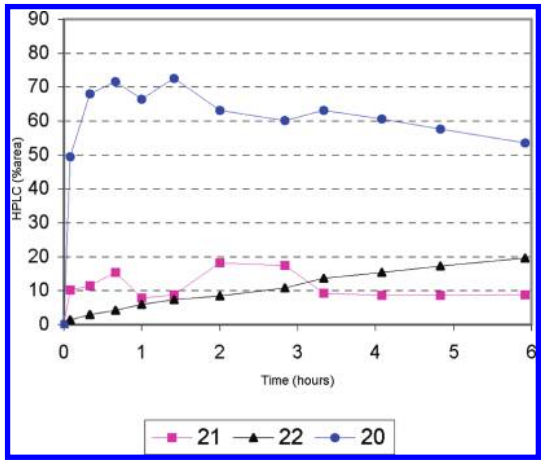


Figure 4. **Stability of bromide 20.**

Route 3: Alternative Process R and D Route. In this approach, the acetonide ring was converted to an epoxide prior to the reduction of the nitro moiety. We envisaged that maintaining the nitro group *para* to the phenol hydroxyl group in the aromatic ring would reduce its nucleophilicity and that

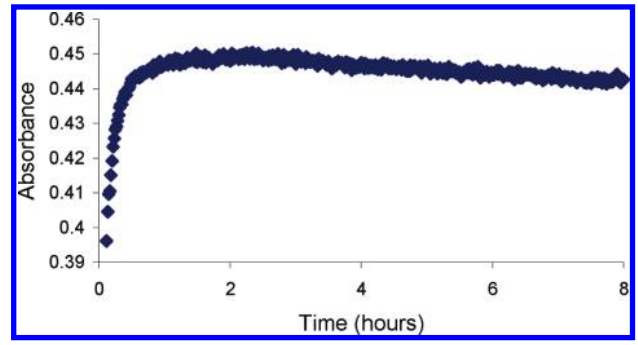


Figure 5. **Monitoring the formation of 20 using ReactIR (carbonyl stretch at 1740 cm^{-1}).**

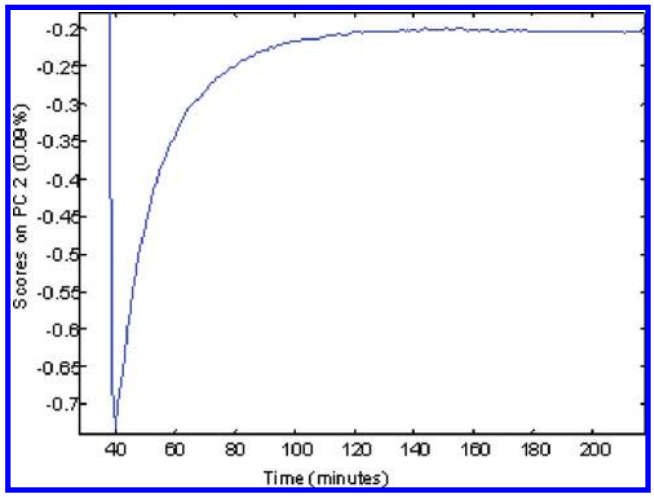


Figure 6. **Monitoring the formation of 20 using Near-IR (third overtone of the carbonyl stretch at 5255 cm^{-1}).**

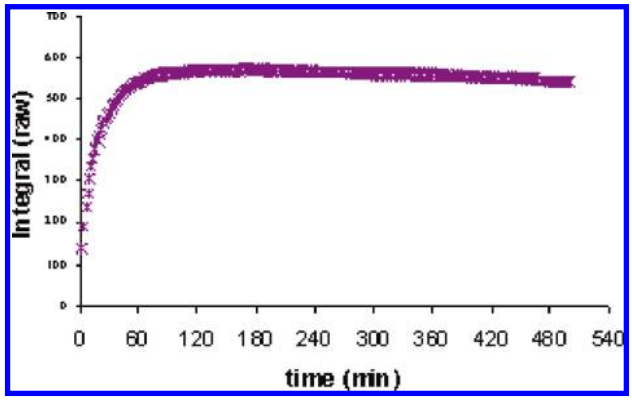


Figure 7. **Monitoring the formation of 20 using ^{1}H NMR (CH_3 at δ = 1.5 ppm).**

Table 8. **Solvent and base screen for the conversion of bromide 20 to epoxide 23[a]**

solvent	base	conversion to **23** (% area by HPLC)
isopropanol	^{i}PrONa	4% after 19 h[b]
methanol	NaOH	91% after 15 min
methanol	Na_2CO_3	8% after 19 h[b]
methanol	NH_3	4.2% after 1 h 30 min[b]
methanol	MeONa	93.9% after 15 min

[a] To the solution of **20** was added solvent (5 volumes) and base (6.2 mol equiv) at 20 °C. [b] The main component is unreacted bromide **20**.

Table 9. **Analyses of pilot-plant batches of epoxide 2**

batch	assay by NMR % w/w	organic purity by HPLC % area	chiral purity by HPLC % area	% yield from **14**
1	88	87.5	98.2	49
2	82	84.2	98.6	52
3	91	90.2	98.5	46

this might reduce stability issues associated with potential epoxy-phenol oligomerisation en route to **24**. This alternative route is detailed in Scheme 9.

Epoxide Formation. The transformation of acetonide **13** into intermediate **24** is described in Scheme 10.

The work carried out for the formation of intermediate **24** was based on the work described previously for the formation of **2**. To the solution of **13** in isopropyl acetate was added 33% HBr in acetic acid (3 mol equiv). The reaction was carried out at 40 °C as it maximised the formation of **25** in a short reaction time; however, this could also lead to the degradation of **25** to **26** and **27** (Figure 8). The optimal reaction time for the formation of **25** was 30−50 min.

The instability of **25** and its facile degradation led to the investigation of *in situ* monitoring techniques to follow its formation on large scale. The conversion of **13** to **25** was followed by ^{1}H NMR (Figure 9). The profile, similar to that of related compound **20** (Figure 7), showed a quick conversion and a relatively stable compound (compared to **20**).

A wash sequence similar to that employed for intermediate **20** was applied, and the resulting solution of **25** could be stored without degradation at 20 °C for at least 24 h.

The conversion of **25** to **28** was achieved by the addition of sodium methoxide in methanol to promote the transesterification of the acetate moiety followed by the ring closure to give epoxide **24**. This conversion could be carried out at temperatures between 5 and 20 °C[24] without detrimental effect on the quality of intermediate **28**. The isopropyl acetate solution of phenolate **28** was stable at 2 °C for at least 26 h, which when compared to its reduced counterpart **23** in the previous route, suggests that our motivation for investigating this route had some validity.

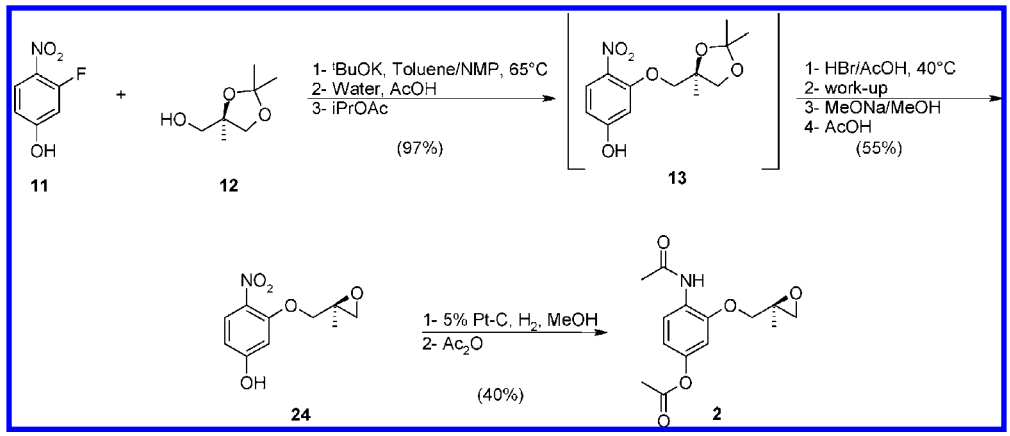
Intermediate **28** was extracted into water, and the addition of this solution onto aqueous acetic acid led to the precipitation of the desired epoxide **24** in relatively good yield (55%) and good purity (95.6% area by HPLC). It is worth noting here that it was not even possible to isolate the corresponding hydroxyl epoxide in the previous route.

Hydrogenation/Acetamidation. The reduction of the nitro moiety of **24** was investigated using hydrogenation conditions as shown in Scheme 11. The aim was to develop a procedure that would chemoselectively reduce the nitro moiety of intermediate **24** in the presence of the epoxide moiety. Previous work[25] has shown that such a transformation can be effected using a catalyst poisoned with ethylenediamine; however, we found that these conditions were unsuccessful for the chemoselective reduction of intermediate **24**, and only unreacted starting material was recovered.

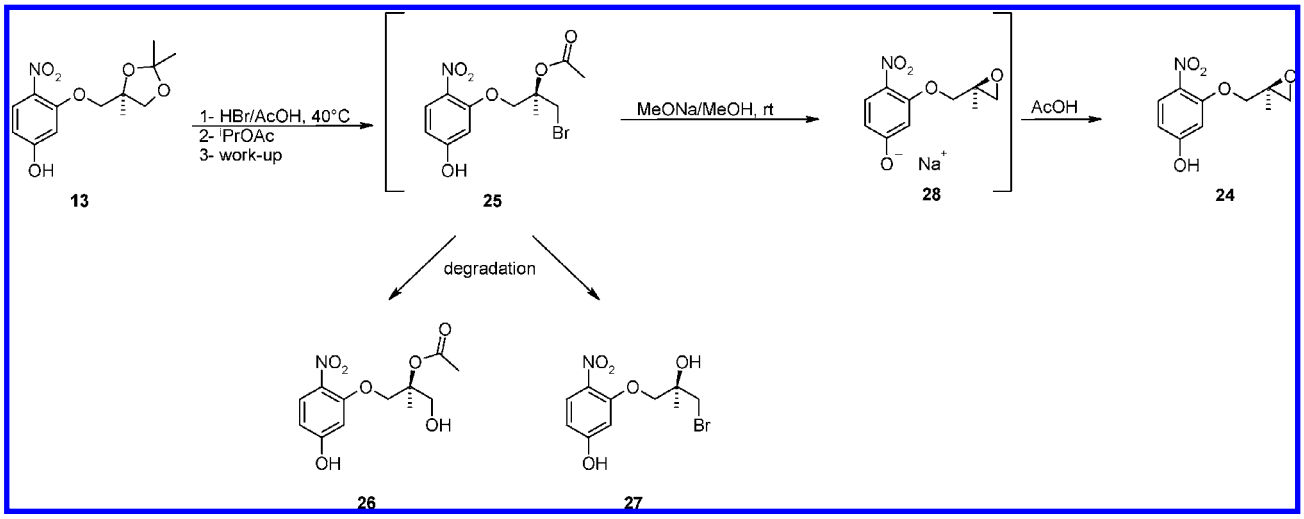
A screen, summarised in Table 10, identified 1% Pt on carbon[26] as the catalyst of choice for the chemoselective reduction of **24** to **29**. Further investigations into the reaction demonstrated that THF was the best reaction solvent and that the presence of triethylamine (3 mol equiv) was necessary to achieve clean and quick conversion.[27] The nitro reduction was performed at 20 °C in 10 volumes of THF under 4 bar of hydrogen, followed by the addition of acetic anhydride (2.5 equiv), leading to the formation of **2**.

(23) From the transesterification of **20** and the transesterification of isopropyl acetate with sodium methoxide.
(24) When addition was carried out at −5 °C, the reaction mixture solidified.
(25) Sajiki, H.; Hattori, K.; Hirota, K. *Chem.—Eur. J.* **2000**, *12*, 2200–2204.
(26) The second-best catalyst was 5% Pt on alumina.
(27) The catalyst used JM18MA was acidic pH 3.5. Use of similar catalyst JM18 with a pH 6.4 with or without base did not give similar uptake under similar reaction conditions.

Scheme 9. **Alternative PR&D route to 2**



Scheme 10. **Alternative formation of epoxide 2**



The isolation of **2** from THF was again troublesome. The reaction volume was such that a concentration would be needed before isolation of **2** could be attempted. The solution of **2** was washed with a saturated solution of sodium bicarbonate and brine, and after distillation *in vacuo*, the addition of an antisolvent, 4-methyl-2-pentanol, led to the recovery of **2** in very low yield.[28] We observed the formation of significant levels of diacetate **31** (12.3% area by HPLC) which would be lost to the liquors during this processing. One possible cause was the presence of residual acetic acid or acetate salts during the distillation,[29] but it became apparent that the levels of acetic acid present in solution after workup were too small to be responsible for the amount of **31** formed. We postulated that water could be the cause of the instability. The level of water present in the solution after workup was 4% w/w. The influence of water on the stability of a THF solution of **2** at reflux was investigated, and the results showed that **2** was stable in THF for at least 24 h if the level of water was less than 1% w/w. We believe that **31** is formed by the mechanism described in Scheme 12. This is supported by the observation of the presence

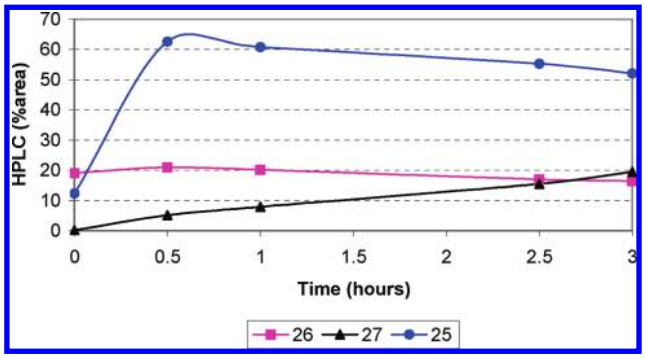


Figure 8. **Stability of bromide 25.**

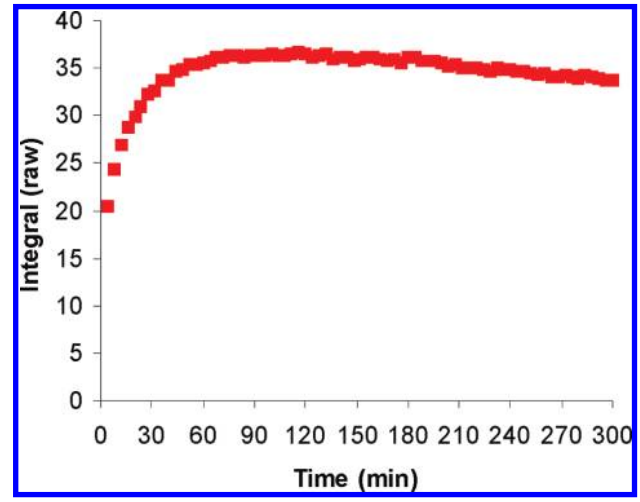


Figure 9. **Monitoring the formation of 25 using ^{1}H NMR (CH_2 at δ = 4.5 ppm).**

Scheme 11. **Hydrogenation/acetamidation of 24**

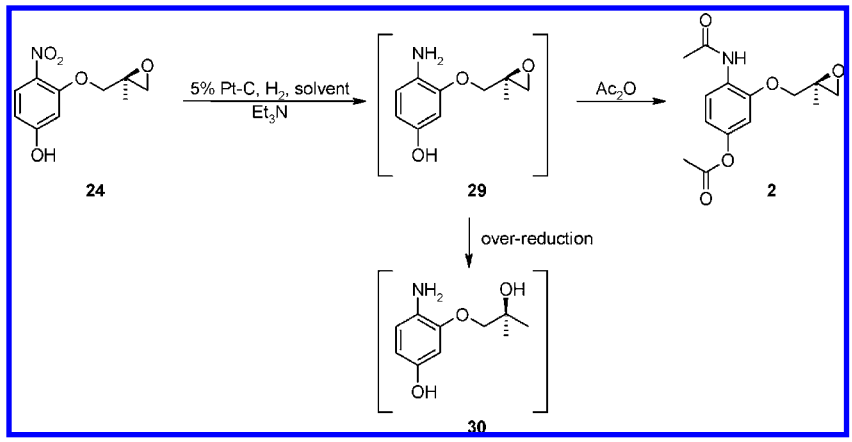
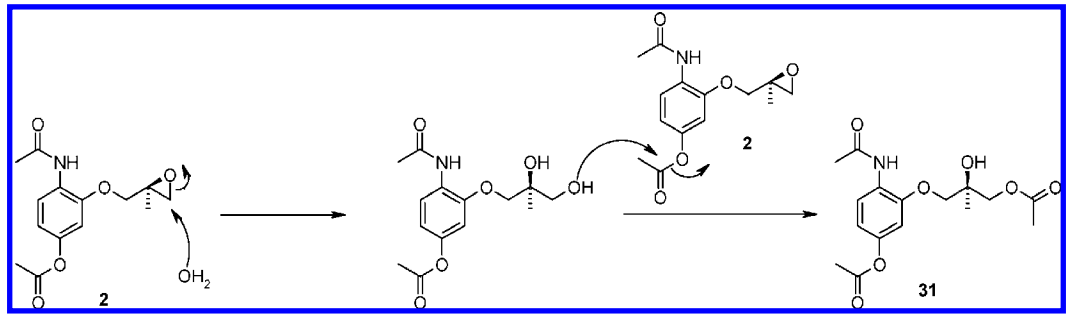


Table 10. **Screened conditions for the hydrogenation of 24**[a]

catalyst	type	solvent	pressure (bar)	diacylated **30**	**2**	acylated **24**
5% Pd/C	315	^{i}PrOAc	2	1	4	0.3
5% Pd/C	38H	^{i}PrOAc	2	1	5.8	12
5% Pd/C	39 paste	^{i}PrOAc	2	1	4.3	2
5% Pd/C	58 paste	^{i}PrOAc	2	1	2.5	0.4
5% Pd/C	394	^{i}PrOAc	2	1	1.4	0
5% Pd/C	437	^{i}PrOAc	2	1	2.7	0
5% Pd/C	472	^{i}PrOAc	2	1	11	30
5% Pd/C	487	^{i}PrOAc	2	1	7	12
5% Pd/C	315	2-MeTHF	2	1	4.5	0.2
5% Pd/C	38H	2-MeTHF	2	1	3	0.3
5% Pd/C	39 paste	2-MeTHF	2	1	2.1	0
5% Pd/C	58 paste	2-MeTHF	2	1	1	0
5% Pd/C	394	2-MeTHF	2	1	0.8	0
5% Pd/C	437	2-MeTHF	2	1	2.1	0
5% Pd/C	472	2-MeTHF	2	1	9.7	16.2
5% Pd/C	487	2-MeTHF	2	1	2.2	0
5% Pt/Al_2O_3	94	AcOEt	2	0	1	1
5% Pt/Al_2O_3	94	AcOEt	4	trace	1	0
2.5% Pd, 2.5% Pt/C	122	AcOEt	4	1.6	1	0
4.5% Pd, 0.5% Ru/C	485	AcOEt	4	1	0	0
5% Pt/graphite	289	AcOEt	4	trace	1	0
1% Pt/C	18MA	AcOEt	4	0	1	0
1% Pt/C	200	AcOEt	4	0	1	0

[a] Reaction time at 20 °C was 17−18 h. The data shown are ratios of products by HPLC. **24** (1 mol equiv), solvent (10 volumes), Et_3N (3 mol equiv), Ac_2O (2.5 mol equiv) and catalyst (25% w/w) were charged in the hydrogenation vessel, and then hydrogen was introduced.

Scheme 12. **Formation of 31**



of the phenol derived from **2**, detected at 7.8% area by HPLC (this relatively low level of this phenol is due to its instability and its tendency to oligomerise as discussed previously).

(28) In spite of an 83% solution yield of **2**, the isolated yield was only 33%, and the material lost to the liquors was only14%.

This suggested that the amount of water carried through needed to be reduced prior to the distillation. Drying agents[30] did not reduce the amount of water significantly. 2-Methyl THF was investigated as an alternative solvent that might offer advantages in postwash drying but was found to be inappropriate because the hydrogenation

Scheme 13. **Formation of 32**

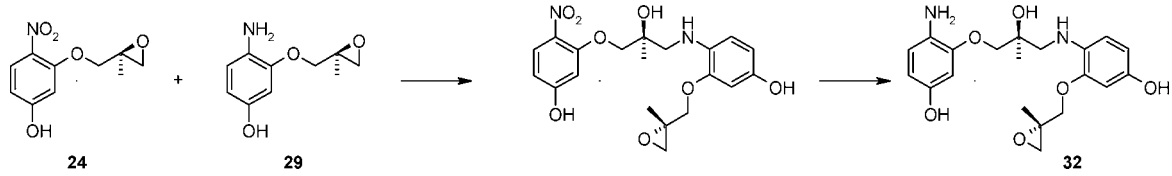


Table 11. **Analyses of batches of candidate drug 1**

origin of **2** (assay in solution)	scale (input of **2**)	solution yield (%)	isolated yield (%)	assay by NMR % w/w	organic purity by HPLC % area	chiral purity by HPLC % area
Route 1 (99.5% w/w)	4.5 kg	80	59	97	98.1	99.7
Route 2 (unoptimised) (81.6% w/w)	36.3 kg	77	40	98	98.5	99.9
optimised Route 2 (96.5% w/w)	18 g	79	67	97	98.4	99.9

profile was adversely affected. We also investigated the use of mixed solvents as a compromise between a quick and clean hydrogenation and an easy isolation of **2**, but this did not provide a positive way forward.

Our final tactic focussed on reducing the solvent quantities for the hydrogenation which would remove the need for distillation as the direct addition of an antisolvent post-workup could then lead to the isolation of **2**. It is in this phase of work where a serious weakness in the alternative route became apparent. When the hydrogenation was carried out at higher reaction concentrations mimicking the plant conditions, the reaction was accompanied by the formation of dimer **32** in high quantities.[31] The formation of dimer **32** was linked to the reaction time, and concentration and experiments showed that **32** was formed *via* *N*-alkylation of **29** by **24** as shown in Scheme 13.

Given that the hydrogen delivery rate was limited in the pilot plant, we knew that the reaction time would increase on scale up and that formation of **32** would always be a detrimental side reaction. In addition, no viable isolation protocol for the desired product **2** without significant degradation (*via* **31**) had been defined from higher-dilution experiments. Thus, whilst this alternative sequence offers an advantage with respect to the stability of intermediate **28** compared to **24**, the converse is true with respect to intermediates **29** and **23** under the reaction/processing conditions associated with them. Overall, we considered that access to **2** using this alternative route was not a practical option, and development work was discontinued.

Optimisation of Route 2. Further development of **Route 2** as a final manufacturing route was undertaken, with the focus on improving the robustness in the knowledge that we would be dealing with unstable intermediates in the three-stage telescope from **14** to **2**. We also concentrated the development work on the reduction of process waste.

The wash sequence during the formation of bromide **20** generated large quantities of waste. This sequence was modified to reduce the waste, whilst not affecting the stability of **20**. The final sequence included sequential washes with water (10 volumes), 1.33 M ammonium hydroxide (15 volumes) and sodium sulfite 17%w/v (15 volumes). This reduction in the wash volumes improved throughput by 51%.

The crystallisation of **2** from the reaction mixture had to be modified to ensure robust isolation of **2** of reliable quality. When the charge of heptane was reduced to 1 volume, no oiling was observed, and **2** precipitated out of solution reproducibly after seeding at 30 °C and further cooling to 5 °C. After these improvements, the 37% isolated yield of **2** was slightly lower than obtained previously when 2 volumes of heptane were used (46−52%). However, the new procedure using less heptane had the advantage of generating homogeneous, higher-quality material (98.8% area vs 84−90% area by HPLC). The higher quality of intermediate **2** more than compensated for the lower isolated yield, since the need for a solution assay prior to reaction with **3** in the final bond-forming step to give **1** was obviated.

Final Alkylation Stage. With a workable process for the final stage having been demonstrated (see above), little work was done to optimisation at this point, given the issues surrounding the upstream chemistry. Given that essentially invariate processing conditions were employed for this stage for both the **Route 1** and **Route 2** manufacturing campaigns and the quality of the amine **3** was comparable throughout, the yield and quality of the output API **1** reflects the quality of the input epoxide **2**. A comparison of the performance of the process against different sources of input epoxide **2** is presented in Table 11. It is clear that the solution yield of **1** obtained in the reaction mixture prior to crystallisation is comparable as is the quality of the isolated material. However, the isolated yield varies and is dependent on the quality of epoxide **2**, with material derived from the optimised **Route 2** delivering 67% based on a single experiment in the laboratory.

Conclusions

A robust and reproducible synthesis of **2**, that did not rely on chromatography or potentially high-energy intermediates, has been developed. The routes developed were capable of providing sufficient quantities of **2** in acceptable quality to assist the development program.

The final coupling of intermediates **2** and **3** leading to the formation of **1** was successful irrespective of the route used to access intermediate **2** and gave good conversion in each case. Nevertheless, the isolated yield of **1** was very dependent upon

(29) Zipperer, B.; Fletschinger, M.; Hunkler, D.; Prinzbach, H. *Tetrahedron Lett.* **1987**, *28* (22), 2513–2516.
(30) $MgSO_4$, molecular sieves.
(31) Five volumes of THF, 14% area of **32** by HPLC. Ten volumes of THF, 5% area of **32** by HPLC.

the quality of intermediate **2**. The use of pure, homogeneous epoxide (using the optimised route) in the formation of **1** led to a dramatic increase in isolated yield, suggesting that efficient crystallisation of **1** is inhibited by impurities introduced with this intermediate.

Experimental Section

2-Methyl-1,2,3-propanetriol (15). A solution of methallyl alcohol (200 g, 2.77 mol, 1 mol equiv) and sodium tungstate dihydrate (9.3 g, 27.7 mmol, 0.01 mol equiv) in water (400 mL) was heated to 60 °C. An aqueous solution of hydrogen peroxide (35% w/w, 346 g, 3.60 mol, 1.3 mol equiv) was slowly added to the reaction mixture at a rate that maintained the internal temperature in the range 60−85 °C. Once the addition was complete, the reaction mixture was stirred for 30 min at 70 °C to destroy most of the remaining peroxides. The reaction mixture was then stirred for a minimum of 2 h 30 min at 100 °C to destroy all the peroxides. The reaction mixture was cooled to 50 °C, and water was distilled off under reduced pressure. The reaction mixture was concentrated in vacuo to afford **15** as a pale-yellow, viscous, opaque oil which was used in the next step without purification. ^{1}H NMR (300 MHz, DMSO) δ 0.97 (s, 3H), 3.21 (m, 4H), 4.02 (br, 1H), 4.37 (br, 2H). GCMS *m*/*z* 107 [M + H].

Racemic (2,2,4-Trimethyl-1,3-dioxolan-4-yl)methanol (16). The crude **15** (292 g, 2.75 mol, 1.0 mol equiv) was dissolved in acetone (1595 g, 27.5 mol, 10 mol equiv). *p*-Toluenesulphonic acid monohydrate (52.2 g, 274 mmol, 0.10 mol equiv) was added, and the resulting mixture was stirred at 20 °C for 2 h. The pH of the reaction solution was then set to 7−8 by the addition of a solution of 0.6 M aqueous sodium bicarbonate, and the acetone was removed under reduced pressure. The aqueous mixture was extracted 5 times with TBME (400 mL). The combined organic layers were dried by azeotropic distillation at atmospheric pressure. [Racemic **16** can be isolated as an oil by further concentration.] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.42 (s, 3H), 1.43 (s, 3H), 1.92 (t, J = 6.6 Hz, 1H), 3.49 (m, 2H), 3.73 (d, J = 8.7 Hz, 1H), 3.98 (d, J = 8.7 Hz, 1H). GCMS (CI) *m*/*z* 147 (M + H), 131 (M − CH_3), 89 (M + H − C_2H_6O).

((*R*)-2,2,4-Trimethyl-1,3-dioxolan-4-yl)methanol (12). To the solution of **16** in TBME was added succinic anhydride (113.3 g, 1.13 mol, 0.41 mol equiv with respect to (wrt) isobutenol), and the mixture was stirred at 20 °C. Lipase PS Amano IM (12.5 g, 0.0625 wt equiv wrt isobutenol) was added to the reaction mixture in one portion. The resulting mixture was stirred at 20 °C for 2−6 h. The enzyme was removed by filtration, and the filtrates were treated with a solution of aqueous sodium carbonate (10% w/w, 792 g, 0.69 mol, 0.25 mol equiv wrt isobutenol). The biphasic mixture was separated, and the aqueous layer was re-extracted with TBME (470 mL). The biphasic mixture was separated, and the combined organic layers were washed with a solution of aqueous sodium carbonate (5% w/w, 117 g, 55.4 mmol, 0.02 mol equiv wrt isobutenol) until the pH of the mixture was 7.5−8.0. TBME was removed by reduced pressure distillation to afford **12** as a pale-yellow oil. This was purified by distillation under reduced pressure to give **12** as a clear, colourless oil in 27% yield (wrt isobutenol) and 95% purity by GC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.42 (s, 3H), 1.43 (s, 3H), 1.92 (t, J = 6.6 Hz, 1H), 3.49 (2H, m), 3.73 (d, J = 8.7 Hz, 1H), 3.98 (d, J = 8.7 Hz, 1H). GCMS (CI) *m*/*z* 147 (M + H), 131 (M − CH_3), 89 (M + H − C_2H_6O).

(*S*)-4-Nitro-3-(2,2,4-trimethyl-[1,3]dioxolan-4-ylmethoxy)-phenol (13). Toluene (142.3 kg) and NMP (73.1 kg) were added to potassium *tert*-butoxide (78 kg, 2.25 mol equiv). A solution of **12** (49.3 kg, 1.15 mol equiv) in toluene (102.3 kg) was added, and the reaction was stirred for 50 mn at 25 °C. A solution of **11** (46.1 kg, 1.00 mol equiv) in NMP (48.6 kg) and toluene (66.6 kg) was added. The reaction was heated at 65 °C for 1 h 30 min. The mixture was cooled to 40−50 °C, and water (235.1 kg) was added, and the two layers were separated. Acetic acid (34.7 kg, 1.9 mol equiv) was added to the aqueous layer, and **13** was extracted into isopropyl acetate (409.3 kg). The organic solution was washed with water (3 × 352.5 kg) to minimise the amount of NMP carried over. The product can be isolated by concentration to dryness in 98% yield. Alternatively, the solution can be used directly in the next stage. ^{1}H NMR (300 MHz, DMSO) δ 1.32 (s, 3H), 1.33 (2*s*, 6H), 3.74 (d, J = 8.7 Hz, 1H), 3.92 (d, J = 9.2 Hz, 2H), 4.00 (d, J = 9.5 Hz, 1H), 4.03 (d, J = 8.7 Hz, 1H), 6.47 (dd, J = 9.2, 2.3 Hz, 1H), 6.61 (d, J = 2.3 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 10.87 (br, 1H). LCMS (ESI) *m*/*z* 306 (MNa^+), 226 (M^+ − CH_3COCH_3).

(*S*)-*N*-[2-(2,3-Dihydroxy-2-methyl-propoxy)-4-hydroxy-phenyl]acetamide (14). To a solution of **13** in isopropyl acetate (16.4% w/w, 318.3 kg, 1 mol equiv) was added methanol (25.8 kg) and 5% Pd on C (57.9% w/w water, 5.3 kg, 0.005 mol equiv). The mixture was warmed to 25 °C, and hydrogen was charged to the reaction at 4.25 bar g. At the end of the reduction, acetic anhydride (19.7 kg, 1.05 mol equiv) was added. The catalyst was removed by filtration.

To the solution of **18** in isopropyl acetate/methanol was added *p*-TSA monohydrate (1.43 kg, 0.045 mol equiv). The reaction was heated at 72 °C for 40 min. The reaction was cooled to 20 °C, and methanol was removed by distillation under reduced pressure. Compound **14** crystallised during distillation and was recovered by filtration in 75% yield and 95% w/w assay. ^{1}H NMR (400 MHz, DMSO) δ 1.13 (s, 3H), 2.02 (s, 3H), 3.27 (m, 1H), 3.45 (dd, J = 10.6, 5.5 Hz, 1H), 3.69 (d, J = 8.6 Hz, 1H), 3.76 (d, J = 9.0 Hz, 1H), 4.71 (t, J = 5.6 Hz, 1H), 4.76 (s, 1H), 6.28 (dd, J = 8.6, 2.4 Hz, 1H), 6.39 (d, J = 2.6 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 8.87 (s, 1H), 9.22 (s, 1H). LCMS (ESI) *m*/*z* 256 (M + H).

(*S*)-3-(2-Methyl-oxiranylmethoxy)-4-nitro-phenol (24). To a solution of **13** (19.6% w/w, 314 g, 217 mmol, 1 mol equiv) in isopropyl acetate at 20 °C was added HBr in acetic acid (33% w/w, 120 mL, 663 mmol, 3.1 mol equiv). The solution was heated at 55 °C for 1 h. The mixture was diluted with isopropyl acetate (620 mL) and cooled to 20 °C. The organic solution was washed sequentially with water (620 mL) and aqueous sodium sulfite (25% w/v, 930 mL). To the organic solution of **25** at 20 °C was added dropwise a solution of sodium methoxide in methanol (25% w/w, 148 mL, 656 mmol, 3.0 mol equiv). After 30 min, water (620 mL) was added to the reaction, and the biphasic mixture was separated. The aqueous solution of **28** was added dropwise to a solution of acetic acid (12.5 mL, 218 mmol, 1 mol equiv) in water (250 mL). Compound **24** crystallised during acidification and was

recovered by filtration in 68% yield and 85% w/w assay. ^{1}H NMR (300 MHz, DMSO) δ 1.40 (s, 3H), 2.80 (dd, J = 5.4, 43.8 Hz, 2H), 4.14 (dd, J = 10.8, 85.1 Hz, 2H), 6.49 (d, J = 9.0 Hz, IH), 6.58 (s, lH), 7.91 (d, J = 9.0 Hz, lH), 10.90 (s, lH). LCMS (ESI) m/z 226 (M + H).

Acetic Acid 4-Acetylamino-3-(2-methyl-oxiranylmethoxy)-phenyl Ester (2). *Route 1: LSL C2.* To a slurry of **7** (16.7 g, 74.6 mmol, 0.85 mol equiv) in butyronitrile (250 mL), was added a toluene solution of **4** (48% w/w, 50 g, 87.8 mmol, 1 mol equiv). Cesium carbonate (28.9 g, 87.8 mmol, 1 mol equiv) was added, and the mixture was heated at 50 °C for 3−5 h. The organic layer was washed with water (2 × 125 mL). The organic layer was concentrated to approximately 3 volumes under reduced pressure, keeping the temperature around 30−50 °C. Xylene (50 mL) was added at a temperature above 50 °C, followed by heptane (150 mL). The solution was cooled to 20 °C, and **2** crystallised. The solid was collected by filtration as a damp, pink heterogeneous solid in 65% yield and 85% w/w assay.

Optimised Route 2. To a slurry of **14** (45 g, 0.18 mol, 1 mol equiv) in acetic acid (90 mL) at 40−45 °C was added HBr in acetic acid (33% w/w, 96 mL, 0.53 mol, 3 mol equiv), keeping the temperature around 40−45 °C. After 1 h 30 min, the mixture was cooled to 20 °C, and isopropyl acetate (450 mL) was added. The organic solution was washed sequentially with water (450 mL), aqueous ammonium hydroxide (1.33 M, 675 mL) and aqueous sodium sulfite (17%w/v, 675 mL) to obtain a final aqueous pH around 7−8. The reaction mixture was cooled to −5 °C, and sodium methoxide in methanol (25% w/w, 93 mL, 0.41 mol, 2.3 mol equiv) was added, keeping the temperature between −10 and 0 °C. After 30 min, acetic anhydride (22.5 mL, 0.24 mol, 1.35 mol equiv) was added, keeping the temperature between −10 and 0 °C. After 20 min, the mixture was warmed to 20 °C, and the organic solution was washed sequentially with water (450 mL) and aqueous sodium bicarbonate (6% w/w, 450 mL). The organic solution was concentrated by half by distillation at atmospheric pressure. The mixture was cooled to 50−60 °C, and heptane (45 mL) was added, keeping an internal temperature around 50−60 °C. The mixture was further cooled to 20 °C, seeded, and cooled to 5 °C. The solid was collected by filtration and washed with a combination of isopropyl acetate (45 mL) and heptane (11 mL). Intermediate **2** was afforded as a white homogeneous solid in 38% yield and 99.5% w/w assay.

Route 3. To a solution of **24** (8 g, 35.5 mmol, 1 mol equiv) in THF (80 mL) and triethylamine (15 mL, 107.6 mmol, 3 mol equiv) was added 1% Pt on C (55.9% water, 1.2 g, 27.1 μmol Pt, 0.0007 mol equiv). The mixture was stirred at 20 °C under 4.0 bar g of hydrogen. After completion of the hydrogenation, acetic anhydride (8.4 mL, 88.9 mmol, 2.5 mol equiv) was added. After 30 min, the catalyst was filtered off, and the organic solution was washed sequentially with saturated sodium bicarbonate (2 × 80 mL) and brine (40 mL). The washed organic solution was concentrated in vacuo to yield **2** in 56% yield.

^{1}H NMR (300 MHz, DMSO) δ [ppm] 1.40 (s, 3H), 2.10 (s, 3H), 2.30 (s, 3H), 2.70−2.80 (m, 2H), 3.90−4.20 (m, 2H), 6.70 (dd, J = 2.4, 8.4 Hz, 1H), 6.90 (d, J = 2.4 Hz, 1H), 7.70 (d, J = 8.7 Hz, 1H), 9.10 (br, 1H). m/z LCMS (ESI) 280 (M + H), 262 (M + H − H_2O), 220 (M + H − H_2O − CH_3CO).

Acetate 4-Amino-1-(4-chloro-benzyl)piperidinium. Piperidin-4-ylamine (94.9%, 24.7 kg, 234 mol, 1 mol equiv) and MIBK (194 L) were heated at reflux for 4−24 h. The mixture was cooled to below 30 °C, and a solution of NaOH (20% w/w, 71.5 kg, 355.3 mol, 1.52 mol equiv) was added, followed by a solution of 1-chloro-4-chloromethyl benzene (37.4 kg, 234 mol, 1 mol equiv) in MIBK (39 L). The mixture was allowed to stir at 20 °C for 6−24 h. The reaction mixture was quenched by addition of water (100 L). The biphasic mixture was separated, and acetic acid (15.5 kg, 257.4 mol, 1.1 mol equiv) was added to the organic layer, resulting in the precipitation of acetate 4-amino-1-(4-chloro-benzyl)piperidinium. The solid was collected by filtration and dried in a vacuum oven at 50 °C overnight. 4-Amino-1-(4-chloro-benzyl)piperidinium was isolated in 65% yield and 99.5% w/w assay. ^{1}H NMR (400 MHz, DMSO) δ 1.35 (dq, J = 3.9, 11.5 Hz, 2H), 1.73−1.72 (m, 2H), 1.78 (s, 3H), 1.97 (dt, J = 2.2, 11.5 Hz, 2H), 2.73−2.64 (m, 3H), 3.41 (s, 2H), 5.80 (b, 2H), 7.38−7.28 (m, 4H). LCMS (ESI) m/z 225/227 (M + H).

***N*-{2-[((2*S*)-3-{[1-(4-Chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl)oxy]-4-hydroxyphenyl}acetamide (1).** To a solution of **2** (18 g at 99% w/w, 63.8 mmol, 1 mol equiv) in isopropyl acetate (17 mL) and methanol (25 mL) at 35 °C was added **3** (70 mL, 70.0 mmol, 1.1 mol equiv). The mixture was heated at 55 °C for 16−24 h. The solution was cooled to 40 °C, and benzoic acid (8.7 g, 71.0 mmol, 1.1 mol equiv) was added. The mixture was heated at 50 °C, and isopropyl acetate (76 mL) was added. The mixture was seeded with **1** (10 mg), and isopropyl acetate (51 mL) was added. The mixture was cooled to 20 °C over 3 h, and the solid crystallised out. The solid was collected by filtration, washed with isopropanol (60 mL), and dried in a vacuum oven at 50 °C. Product **1** was recovered in 65% yield and 96.9% w/w assay. ^{1}H NMR (400 MHz, CD_3OD) δ 1.35 (s, 3H), 1.73−1.60 (m, 2H), 2.03 (d, J = 11.7 Hz, 2H), 2.09 (s, 3H), 2.17 (t, J = 11.7 Hz, 2H), 3.05−2.89 (m, 4H), 3.14 (d, J = 12.3 Hz, lH), 3.54 (s, 2H), 3.88 (s, 2H), 6.36 (dd, J = 8.5,2.6 Hz, lH), 6.47 (d, J = 2.6 Hz, lH), 7.49−7.18 (m, 8H), 7.92 (m, 2H). m/z LCMS (ESI) 462.20 (M + H).

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Supporting Information Available

Analytical methods (HPLC and GC) along with ^{1}H NMR of all intermediates and product cited in this manuscript. This material is available free of charge via the Internet at http://pubs.acs.org.

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