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Development of a Scalable Synthesis of Mevidalen (LY3154207), an Orally Available Positive Allosteric Modulator of the Human Dopamine D1 Receptor

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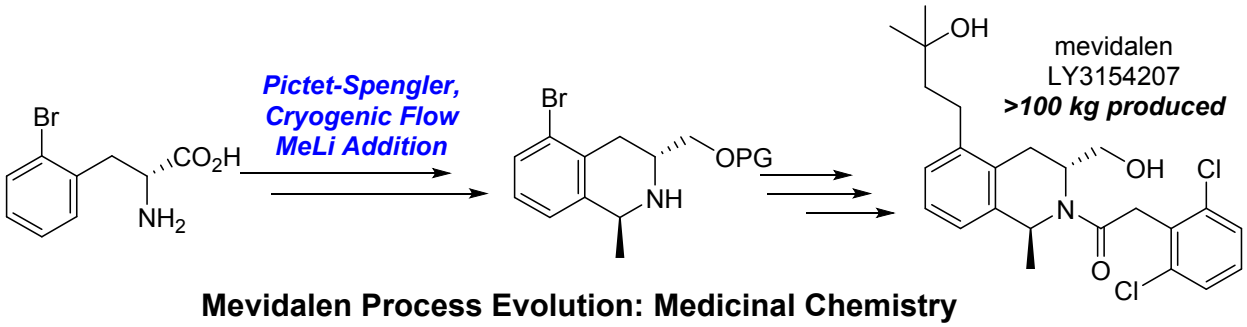


Mevidalen Process Evolution: Medicinal Chemistry Through three GMP Production Campaigns!

TOC Graphic

ABSTRACT The evolution from early medicinal chemistry to large-scale production of the chemical synthesis of Lilly D1 positive allosteric modulator (PAM) mevidalen (LY3154207) and its hydroxybenzoate cocrystal is outlined. The issues and steps taken to resolve them are outlined across several generations of synthesis, including unexpected issues that arose during cryogenic addition of MeLi to a key imine intermediate and the use of flow chemistry to enable the large-scale production. Ultimately a process that was used to deliver >100 kg of API to support ongoing clinical trials is described.

KEYWORDS: continuous processing, flow chemistry, tetrahydroisoquinoline, mevidalen, process development, co-crystal, D1 PAM, LY3154207.

1. INTRODUCTION

Activation of the D1 receptor holds significant promise for the treatment of several neurological disorders. The positive allosteric modulation approach to increase D1 receptor activity is especially promising since it has the potential to address several issues associated with known D1 receptor agonists. Binding at an allosteric site of the D1 receptor potentially addresses pharmacological selectivity issues associated with orthosteric agonists, and also provides an opportunity to address the chemical stability issues of some known D1 agonists by requiring a different pharmacophore. Additionally, the more physiologically relevant mode of action of a D1 PAM may result in a lower propensity for overstimulation and tolerance development, as well as a potentially better safety profile.[1] For those reasons the D1 positive allosteric modulator mevidalen (LY3154207, **3**) and mevidalen hydroxybenzoate (**3•HBA**) is currently in phase 2 development by Eli Lilly and Company for the treatment of Lewy body dementia (PRESENCE, NCT03305809).[2]

As part of the journey of this molecule from early discovery chemistry through preclinical toxicology and ultimately into patients, significant investment was required to enable the supply of material at sufficient scale meeting the relevant quality standards. This article highlights the

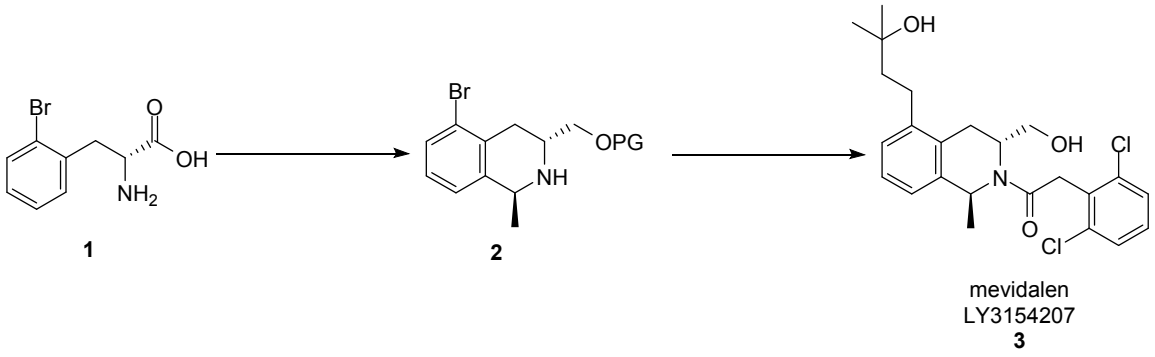
evolution of our synthetic chemistry strategy for this molecule from early discovery to phase 2 clinical testing.

2. DISCUSSION AND RESULTS

In the first part of this account, focus will be on the synthesis of intermediate **2** (Scheme 1). The second part will discuss the conversion of **2** to **3** and its 4-hydroxybenzoic acid (HBA) co-crystal (**3•HBA**).

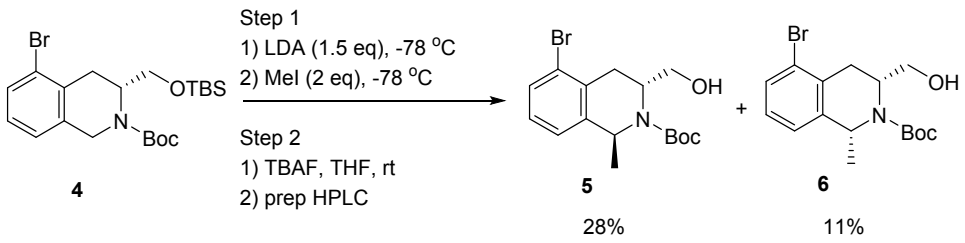
2.1. Discovery Chemistry Synthesis of **2**.

Our overall strategy for the synthesis of **3** involved two main phases: the synthesis of an intermediate that already had key structural features installed and would allow access to a variety of potential structure-activity relationship (SAR) analogues[1] and the conversion of this intermediate to **3** (Scheme 1). Intermediate **2** was identified as being capable of achieving both goals.



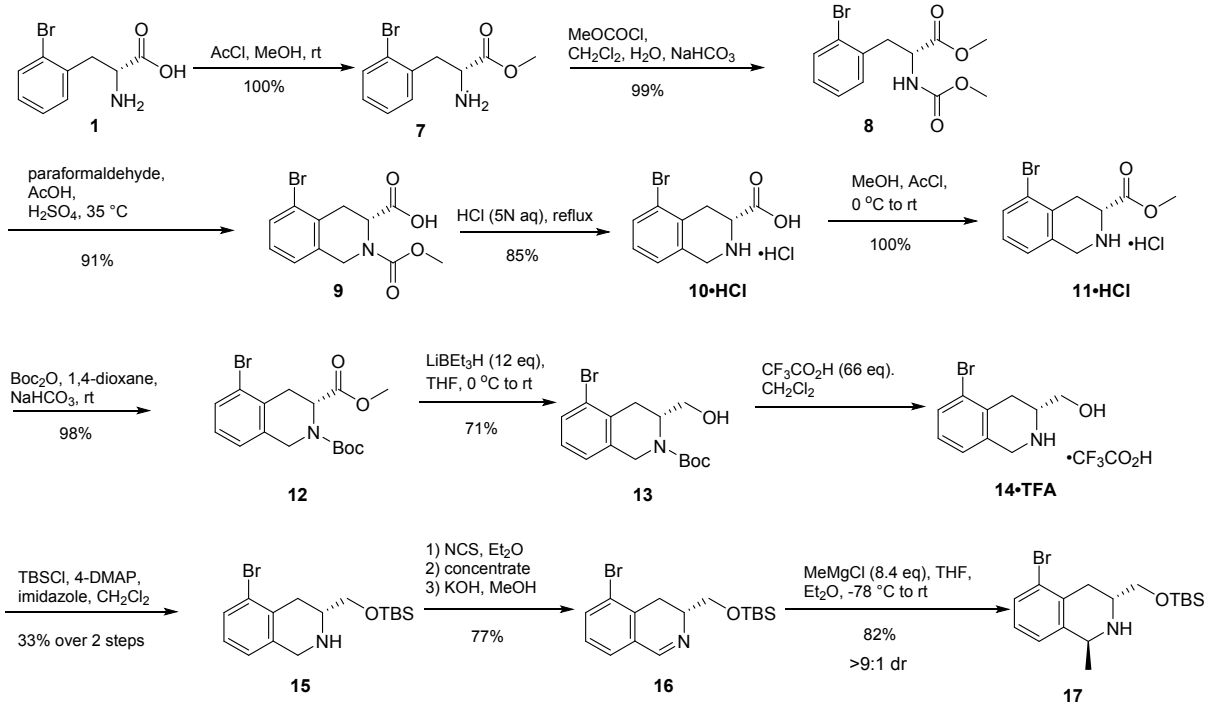
Scheme 1: Overall synthetic strategy for mevidalen (LY3154207, **3**).

Early medicinal chemistry routes to analogous compounds that preceded **3** in our SAR relied on deprotonation of a Boc protected tetrahydroisoquinoline (THIQ) with LDA and subsequent trapping with MeI to install the C-1 methyl group. This approach was unattractive for large scale work for several reasons, including the cryogenic conditions employed, poor diastereoselectivity and difficult isomer separation. When attempted on relevant substrate **4** (Scheme 2), a mixture of diastereomers and unconsumed starting material was obtained. This mixture could only be separated by deprotection and preparative HPLC affording the desired diastereomer **5** in 28% yield over the 2 steps.



Scheme 2: Early approach to installation of C-1 methyl group**.**

Efficient installation of the C-1 methyl group was one of the key route issues that needed to be addressed and early work focused on alternate methods. Ultimately, the benzylic oxidation to form imine **16**, followed by addition of MeMgCl at low temperature allowed the highly diastereoselective installation of the C-1 Me group (Scheme 3).[3]



Scheme 3: Initial discovery chemistry route to intermediate **17.**

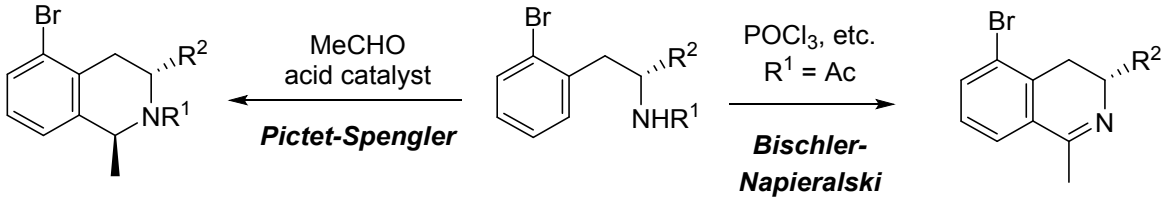
Synthesis of **17** began with (*R*)-2-bromophenylalanine (**1**). Esterification followed by methyl carbamate formation afforded the fully protected **8**, and the THIQ ring was subsequently formed through a Pictet−Spengler reaction[4] (Scheme 3). Over several steps, **9** was converted to imine **16** after *N*-chlorination and base-mediated dehydrohalogenation.[5] Finally, addition of MeMgCl in diethyl ether to this imine delivered **17** with good *trans* diastereoselectivity (>9:1 dr).[3]

This intermediate was prepared in 11 overall steps and 11% overall yield. While many of the steps were high yielding and gram quantities were delivered for early SAR studies, there were many arguably unproductive protecting group manipulations with potential opportunities to shorten the sequence and eliminate numerous chromatographic separations. Additionally, amine **17** is an oil which would present handling, isolation and potential stability challenges at this key hold point in the synthesis.

2.2 Preclinical toxicology route to 2.

In order to prepare **3** (LY3154207) in quantities sufficient for preclinical toxicology studies (ca. 170 g), the initial focus was on reducing the number of chromatographic purifications, streamlining the protecting group manipulations and installing the C-1 Me group as part of the cyclisation strategy towards this key intermediate. While one of the key issues had been resolved, and the methyl group installation afforded good *trans*-selectivity and retained the ee of the starting amino acid throughout, the synthesis was longer than necessary with too many protecting group manipulations.

Only minor changes were made to the first two steps and early development activities focused on attempts to install the methyl group as part of the skeletal construction using Bischler-Napieralski or Pictet-Spengler approaches (Scheme 4). If this could be achieved, there was potential to eliminate both the early carbamate protection step and the 2-step methyl group introduction that occurred at the end of this sequence.



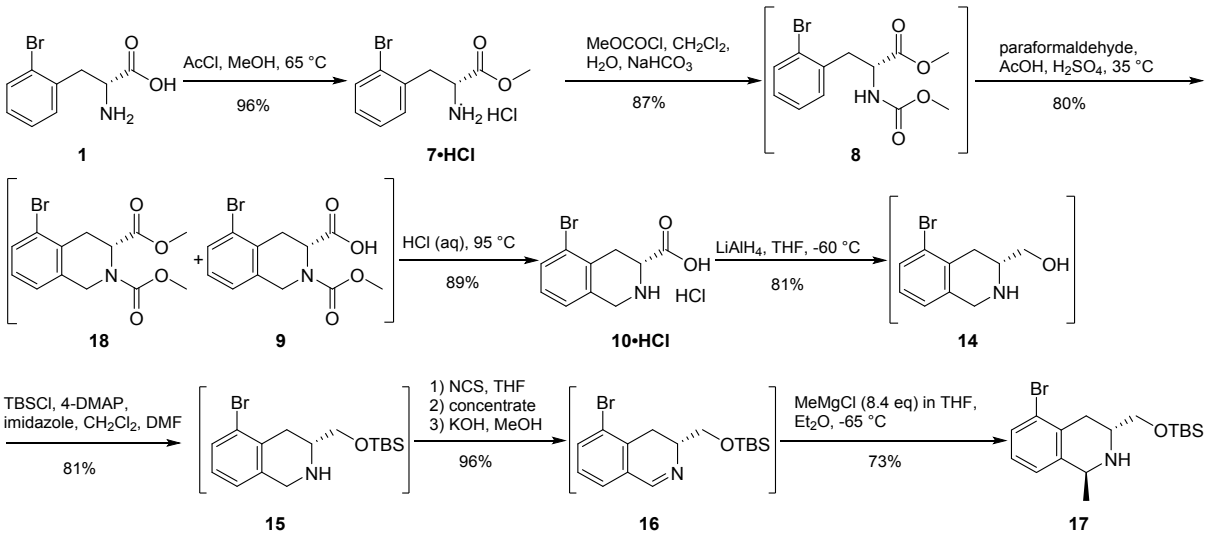
Scheme 4: Strategies for the introduction of the C-1 methyl group during cyclisation**.**

Many attempts were made to perform the Pictet-Spengler cyclisation using acetaldehyde in place of formaldehyde ($R^2 = CO_2Me$, R^1 = H, Boc, CO_2Me) but in no case was the desired cyclisation product formed, even in small quantities.

Attempts to form the imine directly through a Bischler-Napieralski type cyclisation were equally unsuccessful under numerous conditions although the cyclisation as reported by Larsen and co-workers[6] performed reasonably well on gram scale using phenylalanine methyl ester as a model substrate. No further action was taken with this potentially promising route, as we felt that significant additional optimization would be required to make it viable. Instead, we focused on streamlining the synthesis through improved selection of protecting groups. These studies revealed that the protecting group on nitrogen was extremely important for the Pictet-Spengler reaction as it needed to be stable under the acidic conditions; after numerous attempts with other groups, it was clear that the methyl carbamate that was originally employed in the first-generation medicinal chemistry synthesis (Scheme 3) was the best in terms of yield and acid stability.

During the Pictet-Spengler reaction partial hydrolysis of the methyl ester occurs, but the mixture of the acid and ester can be telescoped into the carbamate deprotection (Scheme 5). Treating this mixture with aq. HCl serves to remove the carbamate and completes the ester hydrolysis allowing the hydrochloride salt (**10**) to be isolated by filtration in 89% yield.

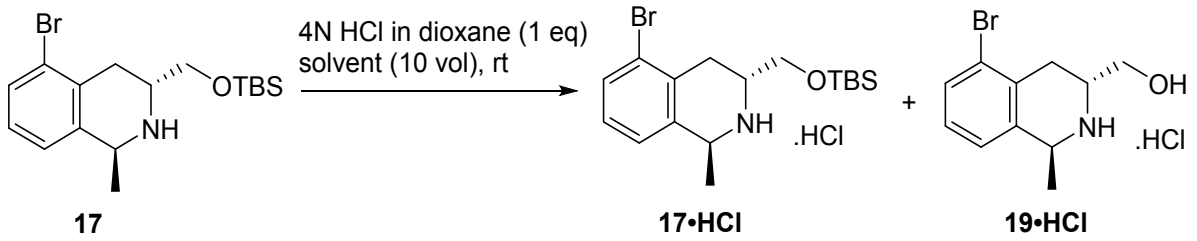
Reduction of the carboxylic acid was achieved using lithium aluminium hydride (LAH) and the crude amino alcohol **14** can be telescoped into the TBS (*tert*-butyl dimethylsilyl) protection. Oxidation to imine **16** was achieved in THF rather than diethyl ether, which was originally used and was not desirable for work at scale, and subsequent addition of Grignard reagent MeMgCl afforded **17** with good levels of diastereoselectivity. Despite significant effort, including purification of **16** via silica gel chromatography, it was not possible to reduce the amount of Grignard used in this final step below 8.4 equivalents.



Scheme 5: Second generation discovery chemistry route to **17**.

This streamlined route afforded **17** in 27% overall yield and 8 steps compared to the first-generation synthesis (11 steps, 11% overall yield) with all nine chromatographic purifications removed over the course of the route through telescoping or isolation of products as solids. The final step required chromatographic purification primarily because **17** is an oil and all efforts to purify it by other means were unsuccessful. This route was used to deliver 3 kg of **17** at one of our large-scale partners.[7] The fact that **17** was an oil presented a number of storage, handling and purification challenges which we sought to obviate through preparation of a stable salt. Hydrochloric acid was the only acid examined at this stage and a study of solvents showed that in most solvents, a significant amount of silyl deprotection occurred, but by using iPrOAc or PhMe as solvent, the hydrochloride salt (**17•HCl**) could be isolated in high yield with no desilylation product (**19•HCl**) observed (Table 1). Recognizing that exposure of the slurry to atmospheric moisture during the salt formation could potentially cause desilylation to occur during larger scale processing, the vials were then left open to atmosphere overnight; in a few solvents significant deprotection began to occur. As a final attempt to assess potential risk, a small amount of water was added to each salt formation. This caused significant dissolution of the solids, but in PhMe and iPrOAc essentially no deprotection was observed. The solid isolated was not appreciably hygroscopic once collected by filtration and this served as a suitable way to store this intermediate during the discovery campaigns.

Table 1. Formation of **17•HCl**.[a]



17 **17•HCl** **19•HCl**

Entry	Solvent	Ratio 17:19 under N_2 [b]	Ratio 17:19 open to air [c]	Ratio 17:19 (+ 1 drop water) [b]
1	iPrOAc	100:0	100:0	100:0
2	PhMe	100:0	100:0	100:0
3	iPrOH	100:0	44:56	28:72
3	MTBE	100:0	100:0	85:14
5	2-MeTHF	100:0	38:63	43:57
6	MeCN	100:0	6:94	6:94

[a] Ratios determined by HPLC analysis. [b] obtained after 1 h. [c] obtained after 19 h.

Head-to-head comparison showed that the iPrOAc crystallization conditions were able to purge some impurities contained in the freebase, allowing a batch of **17** with 94.8% purity by HPLC to be upgraded to >98% purity during the salt formation. These conditions were selected for further use.

2.3. Process Development Synthesis of 2.

As mevidalen entered clinical development, a route that could provide >100 kg of **17**, or an equivalent intermediate, was required. While alternate routes would be sought, it was felt that the discovery route (Scheme 5) was suitable for this stage of development since the unnecessary protecting group manipulations had been removed from the route. In order to prepare the synthesis route for production scale, attention was turned to improvement of the individual steps in the sequence. Since entering clinical development, three discrete manufacturing campaigns using this technology have taken place over several years to fund our clinical studies. The following section describes the development chemistry and the results from these campaigns.

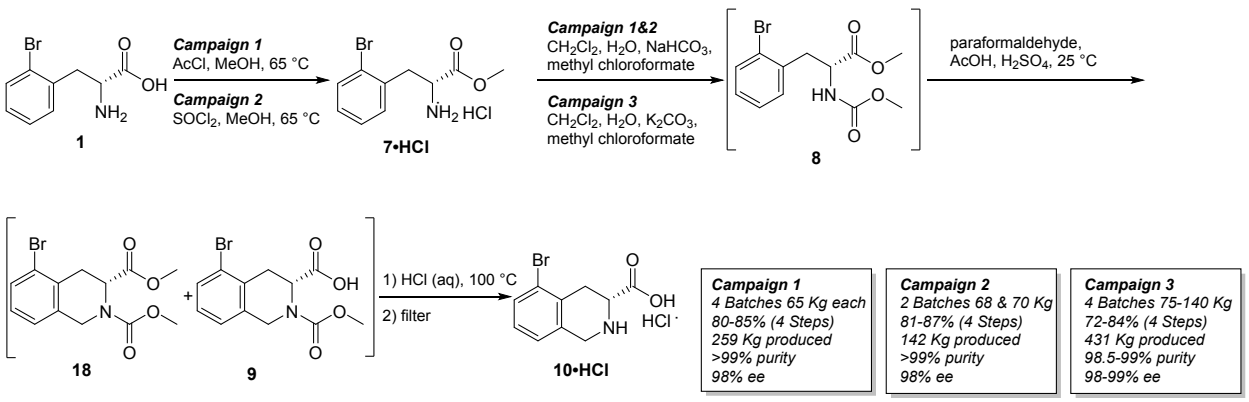
2.3.1 Steps 1–4 (Synthesis of 10•HCl)

The production route did not significantly differ from the previous route over the first four steps, only minor changes to stoichiometry and workups were implemented to afford hydrochloride **10•HCl**. These steps were robust and tolerated residual solvents from previous processing steps, enabling the sequence to be fully telescoped.

While esterification of **1** had performed well in the first manufacturing campaign using the conditions described in the discovery route, the long reaction time (typically ~20 h) and high MeOH volumes prompted additional optimization work. It was found that by replacing acetyl chloride with thionyl chloride (Scheme 6), the reaction could achieve complete conversion in 3 h at laboratory scale and could be performed at higher concentration (4 V; V = liters of solvent per kg of limiting reagent) with no stability issues over 44 h. In the methyl carbamate formation (step 2), a biphasic mixture of CH_2Cl_2 and aq. $NaHCO_3$ was used in first two campaigns, which required 20 V CH_2Cl_2 and 12 V water.[8] Attempts to reduce these volumes lead to lower purity **8**. It was assumed that the low aqueous solubility of $NaHCO_3$ drove the use of large volume of solvent and so various bases were then screened to replace $NaHCO_3$. K_2CO_3 showed comparable results and allowed the overall solvent volume to be reduced from 32 V to 8 V in the subsequent campaign. No further changes were made in the 3rd campaign when applying this four-step sequence.

Optimization of the Pictet-Spengler reaction centered around practical improvements and ensuring robustness. Initially the workup used 40 V of solvent, so efforts were made to lower the reaction solvent volume to enable waste reduction in the workup. Indeed, it was possible to reduce the volume from 7.5 V AcOH and 2.5 V sulfuric acid to 3 V and 1.5 V, respectively. This modification worked well, although the yield of one of the production runs in campaign 3 was reduced due to difficulty in the aqueous separation (72% vs average yield of 82% for other batches in campaign 3).

Little change was made to the acidic hydrolysis to form **10•HCl** (Step 4), but several changes were made to the workup and isolation. Stress testing showed both acetic acid and sulfuric acid could be carried through from the previous step with no detrimental effects. The previous route (section 2.2) involved evaporation to dryness after extraction to afford a sticky solid and, in turn, a heterogeneous reaction mixture. It was found that the extract from the Pictet-Spengler reaction could be taken directly into this hydrolysis thus alleviating the issues of handling the sticky solid, which would have proven challenging on scale.



Scheme 6: Production process for **10•HCl.**

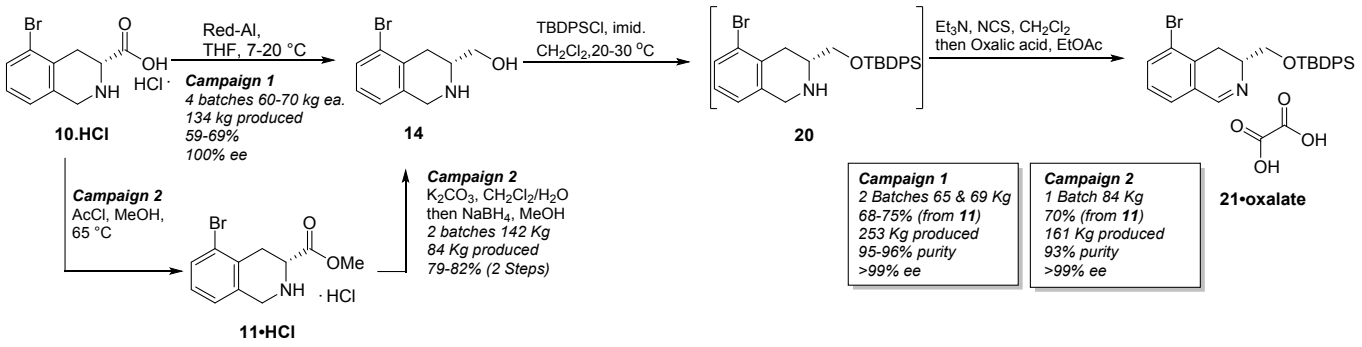
At the end of these four telescoped steps, the material was obtained by filtration in 97–98% purity as determined by HPLC, and it was found that this could be increased to >99.0% HPLC area by slurrying the solids in CH_2Cl_2.

2.3.2 Steps 5–7 (Synthesis of 21•oxalate)

The reduction of carboxylic acid **10•HCl** to alcohol **14** was achieved at laboratory scale using LAH but this has considerable drawbacks on larger scale.[9] We sought to eliminate the use of LAH and also improve the workup to avoid issues associated with the aluminium residues that are generated. A survey of hydride-based reductants that were capable of the direct transformation of **10** to **14** was performed and Red-Al® was found to be a good replacement for LAH (Scheme 7), with borane complexes generally affording lower purity profiles by HPLC. Freebasing the starting material added several additional processing steps and did not improve the reaction profile and so was deemed unnecessary, even though the additional acid would quench the reductant. The corresponding methyl ester (**11**) reduced cleanly with Red-Al®, but it proved difficult to control unwanted hydrolysis of this ester, hence it was decided to proceed via direct reduction of **10•HCl**. One of the major issues with performing an aluminium hydride reaction on scale is the quench and subsequent workup. In our discovery route, a Fieser workup was employed allowing the aluminium residues to be removed by filtration.[10] It was found that simply quenching the reduction with 10 V of saturated aq. NaCl gave good layer separation with minimal product loss to the aqueous layer. Addition of *n*-heptane anti-solvent then caused precipitation of **14** from the reaction mixture, thus significantly simplifying the workup and isolation. The modified process using Red-Al® was used in campaign 1 to prepare 134 kg of **14**.

Despite Red-Al® having been successfully applied to a large-scale preparation of **14**, a significant impurity that arose was the debrominated side product. Pilot reactions suggested that this could be avoided by using sodium borohydride for reduction of the methyl ester (**11**), but it was not possible to avoid partial ester hydrolysis during the Pictet-Spengler reaction. Therefore, we chose to implement a re-esterification step in later campaigns, with the benefits gained in the reduction outweighing the disadvantages of an additional step (Scheme 7).

The conditions that were used to prepare **7•HCl** from **1** (Scheme 6) were equally applicable to the formation of **11•HCl** from **10•HCl** and successfully applied in campaign 2 (Scheme 7). It was found that **11**, obtained after free basing in CH_2Cl_2/aqueous K_2CO_3 could be solvent swapped into methanol and reduced cleanly with portion wise additions of $NaBH_4$. Thermal hazard analysis of the borohydride reduction revealed a high adiabatic temperature rise (89 °C) and a maximum heat flow of 455 W/kg. Portion wise addition of $NaBH_4$ was used to help enable the safe venting of hydrogen gas generated during the addition. This new process was used to deliver 161 kg of **21•oxalate** in our second production campaign.



Scheme 7: Production process for **21•oxalate.**

The protection of the primary alcohol, as described in the discovery synthesis, posed a few issues; firstly, DMF was used as a co-solvent in the protection, leading to issues in its removal at scale. Secondly, as described above (section 2.2), the TBS group was prone to spontaneous deprotection under certain conditions, which suggested that it might be advantageous to find a more stable alternative. Finally, we reasoned that diastereoselectivity could be potentially improved in the organometallic addition to imine **16** if a more sterically encumbering protecting group were used. The bulkier and more stable *tert*-butyldiphenylsilyl (TBDPS) group was considered and so a small batch was carried out to test the organometallic addition to imine **21**. While the TBPDS group

fulfilled the majority of these criteria, it was not clear whether it had a positive impact on diastereoselectivity in comparison to factors such as solvent and additive, however, the advantages outlined above were sufficient and so TBDPS was selected in place of TBS. For the protection step, a small solvent screen showed that THF gave a heterogeneous reaction mixture and lower assay purity while CH_2Cl_2 and DMF gave homogeneous mixtures and higher assay purity. As a result, CH_2Cl_2 was selected as this was a suitable solvent for telescoping into the subsequent oxidation reaction. Attempts to replace imidazole with Et_3N or iPr_2NEt met with little success, affording slower reactions and low *in situ* purity. Initial studies showed that this mixture could be directly telescoped into the oxidation step and that an aqueous workup between these steps did not improve the outcome and was therefore unnecessary. In the largest scale discovery synthesis (Scheme 5), THF was used as solvent, with KOH/MeOH as base/cosolvent, but the reaction also performed well in CH_2Cl_2 allowing the telescoping of the protection directly into the oxidation. The oxidation occurs in two discrete stages: chlorination followed by elimination to the imine. By adding triethylamine and cooling to 0 °C before addition of NCS, a significant improvement in assay purity was achieved (92.0–95.6% compared to the original procedure, which gave 81.6% purity).

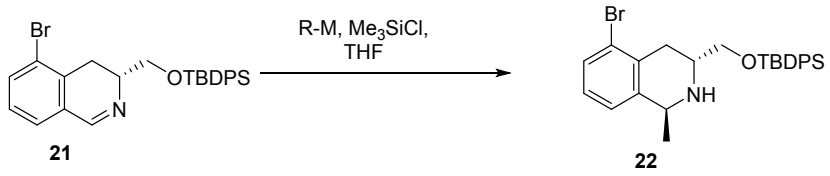
Aqueous workup served only to remove salts and excess base. Little improvement to the impurity profile was realized. We therefore sought a strategy to isolate the imine that would provide good impurity control going into the final step of the sequence. Initial studies showed that the oxalic acid and HCl salts formed easily, but that the wet cake of the oxalate salt was more stable and was therefore selected for additional study. This salt (**21•oxalate**) was highly soluble in CH_2Cl_2 and THF, but EtOAc gave suitable solubility for crystallization and excellent impurity rejection. The major impurities that were rejected during this crystallization were the isoquinoline that was formed by overoxidation of **21** and the dehalogenated imine, which was believed to be formed during the Red-Al® reduction and is further controlled in the isolation of **22**.

2.3.3 Steps 8–9 (Synthesis of 22)

With a stable imine salt in hand, where the input purity can be highly controlled, addition of organometallic reagents was studied. One of the major issues with the original procedure was that a significant excess of Grignard reagent was required to achieve full conversion and the reaction was quite slow, taking >16 h to reach completion. Suspecting that the imine was not especially

electrophilic,[11] a survey of potential activators was performed. From this study it was clear that many of the activators studied did not accelerate the reaction, however the use of chlorotrimethylsliane (TMSCl) or BF_3•OEt_2 accelerated the reaction but resulted in reduced diastereoselectivity (3:1), presumably through formation of an iminium ion intermediate.[12,13] Increasing the reaction temperature also accelerated the reaction, but significantly decreased the assay purity of the product. Given the relatively clean reaction profile, (TMSCl) was selected for further study (Table 2) and it was found that by lowering the temperature to -60 °C improves the diastereoselectivity (Entry 2) and this can be further increased by using methyllithium as the organometallic reagent (Entry 3).

Table 2: Optimization of organometallic addition to **21**.



21 **22**

Entry	R-M	TMSCl (equiv.)	Solvent volume	Temp	22[a]	21 [a]	dr [a]
1	MeMgBr (5 equiv.)	1.1	20 V	-10 °C	70%	17%	3:1
2	MeMgBr (5 equiv.)	1.1	20 V	-60 °C	59%	4%	5:1
3	MeLi (5 equiv.)	1.1	20 V	-60 °C	57%	7%	12:1
4	MeLi (5 equiv.)	1.5	20 V	-60 °C	75%	5%	10:1
5	MeLi (5 equiv.)	0.5	20 V	-60 °C	25%	10%	n.d.
6	MeLi (5 equiv.)	2.0	20 V	-60 °C	68%	6%	6.9:1
7	MeLi (4 equiv.)	1.5	20 V	-60 °C	78%	3%	12:1
8	MeLi (3 equiv.)	1.5	20 V	-60 °C	80%	3%	9.2:1
9	MeLi (2 equiv.)	1.5	20 V	-60 °C	85%	1%	10:1
10	MeLi (2 equiv.)	1.5	5 V	-60 °C	57%	1.3%	8.9:1
11	MeLi (2 equiv.)	1.5	10 V	-60 °C	68%	3%	7.1:1

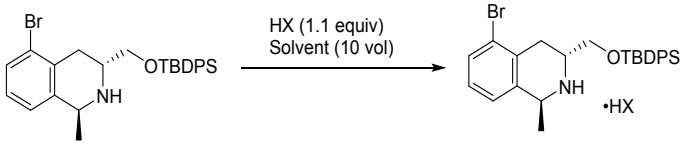
12	MeLi (2 equiv.)	1.5	15 V	-60 °C	65%	3%	8.2:1

a) Determined by HPLC analysis.

The best conditions from this study were those in entry 9, but it was preferred to perform the reaction at higher concentration for efficient use of the available reactors, and so the conditions employing 10 V of solvent were selected (entry 11) and it was found that the purity profile could be increased by further decreasing the temperature of the reaction. Additionally, the oxalate salt could not be employed directly in the organometallic addition but must be free based with aqueous potassium carbonate in CH_2Cl_2 prior to the organometallic reaction with water content below 0.1% being acceptable for forward processing.

As with compound **17** (section 2.2), it was desirable to prepare **22** as a salt that could be readily isolated with additional opportunity to improve the purity of the material, especially diastereomeric purity. The HCl and oxalic acid salts were examined first since the former had successfully been used at this stage in the discovery synthesis and the latter formed a salt with imine **21**. Using a sample of **22** that contained significant amount of the undesired diastereomer (3:1 dr) it was found that in EtOAc, HCl formed a salt which improved purity, but did not change the dr, while oxalic acid did not form a precipitate. As such, a screen of 17 acids and 5 solvents was performed. Only a small number of combinations formed solids (Table 3), but the combination of EtOAc and sulfuric acid afforded a significant improvement in the diastereomer ratio. On further analysis of the salt formed from these conditions, it became clear that a hemisulfate salt had formed (**22•Hemisulfate**).

Table 3. Selected acids screened in the formation of salts **(22•X)**



22
dr 3:1

22•HX

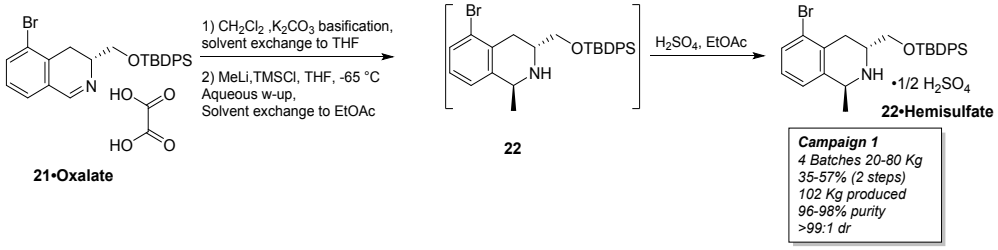
Solvent	Acid		
	D-(+)-DBTA	D-(+)-malic acid	H_2SO_4[c]
2-propanol	-[a]	11.6:1	-[a]
EtOAc	4:1	-[a]	37:1

Acetone	**-** [a]	**-** [a]	**10:1**
MeCN	**-** [a]	**-** [a]	**6.1:1**
PhMe	**-** [a]	**8.5:1** [b]	**-** [a]

Diastereomeric ratios of isolated salts, determined by HPLC. a) No solid formed b) 5 V of solvent used c) 0.55 equiv.

To robustly remove impurities and undesired diastereomer we sought to recrystallize the hemisulfate salt. Analysis of a small number of solvents showed that THF/EtOAc was a suitable solvent system for the crystallization to improve purity and dr, allowing a pilot batch with 93% assay purity and 15.6:1 dr to be upgraded to 96% assay purity and 117:1 dr.

This sequence was then applied in the production of 102 kg of **22•hemisulfate** (Scheme 8).

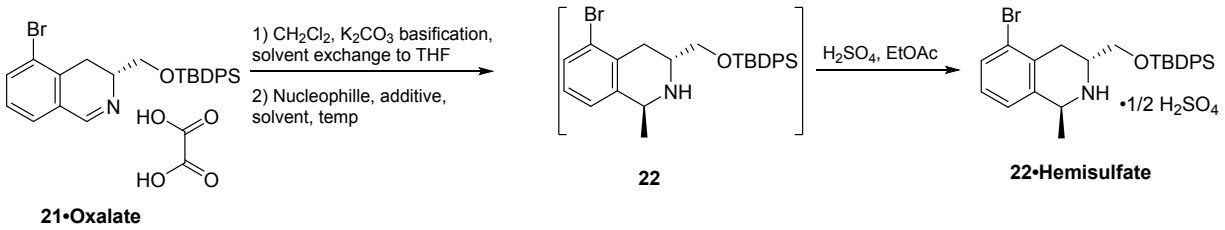


Scheme 8: First production campaign for **22•hemisulfate**.

The first clinical supply manufacturing campaign utilized batch mode cryogenic conditions for the addition of MeLi to imine **21**. While a 20 kg batch performed as expected (Table 4, Entry 1), scaling the addition reaction to 80 kg lot size resulted in a substantial increase in impurities reaction profile and isolated yield (Entry 2). In order to complete the first campaign to deliver **22•hemisulfate**, the batch size was limited to 40 kg and material was processed accordingly (Entries 3–6).

Given the unexpectedly poor performance of the MeLi at 80 kg scale, Grignard reagent addition was revisited in anticipation of the second clinical supply manufacture. It was shown that MeMgBr could be successfully utilized in batch mode under non-cryogenic conditions to afford acceptable results (Entry 7). However, superior results were obtained by conversion of the batch MeLi process to flow mode (Entry 8).

Table 4: Performance of C-1 methyl installation across campaigns 1 & 2.



21•Oxalate **22** **22•Hemisulfate**

Entry	Campaign	Input (kg)	Nu	Mode	Solvent	Additive	Temp	dr[a] of **22**	yield	dr [a] **22• Hemisulfate**
1	1	20	MeLi	Batch	THF/MeTHF	TMSCl	-75 °C	89:11	58%	99.7:0.3
2	1	80	MeLi	Batch	THF/MeTHF	TMSCl	-75 °C	87:13	35%	99.8:0.2
3	1	40	MeLi	Batch	THF/MeTHF	TMSCl	-75 °C	87:13	54%	99.8:0.2
4	1	40	MeLi	Batch	THF/MeTHF	TMSCl	-75 °C	88:12		
5	1	40	MeLi	Batch	THF/MeTHF	TMSCl	-75 °C	87:13	54%	99.9:0.1
6	1	40	MeLi	Batch	THF/MeTHF	TMSCl	-75 °C	87:13		
7	Demo	0.29	MeMgBr	Batch	PhMe	none	37 °C	82:18	60%	99.9:0.1
8	2	112.8	MeLi	Flow	THF/MeTHF	TMSCl	-75 °C	86:14	70%	99.4:0.6

a) Determined by HPLC analysis.

Analysis of the 80 kg batch record revealed that the MeLi addition time had been almost 4 h instead of the usual 1 h. Subsequent studies confirmed that the addition product was not stable in the presence of MeLi under the reaction conditions. This caused us to consider continuous flow conditions for the reaction, since under flow conditions the amount of time the product spent in the presence of MeLi was significantly reduced and consistent. Continuous flow also offered superior heat and mass transfer properties upon scale-up, which afforded consistent reaction performance between the lab model and production.

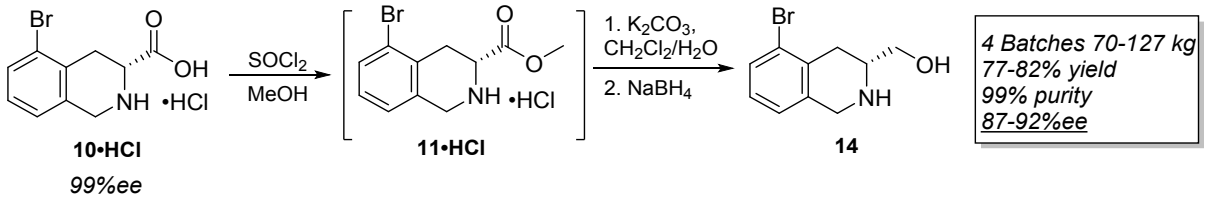
A number of factors were studied in the development of a flow process capable of delivering **22•hemisulfate**; the concentration of the feed solution of **21** was studied and it was found that using 10 V of THF gave the best assay purity product at -70–80 °C and it was found that 2 equivalent of MeLi in 2-MeTHF was sufficient. Performing the reaction at -10–0 °C worsened the dr (5:1), that performing the reaction at -78 °C and -40–50 °C both gave similar diastereoselectivity (>6:1). The reaction was ultimately performed at -78 °C since it was easier to maintain a constant

temperature using a dry-ice bath. Indeed, application of the flow chemistry performed well at 113 kg scale, affording 70% yield and reasonable diastereoselectivity (86:14 dr) which was improved to >99:1 through the salt formation. In total, this new process afforded 101 kg of **22•hemisulfate**.

2.4 Issues encountered during Campaign 3

A further campaign to prepare 344 kg of **22•hemisulfate** was required to support the production of 100 kg of **3** for advancing clinical trials and so this sequence was executed again with some changes to the process based on issues that were encountered in the previous campaigns and incorporating the flow chemistry solution for the critical MeLi addition. The following paragraphs outline those issues, the changes made in response and their implementation.

While most of the process was unchanged from campaign 2, a change was made to the esterification (from AcCl to $SOCl_2$) to afford **11•HCl** to improve reaction rate (Scheme 9). As with step 1, this afforded **11•HCl** in high yield. While freebasing this HCl salt with K_2CO_3 can cause hydrolysis of **11** back to **10** in MeOH, this issue was obviated in CH_2Cl_2 and so a solvent swap from MeOH to CH_2Cl_2 was performed before the freebasing step. This ester can then be cleanly reduced to **14** by portion wise addition of $NaBH_4$ to control the evolution of hydrogen during the reaction.



10•HCl
99%ee

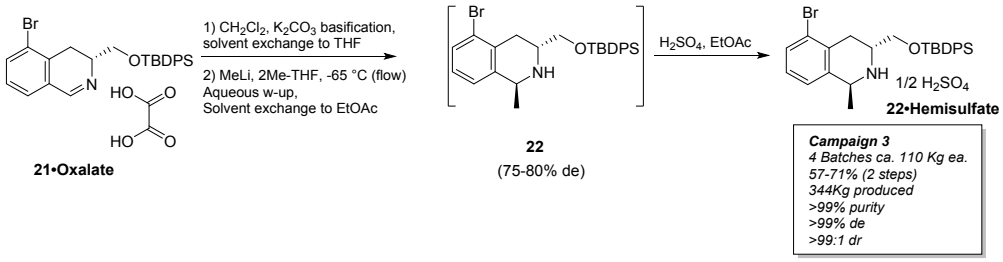
11•HCl

14

Scheme 9: New process for preparation of **14**.

While the new procedure for reduction avoided aluminium hydride reagents, some issues were encountered in manufacture. The enantiomeric excess was eroded from ca. 98% to ca. 91% over the course of esterification and ester reduction. It was not determined with certainty which step was responsible, but the enantiomeric purity of **10** was easily ruled out as a possible cause and laboratory studies were unable to replicate the erosion during the borohydride reduction step, which may implicate the ester formation. Laboratory scale work showed that the ee of the material could be improved in the final salt formation to afford **22•hemisulfate** and so the ensuing steps

were performed per the normal process with no new modifications, until the final purification (Scheme 10).



Scheme 10: Production of **22•hemisulfate** (Campaign 3).

Additional screening work in batch mode and flow determined that TMSCl was not necessary in order to achieve high dr when MeTHF was used as solvent at low temperature. It is not understood if this is purely a solvent effect or what the precise role of TMSCl was when used in conjunction with MeLi. The third pilot plant campaign proceeded without TMSCl and used pure MeTHF as reaction solvent. Four batches, each consuming ~110 kg of **21** were conducted; the crude reaction profiles were generally consistent and the in-situ purity of **22** ranged from 84.5–87.1 HPLC area% with the diastereomer present at 10.1–11.3 HPLC area% (dr = 7.0–8.6:1). Cryogenic conditions were readily obtained at plant scale by submerging a plug flow reactor (PFR) in a cryogenic bath and using dry ice and ethanol to cool the process (Figure 1).

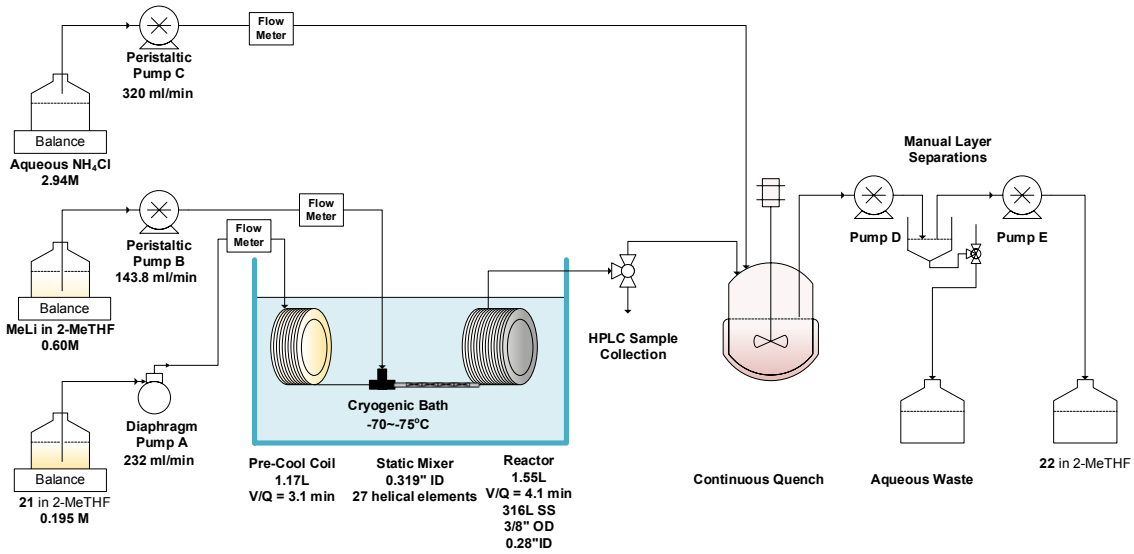


Figure 1. The process flow diagram of the experiment with continuous quench and phase separation.

During the isolation of **22•hemisulfate** it was found that low ee and low de were encountered in the isolated solids. After a laboratory investigation, it was found that seeding the initial crystallization from EtOAc with 2% (w/w) **22•hemisulfate** was crucial to ensure a consistent partial rejection of diastereomer and enantiomer. In the recrystallization from EtOAc/THF, partial dissolution of the crude salt in THF followed by removal of the solid fraction by filtration was implemented. Removal of the solid phase purged most of the enantiomer as scalemic material; antisolvent addition and cooling finished the crystallization of high purity product. Laboratory studies showed that removal of the enantiomer by crystallization appeared to have a kinetic parameter and that aging of slurries of **22•hemisulfate** resulted in reduced chiral purity as the enantiomer began to crystallize out over time indicating that the process was at stochastic risk for low ee if the enantiomer was present at significant levels. For the third manufacturing campaign, **22•hemisulfate** was isolated in yields ranging between 57–71% (corrected for assay and purity) with dr > 99.8:0.2 and ee >99.8%, which were similar quality parameters when compared to the second manufacture. Yields suffered due to the required purge of enantiomer, but the yield from the first batch in particular (57%) was reduced further due to challenges encountered during its purge and potentially dryer hang-up. This new process allowed the production of 344 kg of **22•hemisulfate**.

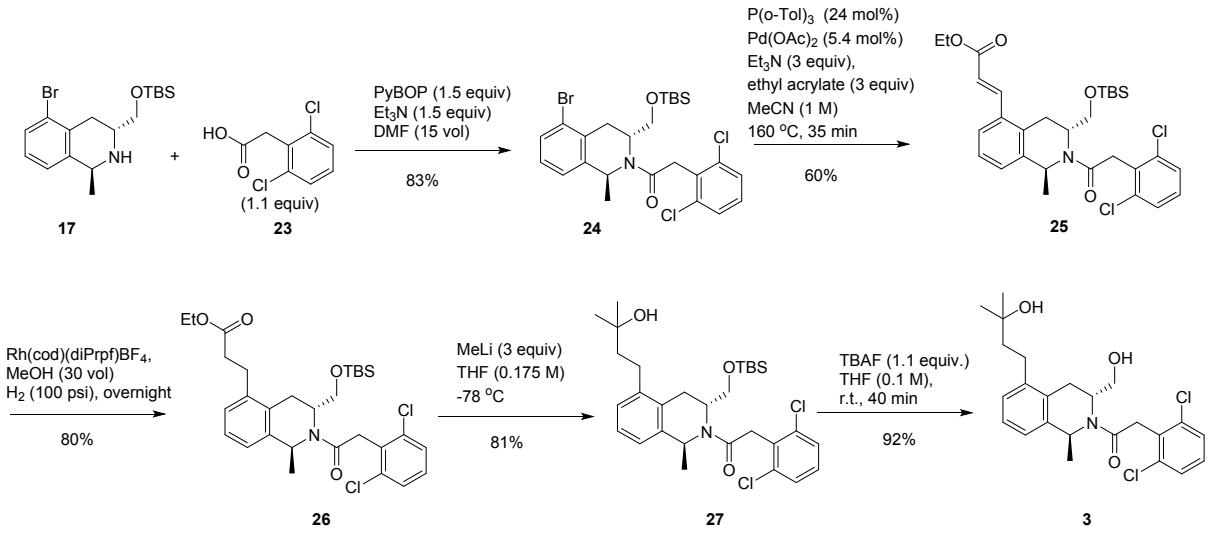
3. Endgame synthesis.

During the discovery phase of this program, the final target compound was **3**. However, development of **3** was complicated by our inability to crystallize it under numerous experimental conditions. Fortunately, we discovered a cocrystal form of **3** that not only possessed excellent solubility but also met the criteria for clinical development. As a result, the 4-hydroxybenzoic acid (HBA) cocrystal (**3•HBA**) has been carried forward into clinical trials and became the final target compound for the process chemistry efforts.[1]

3.1 Discovery Chemistry Synthesis of 3.

The medicinal chemistry conversion of intermediate **17** to **3** was achieved in 5 steps and 30% overall yield (Scheme 11). This sequence was potentially manageable at scale, but there were opportunities to simultaneously shorten the route and remove some of the more challenging steps. For further development, we therefore sought to install the side chain in such a way as to avoid the

unnecessary use of ethyl acrylate (used in the conversion of **24** to **25**) and MeLi (used in the subsequent formation of **26**), by using an alkene with the gem-dimethyl group already installed. We also sought to replace the expensive rhodium catalyst that was employed to avoid dehalogenation. Finally, the Heck coupling (**24** to **25**) was performed at a temperature considerably in excess of the boiling point of the solvent.



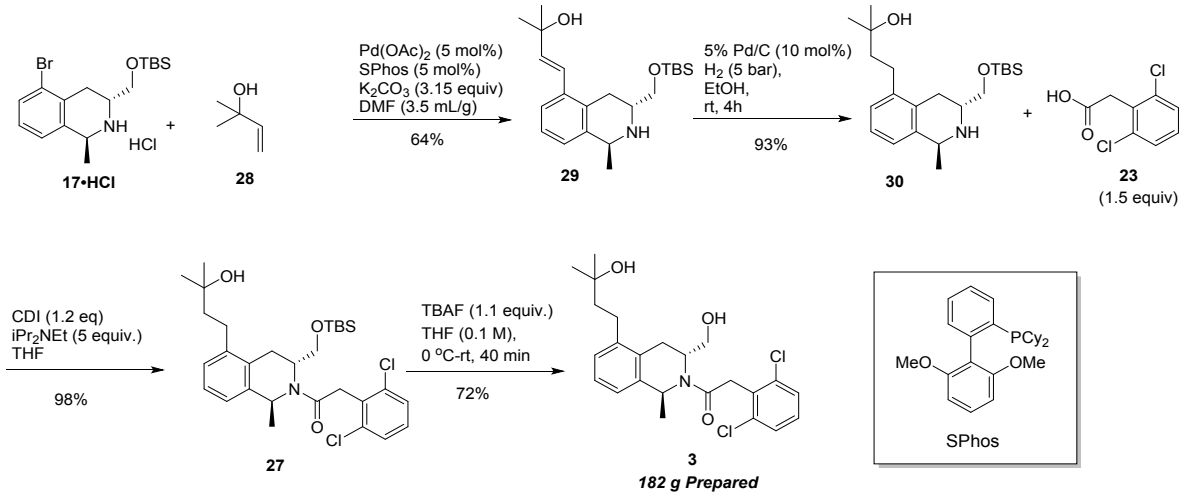
Scheme 11: Initial medicinal chemistry synthesis of 3.

3.2 Preclinical toxicology route to 3

In the medicinal chemistry route, the Heck reaction of aryl bromide **24** was performed after the installation of the amide, which lead to several byproducts due to dechlorination or Heck coupling in the amide portion of the molecule. We felt that if the order of steps could be changed to allow introduction of the amide after this reduction, a less expensive catalyst might be employed. For this reason, the Heck coupling was performed directly on **17** instead (Scheme 12). To shorten the sequence and obviate the use of ethyl acrylate and MeLi, readily available and inexpensive 2-methyl-3-buten-2-ol (**28**) was selected as the coupling partner.

Starting with conditions that were obtained for the same transformation on a different aryl halide during another discovery program a small number of bases were surveyed (iPr_2NEt, Cy_2NMe and K_2CO_3). When using freebase **17**, Cy_2NMe was preferred base, but if **17•HCl** was used directly, potassium carbonate was the superior base, affording **29** in reasonable yield. This Heck reaction performed on compound **24** (Scheme 11) was considerably less efficient as significant

participation of the aryl chlorides was observed. As expected, the alkene reduction could be achieved easily using palladium on carbon at modest pressure. The amide formation was facile using 1,1'-carbonyldiimidazole (CDI) as a simple, inexpensive and non-allergenic[14] coupling agent with easily purged byproducts. Identical TBS deprotection conditions were then employed to generate **3**.



Scheme 12: Second generation discovery synthesis of 3.

3.3. Process Development Synthesis of 3.

The second-generation route was substantially more practical for operation at scale than the first-generation medicinal chemistry route. Several points for development had been identified, and these focused primarily on intermediate isolations and elimination of undesirable reagents and solvents. From this point forward, **22•hemisulfate** (see section 2.3.3) was used as the starting material to fund all development work for the final steps.

While the Heck reaction was suitable for medium scale-work, optimization was merited for further scale-up. Issues included low crude purity after the coupling, phase separation challenges caused by the dark color of both liquid phases during workup, and a considerable amount of solid, which further complicated the separation. By switching from DMF to toluene as the reaction solvent and performing a freebasing step prior to the Heck reaction, a considerably cleaner crude material was obtained. This enabled an effective crystallization of **32** (Scheme 13) after a solvent swap into *n*-heptane. During the initial development phase, it had been observed that the reaction progressed

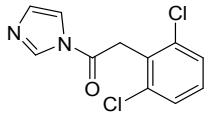
faster with increased temperature. However, during the scale up the highest internal temperature reached in the reactor was 109 °C. Any further attempts to increase the internal temperature by increasing the jacket temperature without reactor pressurization resulted only in more vigorous boiling. These conditions were applied in the first GMP production campaign to prepare 10 kg of **3•HBA**. It became evident that the Heck reaction was slower than desirable on pilot plant scale since the two batches required 63 and 77 h, respectively, of reaction time to achieve the end of reaction specification for conversion.

In the next round of development, in order to speed the Heck coupling reaction rate, the process was performed in a sealed pressure vessel to allow access to higher temperatures. After sealing, the reactor was allowed to self-pressurize with all the pressure being supplied by the toluene vapor pressure since the internal temperature exceeded the atmospheric pressure boiling point. It proved possible to decrease the amount of the palladium acetate and SPhos from 0.03 equivalents to 0.015 equivalents, which served to increase the efficiency of the subsequent palladium scavenging operation. Finally, the amount of the 2-methyl-3-buten-2-ol was decreased from 5 equivalents to 2.5 equivalents and the reaction volume was decreased from 9 to 4.5 V.

The hydrogenation conditions defined during the discovery program were largely suitable for manufacturing scale work. Reaction optimizations decreasing the ethanol solvent amount from 12 to 8 L/kg olefin, use of lower catalyst loading (3 mol% vs. 10 mol%), and isolation of **33** after solvent exchange from to ethanol to heptane to crystallize the product with subsequent isolation by filtration.

The amide formation developed to this point was slow and often required additional charges of CDI to reach completion. A survey of solvents suggested that THF should be retained, as THF balanced speed of reaction, starting material solubility and TBDPS group retention. Reasonable reaction times could be obtained by increasing the amide bond formation temperature from 45 ºC to 65–70 °C. Additionally, the use of EtOAc during the work up with aq. NaOH was of concern due to the potential hydrolysis of EtOAc. This was important because it was shown that a single basic wash was not sufficient to fully hydrolyze the residual acylimidazole intermediate (**31, Figure 2**) and remove residual 2,6-dichlorophenylacetic acid (**23**). Isolation of **34** by solvent evaporation alone lead to significant foaming and potential contamination with **31**. Substitution of

EtOAc with iPrOAc as the extraction solvent enabled the use of multiple basic washes of sufficient duration to hydrolyze **31** and remove **23** while minimizing solvent hydrolysis.



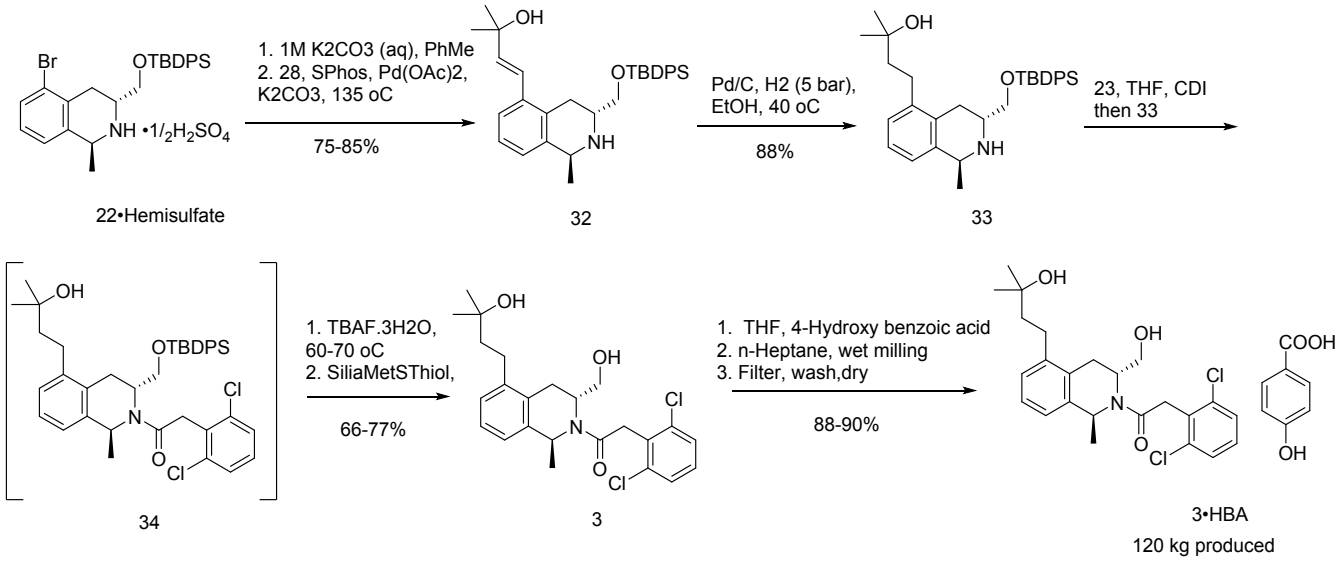
31

Figure 2: Structure of active amide intermediate during amide formation.

Since TBDPS-protected amide **34** was challenging to isolate, attention was paid to developing a process where the iPrOAc workup solution could be telescoped directly into the deprotection step. It was found that by adding TBAF•3H_2O to the crude iPrOAc solution and heating to 60 °C, the deprotection was complete in <1 h at laboratory scale. After aqueous workup, the crude iPrOAc solution was treated with Biotage MP-TMT to obtain material with Pd content within specification. During work to break the co-crystal **3•HBA** with base, crystallization of the free form of **3** was observed for the first time. Subsequently during laboratory-scale Pd scavenging trials, a product solution obtained after removal of the scavenger by filtration through Celite was concentrated to approximately 4 V and allowed to stand overnight at room temperature. During this time, **3** crystallized from solution, which provided an attractive potential impurity control element. The crystalline free form has solubility of 18 mg/mL in iPrOAc. After further study, this crystallization was included in the next GMP campaign. Initial discovery and development of the HBA co-crystal[1] had been conducted with pure API in isopropanol/heptane as solvent but it was now possible to precipitate the free form of **3** directly from the post-work up iPrOAc solution following the TBDPS deprotection. This crystallization efficiently removed the TBDPSOH generated from the deprotection but did not eliminate the tetrabutylammonium salts, so an aqueous wash was employed to remove them before the co-crystal formation to deliver **3•HBA** with suitable purity. Low levels of related substances were adequately purged during the intermediate crystallizations as well as the final **3•HBA** crystallization.

With this development work in hand, the process (Scheme 13) was applied to the manufacture of 53.9 kg of **3•HBA**. A third manufacturing campaign was performed delivering 119.8 kg of **3•HBA** in a very similar manner to the previous campaigns, with optimizations made either to reduce reactor residence times or to reduce solvent volumes in reactions and workups. Compared to the second manufacturing campaign, the Heck coupling was conducted at higher concentration (3.5

L/kg toluene vs. 4.5 L/kg) and higher temperature (130–135 vs. 120–125 ºC). To improve substrate solubility and reaction kinetics, the hydrogenation was performed in ethanol at 40–45 ºC compared to the previous campaign (20–25 ºC). The amide bond formation step was conducted at higher concentration in THF (4.0 L/kg vs. 5.5 L/kg), the telescoped deprotection step utilized less *i*-PrOAc solvent (3 L/kg vs. 4 L/kg) and a more cost effective Pd scavenger was utilized (SiliaMetS Thiol replaced Biotage MP-TMT). Finally, **3•HBA** was wet milled to reduce the particle size.



Scheme 13: Results from third clinical trial supply manufacturing campaign of 3•HBA.

5. Conclusions

In summary, a new process has been developed that enabled the study of mevidalen (**3**) hydroxybenzoate in clinical trials for the potential treatment of Lewy body dementia. The overall yield, step count and production quantities for these campaigns are outlined in Table 5. The initial medicinal chemistry route to **3** was relatively long with some superfluous protecting group manipulations leading to a low overall yield (Entry 1). These were eliminated in the route used to deliver materials for preclinical toxicology experiments, resulting in a shorter and higher yielding procedure (Entry 2). As **3** entered clinical study, the route was adjusted to use a more robust silicon protecting group and to isolate two key intermediates as salts (**21** and **22**), allowing facile isolation and impurity rejection. The manufacturing of this material to supply clinical trials was performed over three separate campaigns: Campaign 1 (Entry 3) suffered from lower than expected yield due to the large-scale cryogenic addition of MeLi to **21** not performing as expected on scale-up

(Section 2.3.3), which was remedied in Campaigns 2 and 3 by use of flow-chemistry. Campaign 3 (Entry 5) suffered some attenuation of overall yield due to the need for an additional processing step to improve the chiral purity of **22•Hemisulfate** after it was unexpectedly eroded during the new reduction procedure (section 2.4).

Table 5: Campaign evolution summary

Entry	Campaign	Yield to intermediate[d]	Yield to 3•HBA[d]	Overall Yield	Total Steps to 3•HBA	Amount produced
1	Med Chem	11.1% (11 steps)[b]	29.7%[a]	3.3%[a]	16[a]	milligrams
2	Preclinical Tox	27.3% (8 steps)[b]	42.0%[a]	11.3%[a]	12[a]	182 g
3	Campaign 1	22.2% (8 steps)[c]	45.0%	10.0%	14	18.8 kg
4	Campaign 2	33.6% (9 Steps)[c]	44.7%	15.0%	14	53.9 kg
5	Campaign 3	32.9% (9 Steps)[c]	46.3%	15.2%	15	119.8 kg

a Only free form (**3**) was synthesized not **3•HBA**. For comparison, these routes are therefore inherently 1 step shorter without concomitant reduction in yield. b) **Intermediate** = **17**. c) **Intermediate = 22•Hemisulfate** d) Yield reported is an average of all the batch yields for each step in that campaign.

Despite the significant progress that has been made in the development of a route capable of the production of >100 kg of **3**, this route suffers from a number of issues: (1) the synthesis route is long and linear, resulting in a lengthy lead time for the API and reduced sourcing flexibility; (2) sourcing large quantities of **1** is problematic as it is not readily available and must be produced on-demand, resulting in long lead times; (3) installation of the C-1 methyl group occurs with good diastereoselectivity but it cannot be performed directly and relies on the oxidation-addition sequence; (4) the C-1 methyl group installation requires cryogenic conditions that were enabled by continuous flow, but this reduces process portability; (5) multiple non-productive protecting group manipulations are required; (6) unknown origin of the ee erosion between esterification and borohydride reduction indicates further process understanding is needed; (7) the atom economy and throughput for intermediate **22•hemisulfate** is hindered due to the heavy bromine, silicon protecting group, and salt form. Subsequent development efforts were undertaken to address these

problems and resulted in identification of improved alternative approaches to the THIQ core of **3**.[15,16]

Experimental Section

Experimental procedures for Campaign 3.

^{1}H NMR spectra are referenced to DMSO at 2.50 ppm and ^{13}C NMR spectra to DMSO at 39.52 ppm.

(*R*)-5-bromo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid Hydrochloride (10•HCl). [1]

To a dry 3000 L glass-lined reactor was charged **1** (105.0 kg, 430.2 mol) and methanol (422 kg), and the mixture heated to internal temperature of 62–65 °C. Thionyl chloride (63.4 kg, 532.9 mol) was added and the mixture was refluxed at 62–65 °C for 2 h. After this time the temperature was adjusted to 30–40 °C and a sample taken for analysis, which showed that <1% of **1** remained. The mixture was concentrated to 1.0–1.5 volumes while maintaining the internal temperature below 40 °C. The mixture was diluted with CH_2Cl_2 (680 kg) and concentrated to 1.5–2.0 V while maintaining the internal temperature below 40 °C. The mixture was diluted with CH_2Cl_2 (621 kg) and cooled to below 10 °C. A solution of K_2CO_3 (120 kg, 868.3 mol) in water (360 kg) was added, maintaining the internal temperature below 10 °C and held for 10 min. Methyl chloroformate (45.2 kg, 1.1 eq, 478.3 mol) was added over 20 min, maintaining the internal temperature below 25 °C, and the mixture stirred at 15–25 °C for 3 h. The phases were separated, and the organic phase was filtered through Celite. To the filtrate was added CH_2Cl_2 (156 kg) and conc. HCl (56.2 kg) in order to adjust the pH to 2–4 over 90 min. The phases were separated, and the organic phase was filtered through Celite and concentrated to 1.5–2.0 V, maintaining the internal temperature below 35 °C. Karl Fisher titration of the organic layer showed the water content was 0.5% (w/w). Acetic acid (439.4 kg) was added over 20 min followed by paraformaldehyde (16.05 kg, 535.0 mol) over 20 min and the mixture was cooled to 0–10 °C. Then H_2SO_4 (387.6 kg) was added slowly, maintaining the internal temperature below 25 °C, then held at 20–25 °C for 20 h. A sample was taken for analysis, which showed that less than 0.2% of **8** remained. The reaction mixture was cooled to 0–10 °C and water (1000 kg) was added, maintaining the internal temperature below 30 °C (5.5 h). EtOAc was added (463 kg) and the mixture was stirred between 6–9 °C for 30 min and the

layers were separated. The aqueous layer was extracted with EtOAc (350 kg) and the combined organic layers were concentrated to afford a solution of **9** and **18** in EtOAc (406.2 kg). In a separate reactor, conc. HCl (1301.2 kg) was heated to 50–60 °C and the EtOAc solution of **9** and **18** was added over 4 h. The mixture was then heated to 96–104 °C for 30 h and then cooled to 50–60 °C. h. A sample was taken for analysis, which showed that less than 0.2% **9** and **18** remained. The mixture was then cooled to 20–25 °C and held for 5 h and then the solids collected by filtration. The cake was washed with water (135.65 kg) and then slurried in CH_2Cl_2 (680 kg) at 20–30 °C for 5 h. The solids were collected by filtration and the wet cake washed with CH_2Cl_2 (138.5 kg). The wet cake was dried under vacuum at 40-45 °C for 50 h to afford **10•HCl** as a white solid (106.4 kg of salt, 87.0% freebase assay, 361.5 mol freebase, 84.0% yield, 99.4% purity by HPLC, 98% ee). ^{1}H NMR (400 MHz, DMSO-d_6) 9.95 (br.s, 2H), 7.62 (d, J = 7.8 Hz, 1H) 7.33 (d, J = 7.3 Hz, 1H), 7.25 (dd, J = 7.8, 7.8 Hz, 1H), 4.47 (dd, J = 5.4, 11.2 Hz, 1H) 4.41–4.29 (m, 2H), 3.29 (dd, J = 5.4, 17.6 Hz, 1H), 2.97 (dd, J = 11.2, 17.1 Hz, 1H); MS (ES+) m/z 256.0, 258.0 (M+H); DSC onset =291.4 °C, max = 297.6 °C.

[(3*R*)-5-Bromo-1,2,3,4-tetrahydroisoquinolin-3-yl]methanol (14).[1]

A dry 3000 L glass-lined reactor was charged with **10•HCl** (127 kg, 89.9% assay, freebase basis, 446.0 mol) and MeOH (1028 kg), then heated to an internal temperature of 62 °C. To the mixture was added $SOCl_2$ (82.2 kg, 690.2 mol) over 5 h, maintaining the internal temperature below 66 °C. After the addition, the mixture was held at 63–65 °C for 10 h and then cooled to 29 °C. The mixture was then concentrated to 1–2 volumes, maintaining the temperature between 18–37 °C. The mixture was diluted with CH_2Cl_2 (874 kg) and concentrated to 1–2 V, maintaining the temperature between 5–9 °C. The mixture was then diluted with CH_2Cl_2 (878 kg) and a solution of K_2CO_3 (123 kg, 890.0 mol) in water (650 kg) was added, maintaining the temperature between 16–25 °C. The mixture was stirred for 20 min, maintaining the temperature between 16–17 °C and then filtered through Celite (20 kg). The layers were separated and the aqueous extracted with CH_2Cl_2 (886 kg). The combined organic phases were washed with water (632 kg) and concentrated to 1–2 volumes maintaining the internal temperature below 30 °C. The vessel was then charged with MeOH (568 kg), concentrated to 1–2 V maintaining the temperature between 10–30 °C, then charged with MeOH (992 kg) and heated to 42 °C. $NaBH_4$ (50.0 kg, 1321.7 mol) was added in portions while maintaining the internal temperature between 42–52 °C. The mixture was then

cooled to 22–24 °C for 2 h and an aliquot taken for analysis. This showed 4% **11** remained and so the internal temperature was increased to 41 °C and additional $NaBH_4$ (2.7 kg, 71.4 mol) was added in portions, maintaining the internal temperature between 43–46 °C. The mixture was then cooled to 22–24 °C for 2 h and an aliquot was taken for analysis. The mixture was concentrated to 5–6 vol. maintaining the internal temperature between 16–26 °C and water (1300 kg) was added over 4 h maintaining the internal temperature below 40 °C. Upon completion of addition, the mixture was stirred between 23–25 °C for 3 h and then cooled to 3–4 °C for 5 h. The solids were collected by filtration and the cake washed with water (220 kg). The cake was then slurried with CH_2Cl_2 (422 kg) and methylcyclohexane (756 kg) at 20–30 °C for 5 h then filtered, washing with methylcyclohexane (105 kg). Finally, the solids were dried under vacuum at 40–45 °C for 24 h to afford **14** as a pale yellow solid (85.35 kg, 78%, 99% purity by HPLC, 91.6% ee, assay 99.8%). ^{1}H NMR (400 MHz, DMSO-d_6) 7.43-7.39 (m, 1H), 7.08-7.06 (m, 2H), 4.74 (ddd, J = 5.4, 5.4, 5.4 Hz, 1H), 3.95-3.85 (m, 2H), 3.53-3.48 (m, 1H), 3.45-3.40 (m, 1H), 2.85-2.79 (sext, J = 1.3 Hz, 1H), 2.67 (dd, J = 3.9, 17 Hz, 1H), 2.43 (s, 1H), 2.23 (dd, J = 10.5, 17 Hz, 1H). MS (ES+) m/z 242.0, 244.2 (M+H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 139.6, 134.2, 129.5, 127.1, 125.5, 125.0, 65.0, 55.2, 48.1, 32.5; DSC onset = 155.4 °C, max = 159.1 °C.

(*R*)-5-bromo-3-(((tert-butyldiphenylsilyl)oxy)methyl)-3,4-dihydroisoquinoline oxalate (21•oxalate).

A dry 3000 L glass-lined reactor was charged with **14** (110 kg, 450.0 mol) followed by CH_2Cl_2 (748 kg) and imidazole (47.0 kg, 690.4 mol) and the contents were stirred between 15–21 °C for 20 min. Then TBDPSCl (170.0 kg, 618.5 mol) was added in portions maintaining an internal temperature below 30 °C. The mixture was then stirred between 21–23 °C for 8 h and then cooled to 3 °C and charged with Et_3N (147.0 kg, 1452.7 mol). The mixture was held between 0–5 °C for 20 min and then charged with *N*-chlorosuccinimide (92.0 kg, 689.0 mol) in 3 portions maintaining the internal temperature below 5 °C. After the addition, the mixture was stirred for 12 h, then an aliquot taken for analysis which showed complete consumption of **20**. The reactor was charged with a solution of NH_4Cl (1140 kg) in water (2084 kg) over 5 h 40 min and then stirred between 3–5 °C for 2.5 h. The layers were separated, and the organic phase was transferred to a different 3000 L glass-lined reactor and twice washed with water (562 kg & 552 kg). The organic layer was

concentrated to 1–2 vol, maintaining the internal temperature between 9–25 °C. The mixture was then diluted with EtOAc (540 kg) and concentrated under vacuum to 1–2 vol. maintaining the internal temperature between 20–43 °C. The mixture was diluted with EtOAc (1504 kg) and residual CH_2Cl_2 measured as 0.02% (w/w). The mixture was then heated to 37 °C and oxalic acid (52.0 kg, 577.6 mol) in EtOAc (462 kg) was charged over 5 h and the mixture was stirred between 39–40 °C for 11 h. The mixture was then cooled to between 6–9 °C for 4 h. The mixture was then filtered and the solids washed with EtOAc (174.0 kg), dried in vacuum in 2 batches at 40–45 °C for 16 h each to afford **21•oxalate** as a tan solid (219.4 kg, 79%, 94.6% purity by HPLC, 88% ee, 77.0% assay freebase basis). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.64–7.57 (m, 4H), 7.49–7.38 (m, 7H), 7.32 (t, J = 7.6 Hz, 1H), 3.92–3.87 (m, 2H), 3.71 (dd, J = 8.0, 11.2 Hz, 1H), 3.06 (dd, J = 6.8, 17.2 Hz, 1H), 2.83 (dd, J = 9.6, 17.6 Hz, 1H), 0.94 (s, 9H) ; ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7 (2C), 159.2, 135.2, 135.1 (2C), 135.1 (2C), 135.0, 132.8, 132.7, 129.91, 129.86, 128.9, 127.9 (2C), 127.9 (2C), 127.4, 123.4, 119.5, 66.4, 57.6, 26.7, 26.5 (3C), 18.7; MS (ES+) m/z 478.1, 480.1 (M+H); IR (ATR, cm^{-1}) 3068, 2958, 2932, 2859, 1714, 1696; DSC onset = 169.8 °C, max = 173.1 °C.

Flow process to prepare (1*S*,3*R*)-5-bromo-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline hemisulfate (22•hemisulfate).

21•oxalate (145.05 kg, 76.3% assay, 231 moles) was charged to a reactor along with CH_2Cl_2 (1539 kg) with agitation. An aqueous solution of potassium carbonate (prepared by adding 65 kg of solid K_2CO_3 to 550 kg of water) was added and the biphasic mixture was stirred at 17 °C. The bottom (organic) layer was removed and the upper layer was discarded. The organic layer was then stirred with water (500 kg) and the layers were separated. The organic phase was then concentrated by vacuum stripping below 45 °C to near dryness. 2-MeTHF (550 kg) was added and the resulting solution was concentrated by vacuum stripping below 45 °C to near dryness. 2-MeTHF (996 kg) was added; Karl Fischer titration of this solution returned 0.04% (w/w) water. This solution was dispensed into shuttle cans for use in the flow process.

The continuous flow equipment set utilized three feed streams: **21** in 2-MeTHF was pumped using a diaphragm metering pump (232 mL/min), MeLi (0.6 M in 2-MeTHF, 143.8 mL/min) was fed by a peristaltic pump, and aq. NH_4Cl (prepared by dissolving 264 kg of solid NH_4Cl in 1152 kg of

water) was fed by a peristaltic pump (320 mL/min, PFA tubing used). All feeds were on balances for periodic mass flow checks and the flow rates were also monitored by inline mass flow meters. The plug flow reactor was constructed of 0.375" OD 316L stainless steel tubing. The volume of the pre-cooling section for the 2-MeTHF solution of **21** was 1.17 L. The MeLi stream was not pre-cooled due to blockages observed during development. After it was pre-cooled, the solution of **21** met the MeLi solution in a T-mixer, which was followed by an in-line static mixer (Koflo Stratos static tube mixer: 0.375'' OD, 0.319'' ID with 27 mixing elements). After the mixer, the main plug flow reactor was constructed of 3/8" OD 316L stainless steel and had volume of 1.55 L. The pre-cooling coil and reactor coil were immersed in an insulated bath containing EtOH and cooled by dry ice. As the process stream left the reaction PFR, it flowed through a sampling valve where HPLC samples could be withdrawn and then into a stirred vessel where the ammonium chloride solution was pumped into it simultaneously. From the quench vessel, the biphasic mixture was intermittently pumped into a manually operated separator (via PFA tubing), where the bottom layer was discarded while the top layer was pumped (via PFA tubing) into product collection shuttle cans for use in the isolation phase.

The process stream (1772 kg, contained in 46 shuttle cans) was pooled in a 3 m^3 glass-lined reactor and the solution was concentrated to near dryness by vacuum stripping below 35 °C. EtOAc (819 kg) was added, followed by water (374 kg). The mixture was stirred and allowed to settle. The bottom aqueous layer was discarded, and the organic layer was concentrated by vacuum stripping to near dryness below 35 °C. The residue was dissolved in EtOAc (799 kg) and polish-filtered to remove any solid materials. The solution was then heated to 48 °C and concentrated H_2SO_4 (1.1 kg, 98%, 11.0 moles) was added over 1 h. Seed crystals of **22•hemisulfate** (1.0 kg, 1.8 moles) was added, and additional concentrated H_2SO_4 (10.05 kg, 98%, 100.4 moles) was added over 2 h. After the H_2SO_4 addition was completed, additional seed crystals of **22•hemisulfate** (1.0 kg, 1.8 moles) were added to ensure that the seed had held. The slurry was held at 45 °C for 3 h, cooled to 19 °C over 4 h, and held at 19 °C for 12 h. The solid was isolated by centrifugal filtration and washed with EtOAc (130 kg). The wet cake was split into two equal portions for the remainder of the isolation phase. Half the cake was transferred to a 3 m^3 glass-lined reactor and THF (252 kg) was added. The mixture was heated to 50 °C with stirring. To remove undissolved solids (scalemic product), the mixture was filtered using a heated filter and the filtrate was sent into a ca. 50 °C pre-heated tank. The dissolution tank and filter cake were washed with THF (16 kg). The

remaining half of the crude cake was dissolved and filtered in a similar manner and combined with the first portion in a 3 m^3 glass-lined reactor. The combined solution was heated to 53 °C and EtOAc (1540 kg) was added over 3 h. After the addition had completed, the mixture was cooled to 19 °C over 3 h. The solid was isolated by centrifugal filtration and the cake was washed with EtOAc (124 kg). The solid was transferred to a vacuum dryer and dried at 40–45 °C for 24 h, at which point analysis indicated that the drying endpoint had been reached. **22•hemisulfate** was obtained as a white solid (92.0 kg, 88.3% assay, 164 moles, 70.1% yield, 99.6% purity by HPLC, 99.9% ee, 99.9:0.1 dr). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (d, J = 7.2 Hz, 4H), 7.54 (d, J = 8.0 Hz, 1H), 7.51–7.44 (m, 6H), 7.28 (d, J = 7.6 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 4.45 (brq, J = 6.4 Hz, 1H), 3.85 (dd, J = 5.2, 10.4 Hz, 1H), 3.80 (dd, J = 4.8, 10.8 Hz, 1H), 3.55 (br sextet, J = 4.8 Hz, 1H), 2.91 (dd, J = 4.4, 17.2 Hz, 1H), 2.66 (dd, J = 10.0, 16.8 Hz, 1H), 1.46 (d, J = 6.4 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 135.2 (5C), 132.56, 132.53, 132.1, 131.0, 130.1, 130.0, 128.00 (2C), 127.96 (2C), 127.9, 126.2, 124.6, 65.2, 50.3 48.5, 30.8, 26.6 (3C), 21.7, 18.9; MS (ES+) m/z 494.1, 496.1 (M+H); LCMS IR (ATR, cm^{-1}) 2930, 2856, 1617, 1589; DSC onset 197.6 °C, max = 199.0 °C .

(*E*)-4-((1S,3R)-3-(((tert-butyldiphenylsilyl)oxy)methyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methylbut-3-en-2-ol (32).

Toluene (3.5 L) was charged into 25 L jacketed vessel followed by 22•hemisulfate (943 g, 1.73 mol) and a slurry formed. Aqueous 1 M K_2CO_3 (5.0 L, 5.0 mol) was charged into the slurry. The mixture was agitated overnight (~18 h) and a clear biphasic mixture formed. The phases were separated and water (5.0 L) was added. The mixture was agitated for ~15 minutes, then allowed settle for ~ 30 minutes and the phases were separated. The toluene solution was azeotropically dried (Dean-Stark) for ~2 hours, until no water was observed in the distillate. Karl Fisher titration of the solution showed that the water content was 0.03% w/w. The solution was cooled to 20–25 °C in a 20 L stainless steel vessel and 2-methyl-3-buten-2-ol (374 g, 4.34 mol) was charged followed by powdered K_2CO_3 (551 g, 3.99 mol). The slurry was degassed with nitrogen for ~25 min and then palladium acetate (5.84 g, 0.026 mol) was charged, followed by SPhos (10.68 g, 0.026 mol) and the mixture was further degassed with nitrogen for 30 The mixture was heated to 132 °C for 29 h and held under nitrogen pressure (4100 mbar).

The mixture was cooled to ~40 °C, filtered through Celite and washed with the mixture of toluene (1.9 L) and water (1.9 L). The phases were separated, and the organic phase was washed with water (2 × 1.9 L). The toluene solution was concentrated at 80 °C under vacuum to approximately 3 L. *n*-Heptane (4.72 L) was added and the mixture was concentrated to ~ 2–3 volumes (3.5 – 5 L). This was repeated twice more and then *n*-heptane (4.72 L) was added and the slurry was cooled to 20–25 °C and agitated for 2 days. The mixture was cooled to 0 °C for 3 h and the solid was collected by filtration, washing twice with heptane (1.9 L). The wet cake was dried at 50 °C under vacuum for 8 hours to afford **32** as a pale yellow solid (702 g, 81%, 99.2% purity by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67–7.64 (m, 4H), 7.48–7.41 (m, 6H), 7.23 (d, J = 7.6 Hz, 1H), 7.08 (t, J = 7.2 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.67 (d, J = 15.6 Hz, 1H), 6.19 (d, J = 16.0 Hz, 1H), 4.69 (s, 1H), 4.10 (q, J = 6.4 Hz, 1H), 3.73–3.65 (m, 2H), 3.22 (sextet, J = 5.2 Hz, 1H), 2.77 (dd, J = 4.0, 16.4 Hz, 1H), 2.34 (dd, J = 10.0, 16.4 Hz, 1H), 2.16 (br, 1H), 1.33 (d, J = 6.8 Hz, 3H), 1.27 (s, 6H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 141.0, 140.8, 136.1, 135.1 (2C), 135.1 (2C), 133.1, 133.0, 131.2, 129.9 (2C), 127.9 (4C), 125.5, 125.3, 122.9, 122.6, 69.4, 67.6, 50.0, 48.4, 30.1 (2C), 29.1, 26.7 (3C), 23.7, 18.9; LCMS (ESI, M+H$^+$) 500.3; IR (ATR, cm^{-1}) 3167, 2969, 2926, 2854, 1589; DSC onset 119.7 ºC, max = 120.6 ºC.

4-((1*S*,3*R*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methylbutan-2-ol (33).

A 20 L pressure vessel was charged with absolute ethanol (5.2 L) followed by 32 (650 g, 1.30 mol). Then Pd/C (166 g, 5% wt, 50% water wet) was charged and the vessel was purged 3 times with nitrogen followed by 3 times with hydrogen. The vessel was pressurised with hydrogen (4300 mbar) and agitated at 40 °C for 17 h. The catalyst was filtered through pad of Celite and washed with ethanol (2 × 650 mL). The ethanol solution was charged into a 20 L jacketed vessel and concentrated at 40 °C under vacuum to 3 V (~ 2 L). *n*-Heptane (3.25 L) was added and the solution was concentrated to ~ 2–3 volumes (~ 2–3 L). This was repeated twice more and then *n*-heptane (2.6 L) was added and the slurry was cooled to 0 °C and held overnight. The solid was filtered, washed with cold heptane (2 × 1.3 L), and then dried at 50 °C under vacuum to afford 33 as an off-white granular solid (594.6 g, 91%, 98.3% purity by HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68–7.62 (m, 4H), 7.49–7.40 (m, 6H), 7.03 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 4.23 (br, 1H), 4.09 (q, J = 6.8 Hz, 1H), 3.69 (m, 2H), 3.21 (sextet, J = 5.6 Hz,

1H), 2.77 (dd, *J* = 3.6, 16.0 Hz, 1H), 2.55 (t, *J* = 8.4 Hz, 2H), 2.37 (dd, *J* = 10.0, 16.0 Hz, 1H), 1.59–1.46 (m, 2H), 1.32 (d, *J* = 6.8 Hz, 3H), 1.13 (s, 6H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 140.8, 140.6, 135.1 (5C), 133.0, 131.9, 129.8 (2C), 127.9 (2C), 127.9 (2C), 126.0, 125.1, 124.2, 68.7, 67.6, 50.1, 48.5, 44.4, 29.1, 29.1, 28.3, 27.1, 26.7 (3C), 23.7, 18.8; LCMS (ESI, M+H$^+$) 502.3; IR (ATR, cm^{-1}) 3192, 2967, 2928, 2857, 1588; DSC onset 91.2 ºC, max = 96.2 °C.

2-(2,6-dichlorophenyl)-1-((1*S*,3*R*)-5-(3-hydroxy-3-methylbutyl)-3-(hydroxymethyl)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one (3). [1]

Tetrahydrofuran (1.375 L) was charged under nitrogen into a 25L jacketed vessel, followed by 2,6-dichlorophenyl acetic acid (**23**, 337 g, 1.64 mol) and the mixture was agitated until a clear solution was obtained. CDI (219 g, 1.79 mol) was added in 3 equal portions and the final solution was agitated for 48 h at 20 °C. The mixture was then heated to 65–70 °C, a solution of **33** (550 g, 1.09 mol) in THF (0.825 L) was added into the reactor at 60-65 °C, and the final mixture was heated to 70 °C for 17 h. 2 M aq. NaOH (0.55 L) was added at 60 °C and the mixture was held at this temperature for 1 h. The mixture was cooled to 20–25 °C and to the vessel were added iPrOAc (1.65 L) and 2 M aq. NaOH (550 mL) with agitation. The phases were separated and the aqueous phase was back-extracted with iPrOAc (550 mL). The combined organic phases were washed with 2 M aq. NaOH (2 × 1.65 L) followed by aq. NH_4Cl (2 × 20% w/w, 1.65 L) and a single aq. NaCl (10% w/w, 1.65 L) wash. NMR analysis showed that the concentration of this solution was 13.32% (w/w) of **32** in iPrOAc. To this solution was added TBAF•3H_2O (298 g, 0.94 mol) at 20–25 °C and the solution was heated to 69 °C for 18 h. The reaction solution was cooled to 20–25 °C and washed with aq. NH_4Cl (25% w/w, 2 × 1.1 L), water (2 × 1.375 L) and aq. NaCl (10% w/w, 1.375 L). The sample was analysed for TBAF content and did not meet the target, so the solution was washed with water (2 × 1.375 L) and aq. NaCl (10% w/w, 1.375 L). To the iPrOAc solution was added SiliaMetSThiol (24.7 g) and the slurry was heated to 50 °C and agitated for 18 h. The scavenger was removed by filtration through a pad of Celite and washed with iPrOAc (0.55 L). This solution was transferred to a clean, dry reactor and concentrated to approx. 1.9 L. Then, iPrOAc (2.75 L) was added and the mixture was concentrated to approx. 1.9 L. This was repeated twice more and precipitation of **3** occurred. The suspension was cooled from 50 °C to 20 °C over 150 mins and then held at 20 °C for 18 h. The suspension was then cooled to 3 °C over 100 minutes and agitated for ~ 5–6 hours. The solids were collected by filtration, washing with iPrOAc (2 ×

0.55 L) that had been precooled to 3 °C. The solids were dried in the oven at 50 °C overnight (18–20 h) to afford **3** as an off-white granular solid (358.7 g, 73%, 99.3% purity by HPLC). ^{1}H NMR (300 MHz, $CDCl_3$) (mixture of rotamers) 7.35-7.15 (m, 6H), 5.24-5.18 (m, 0.43H), 5.05 (ddd, *J* = 6.7, 6.7, 6.7 Hz, 0.56H), 4.57-4.47 (m, 0.43H), 4.41-4.25 (m, 0.56H), 4.20-4.08 (m, 2.44H), 3.56-3.39 (m, 2.20H), 3.08-2.93 (m, 3.27H), 2.74-2.72 (m, 1.62H), 1.88-1.48 (m, 4.86H), 1.35-1.23 (m, 9.70H), 0.94-0.84 (m, 0.95H); ^{13}C NMR (75 MHz, DMSO-d_6) (mixture of rotamers) 167.3, 167.0, 141.4, 141.0, 139.2, 139.1, 135.54, 135.50, 133.5, 133.2. 131.2, 130.7, 129.2, 129.1, 128.0 (2C), 127.8, 127.5, 126.5, 126.3, 123.9, 123.8, 68.8, 62.2, 62.0, 59.1, 54.0, 52.8, 52.5, 51.2, 45.0, 44.9, 36.7, 36.5, 29.4, 29.3, 29.1, 29.0, 27.5, 27.4, 25.5, 25.3, 25.1, 23.4, 23.3 ; MS (ES+) m/z 450.2, 452.2 (M+H); $[a]_D^{20}$=-39.4 ° (c=0.95, MeOH).

2-(2,6-dichlorophenyl)-1-((1*S*,3*R*)-5-(3-hydroxy-3-methylbutyl)-3-(hydroxymethyl)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one hydroxybenzoic acid co-crystal(3•HBA)[1]

To a dry 5 L jacketed vessel was charged 4-hydroxybenzoic acid (92 g, 0.67 mol), followed by **3** (300 g, 0.67 mol) and THF (750 mL). The mixture was agitated at 45–50 °C until a clear solution formed. Additional THF was added (114 mL) and then *n*-heptane (480 mL) was added at 50 °C. A slurry of seed crystals (1.95 g) in 5% (v/v) THF/*n*-heptane (30 mL + 3 mL rinse) was added and precipitation occurred. The slurry was stirred at 50 °C overnight and *n*-heptane (1260 mL) was added to the mixture over 4.5 h maintaining the internal temperature between 45–50 °C. The mixture was then cooled to 20 °C over 4 h and held overnight at 20 °C. The mixture was then circulated through a slurry mill, maintaining internal temperature between 20–30 °C. The slurry was then heated to 57–62 °C at the rate of 15 °C/h and held at this temperature for 40 min before cooling to 20–25 °C over 4 h. The slurry was then agitated for 30–40 min at this temperature, before heating to 57–62 °C at the rate of 15 °C/h and holding again at this temperature for 40 min. The slurry was then cooled to 20–25 °C over 4 h and held at this temperature for 10–15 h. The solids were collected by filtration, washing with 33% THF/*n*-Heptane (600 mL), then 5% THF/*n*-heptane (600 mL) and the material dried in the oven at 50 °C to afford **3•HBA** as a white solid (339.0 g, 86%, 99.8% purity by HPLC). ^{1}H NMR (mixture of rotamers, 400 MHz, DMSO-d_6) δ 12.40 (br, 1H), 10.21 (br, 1H), 7.79 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.32 (t, *J* = 8.4 Hz, 1H), 7.16–7.01 (m, 3H), 6.82 (d, *J* = 8.8 Hz, 2H), 5.21 (q, *J* = 6.4 Hz, 0.3H), 5.03 (q, *J* = 6.4

Hz, 0.7H), 4.96 (br, 0.7H), 4.65 (brt, J = 4.8 Hz, 0.3H), 4.62–4.36 (brm, 1H), 4.29–4.21 (m, 2.7H), 4.10 (d, J = 16.8 Hz, 0.3H), 3.40–3.25 (brm, 3.3H), 2.97 (dd, J = 4.4, 15.6 Hz, 0.7H), 2.89–2.83 (m, 1H), 2.75–2.60 (m, 1.7H), 2.45–2.38 (m, 0.3H), 1.66–1.54 (m, 2H), 1.49 (d, J = 6.8 Hz, 0.9H), 1.23 (d, J = 6.4 Hz, 2.1H), 1.18 (s, 0.7H), 1.17 (s, 0.7H), 1.16 (s, 0.3H), 1.16 (s, 0.3H); ^{13}C NMR (mixture of rotamers, 100 MHz, DMSO-d_6) δ 167.3, 167.2, 167.0, 161.6, 141.5, 141.1, 139.3, 139.1, 135.6, 135.5, 133.6, 133.2, 131.5, 131.2, 130.7, 129.2, 129.1, 128.0, 127.9, 127.5, 126.5, 126.4, 123.9, 123.8, 121.4, 115.1, 68.8, 62.3, 59.1, 54.0, 52.8, 52.5, 51.2, 45.04, 44.97, 36.8, 36.5, 29.4, 29.3, 29.14, 29.06, 27.5, 27.4, 25.3, 25.1, 23.4, 23.3; IR (ATR, cm^{-1}) 3409, 3254, 2977, 1682, 1627, 1607, 1590; DSC onset = 162.5 °C, max = 165.6 °C; LCMS (ESI, M+H$^+$) 450.2, 452.2.

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ASSOCIATED CONTENT

Supporting Information. Scans of spectral data for key compounds are available in Supporting Information.

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