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Development of a Manufacturing Process for Sibenadet Hydrochloride, the Active Ingredient of Viozan

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Abstract:

A process for commercial manufacture of the dual D_2-β_2 receptor agonist sibenadet hydrochloride has been developed. The process relies upon introduction of operationally simple chemistry at the final stages where two key intermediates are reacted to assemble the final molecule, isolated by crystallization. A nine-stage sequence for synthesis of the key amine hydrochloride intermediate was developed, and modifications to the original process are described. Major strategic improvements were made in definition of the final route to the "side chain" precursor molecule, the second key intermediate, hinging around a thiyl radical addition and subsequent high-yielding telescoped processes for synthesis of this highly crystalline benzoate ester. Development of these chemistries is discussed, together with some issues surrounding definition of the final validated commercial processes.

Introduction

Sibenadet hydrochloride (**1**) (Figure 1) is a highly potent drug designed for treatment of patients with chronic obstructive pulmonary disease,[1,2] a condition for which there is a definite clinical need, and exerts its biological effects through a combination of β_2 adrenoceptor and D_2 dopamine receptor agonist activities. Whilst the high potency of this compound via an inhalation route of administration meant that cost of goods constraints could be relaxed, the predicted size of the market led us to forecast manufacturing volumes of several tonnes per year.

Thus, throughput became the main focus of our efforts in developing a synthetic route suitable for scale-up to commercial manufacture. The success of these efforts relied heavily on the introduction of a facile entry to the final compound, elimination of chromatographic purification, and definition of efficient chemistry for construction of the side chain precursor.

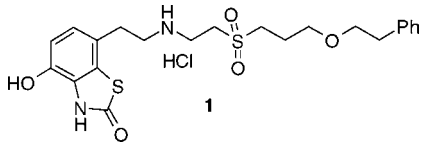

Figure 1. **Sibenadet Hydrochloride.**

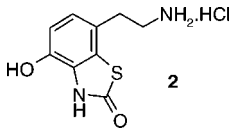

Figure 2. **Key benzothiazolone amine hydrochloride intermediate.**

Results and Discussion

Route Strategy. All routes investigated employed the benzothiazolone amine hydrochloride **2** as a key intermediate (Figure 2). This compound has been described previously in the literature as a D_2 receptor agonist,[3] and its modification by appending a variety of groups to the amino function was an important element of the medicinal chemistry programme that led to the discovery of **1**. The synthetic strategy that we embarked upon involved adopting key intermediate **2** as antecedent to **1** and concentrating efforts on finding an efficient method for the downstream chemistry. Notwithstanding this strategy, considerable improvements in the synthetic route and processing steps to **2** were needed to ensure adequate throughput.

Route Development for Benzothiazolone Amine Hydrochloride 2. The final route used for large-scale preparation of **2** is outlined in Scheme 1. Initial preparations employed the known route to trifluoroacetamide **3**,[3] deprotection of which was achieved in three separate steps. Early on we were able to demonstrate that this circuitous deprotection, involving displacement, hydrolysis, dealkylation, and deacylation, could be streamlined simply by heating **3** with 48% aqueous hydrobromic acid, which effected a similar set of transformations in a single operation to give the crystalline hydrobromide salt **2a**. Once it had been established that analogous chemistry was feasible using acetyl protection instead of trifluoroacetyl for the primary amine function, efforts were focused on process development of this chemistry, culminating in the nine-stage sequence.

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(1) Hiller, F. C.; Alderfer, V.; Goldman, M. *Respiratory Medicine* **2003**, *97* Suppl. A, 45.

(2) Bonnert, R. V.; Brown, R. C.; Chapman, D.; Cheshire, D. R.; Dixon, J.; Ince, F.; Kinchin, E. C.; Lyons, A. J.; Davis, A. M.; Hallam, C.; Harper, S. T.; Unitt, J. F.; Dougall, I. G.; Jackson, D. M.; McKechnie, K.; Young, A.; Simpson, W. T. *J. Med. Chem.* **1998**, *41*, 4915.

(3) Weinstock, J.; Gaitanopoulos, D. E.; Stringer, O. D.; Franz, R. G.; Hieble, P.; Kinter, L. B.; Mann, W. A.; Flaim, K. E.; Gessner, G. *J. Med. Chem.* **1987**, *30*, 1166.

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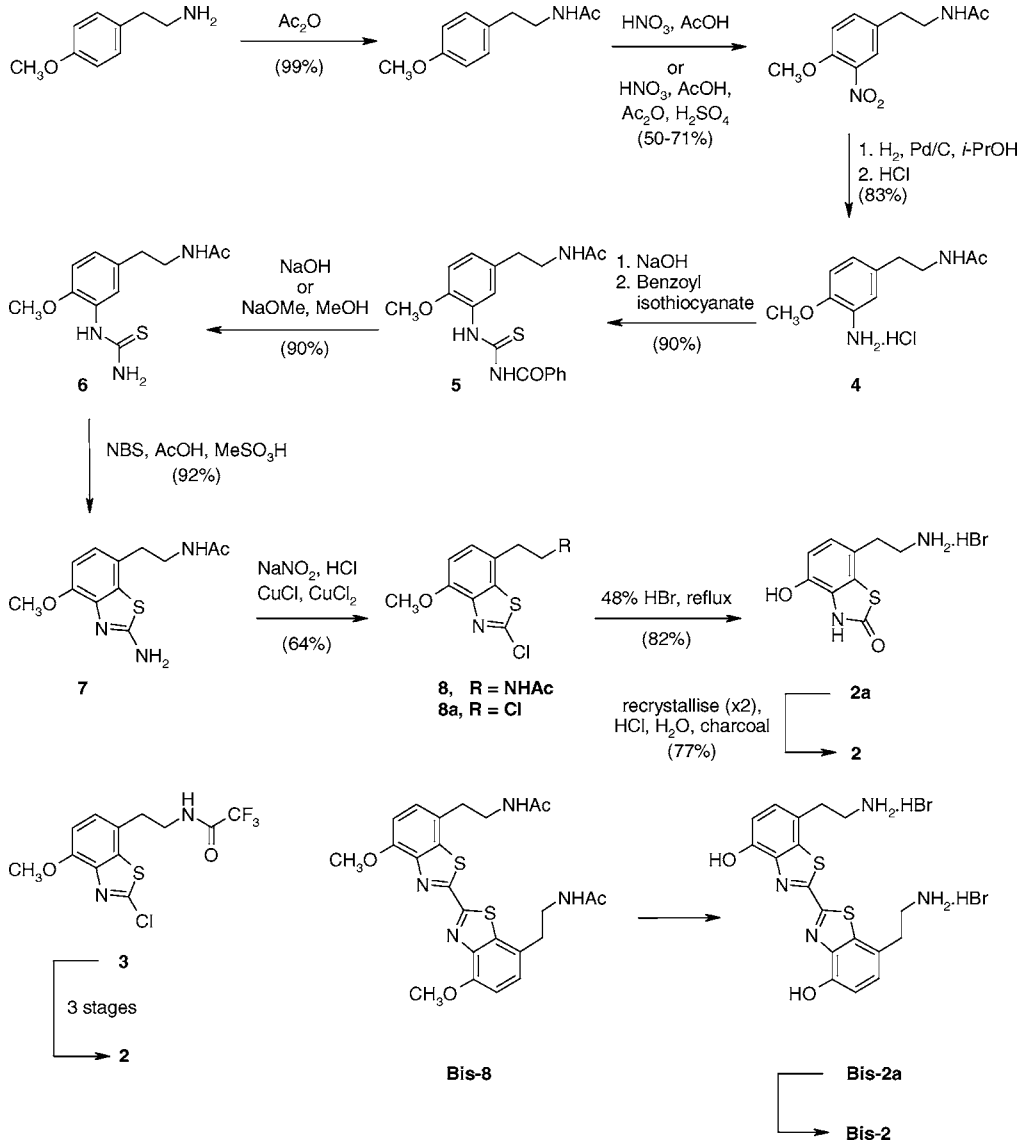
Scheme 1. **Synthetic route and conditions used for large-scale production of 2**



Of the three stages used to convert 2-methoxyphenylethylamine to the crystalline aniline hydrochloride salt **4**, the protection and reduction steps were relatively straightforward. For the nitration stage, 70% nitric acid in acetic acid was employed initially. Hazard testing concentrated mainly on the thermal characteristics of the reaction. A Dewar flask experiment in which the reagents were combined in one portion showed a 12 °C temperature rise over 15 min, and when the mixture had reached 35−40 °C, the temperature increased dramatically reaching a maximum of 103 °C over the next 10 min with heavy gas evolution. Reaction calorimetry using 10 mole equiv of 70% nitric acid and 3 weight equiv of acetic acid with addition of substrate to the nitrating media predicted an adiabatic temperature rise of 36 °C with accumulation (heat was evolved for an hour after the addition was complete). The calorimetry showed that reaction begins as soon as addition of substrate solution to the nitric acid is started but can stall if the temperature drops below 15 °C. This meant that accumulation could be minimized by running the reaction in semibatch mode, with controlled addition of the substrate dissolved in acetic acid to the nitric acid between 15 and 25 °C. Replacing nitric acid with acetyl nitrate prepared in situ as nitrating agent, a modification introduced by an outsourcing partner, offered considerable advantages for this stage. This procedure used fewer equivalents of nitrating agent and was also shown to be safe to run in the alternative addition mode with fuming nitric acid being added in small aliquots keeping the reaction mixture between 15 and 25 °C after each aliquot addition. These modifications resulted in significant reduction in byproducts derived from over-nitration and hence enhanced yield.

Upon attempted thiocarbamoylation of **4**, it soon became clear that formation of the thiourea **6** using simple thiocyanate salts was problematic, being seriously compromised by formation of significant amounts of the symmetrical thiourea derived from two molecules of **4**. During scale-up, we were only able to avoid this by introducing a protecting group, reacting the free base obtained from **4** with benzoyl isothiocyanate prepared in situ from ammonium thiocyanate and benzoyl chloride. This gave the benzoyl thiourea **5**, isolable by precipitation and filtration, and a deprotection

Table 1. **Conditions investigated for oxidative cyclization of 6 using 1 equiv of NBS**

scale (mmol of **6**)	solvents	conditions	isolated yield of **7** **(%)**	HPLC purity (%)
15	TFA	ambient (NBS addition)−60 °C 30 min	87	94
37	TFA	ambient (NBS addition)−60 °C 30 min	82	92
37	$MeSO_3H$	5 °C (NBS addition)−ambient 5 hr	81	91
94	$MeSO_3H$ + 10% v/v AcOH	5 °C (NBS addition)−ambient 5 hr	96	94
1.9	AcOH + 2 equiv of H_2SO_4	ambient temperature 21 h	52 (oil precipitated)	88

step was now required to liberate the cyclization precursor **6**. Fortunately this was easily achieved by treatment with alkali, and the two-step sequence afforded material of good quality and in 81% isolated overall yield.

Next came the oxidative cyclization of **6** to furnish the benzothiazole nucleus as the 2-amino benzothiazole derivative **7**. *N*-Bromosuccinimide served as a suitable replacement for bromine, allowing good control in the charging stoichiometry. This proved crucial in controlling the formation of a ring-brominated byproduct, a troublesome impurity that is not removed downstream. Choice of solvents for the cyclization stage was limited by the tendency for precipitate formation prior to complete conversion during this process, and acidic media were found to alleviate this problem. The reaction worked well in neat methanesulfonic acid, but concerns over bulk availability prompted a search for an alternative. A number of acidic media combinations were investigated in the laboratory, and selected data are shown in Table 1.

Although TFA was suitable in the laboratory, its volatility and corrosive potential precluded its use at scale, and whilst the sulfuric/acetic acid system looked promising, the isolated yield and purity of **7** from these reactions did not rival those from the methanesulfonic acid system and the reactions were attended by significant oiling out of material hindering product isolation. This unsuccessful attempt at methanesulfonic acid replacement represented an opportunity for subsequent process improvement but was not addressed further during activities described herein. Because of the tendency for the solvent to freeze in neat methanesulfonic acid (mp 20 °C) runs at around 5 °C, we investigated cosolvents, and ultimately a mixture comprising methanesulfonic acid and around 10% v/v acetic acid proved best. The proportion of acetic acid was increased to around 20% v/v during scale-up trials without significant impact on yield or quality. A slight deficiency of NBS was employed to avoid formation of the ring-brominated impurities in the reaction, and the product was precipitated upon basic quench and isolated in around 84% yield.

A few unsuccessful attempts were made to convert **7** into benzothiazolone derivative **2** directly, using known hydrolytic/diazotization protocols. However, conditions found to modify the 2-amino group (e.g., sodium nitrite in a mixture of hydrochloric acid, formic acid, and acetic acid[4]) also led to significant decomposition during attempted hydrolysis of the putative diazonium salt, and recourse to the 2-chloro intermediate **8** defined the development work needed for the substitution of amino for chloro via diazotization. Optimal conditions for this process involved controlled addition of aqueous sodium nitrite to a solution of **7** in concentrated hydrochloric acid containing defined sub-stoichiometric quantities of copper(I) and copper(II) chloride. It was found that controlling the temperature during dissolution and reaction of **7** as well as the reaction time minimized formation of an impurity identified by HPLC-MS as the chloroethyl derivative **8a**. Whilst it was shown that a solution of the starting material in the reaction acid was stable at 25 °C overnight, heating at 45 °C for 2 h before recooling and submitting to the reaction conditions resulted in formation of 5−8% **8a**. However, **8a** was also produced on extended reaction times (>3 h) at normal reaction temperature (<18 °C), suggesting that there may be more than one possible pathway for its formation (i) by reaction of chloride ion with the primary diazonium salt formed as a result of partial hydrolysis of the acetyl group and (ii) through the intermediacy of the *N*-nitroso amide in the reaction medium leading to the same diazonium salt. Although **8a** could be effectively removed during workup, the temperature during dissolution of **7** was kept below 30 °C and the sodium nitrite addition time was limited to 2.5 h in order to minimize this side reaction.

In addition, we found that evolution of nitrogen from the process caused a certain amount of frothing in the reaction vessel. Unless care was taken to introduce the sodium nitrite solution below the surface of the substrate solution, significant decomposition of the nitrite could ensue as contact with acidic froth occurred, necessitating addition of further quantities of nitrite to achieve good conversions. In the laboratory, quenching the reaction mixture into water did not always give reliable precipitation of the product **8** as a solid, and oiling was sometimes encountered. On the pilot plant, this was overcome by using a two phase quench mixture comprising defined quantities of water and methyl isobutyl ketone, which gave reliable precipitation and also improved the purity of **8** somewhat. This stage produced the largest number of impurities of any of the nine-stage sequence, with the major one (2−4%) identified by HPLC-MS and NMR as the bis-benzothiazolone **Bis-8**, which was shown to carry through to an analogous bis-benzothiazolone hydrobromide **Bis-2a**, removed by filtration during conversion of **2a** to the hydrochloride **2** (vide infra). Although we considered the diazotization process operable on a large scale, the volume efficiency of the stage was low and could benefit from further optimization.

(4) Jones, G. H.; Venuti, M. C.; Alvarez, R.; Bruno, J. J.; Berks, A. H.; Prince, A. *J. Med. Chem.* **1987**, *30*, 295.

The final deprotection stage that converted **8** into **2a** was accomplished by heating in 48% aqueous hydrobromic acid. Efficient scrubbing of the methyl bromide byproduct (bp 4 °C) was required on pilot plant scale to avoid release into the atmosphere. A mixture of 13% w/w ammonia (density 0.880) and 87% methanol proved the most suitable medium for scrubbing the gas. Aqueous ammonia alone and sodium hydroxide solution did not remove the gas. In the pilot plant, the gaseous reaction effluent was passed sequentially through the ammonia solution and then through a dilute hydrochloric acid scrubber solution (via appropriately placed "trap" vessels) to prevent ammonia release.

Although smooth deprotection/hydrolysis was observed, it was important to avoid an extended reaction time; otherwise appreciable decomposition could occur giving rise to impurities that were not easily removed. It was found that the conversion from hydrobromide to hydrochloride salt by recrystallization from hydrochloric acid in the presence of charcoal was an effective means of purification, and a second recrystallization then provided material of acceptable quality.

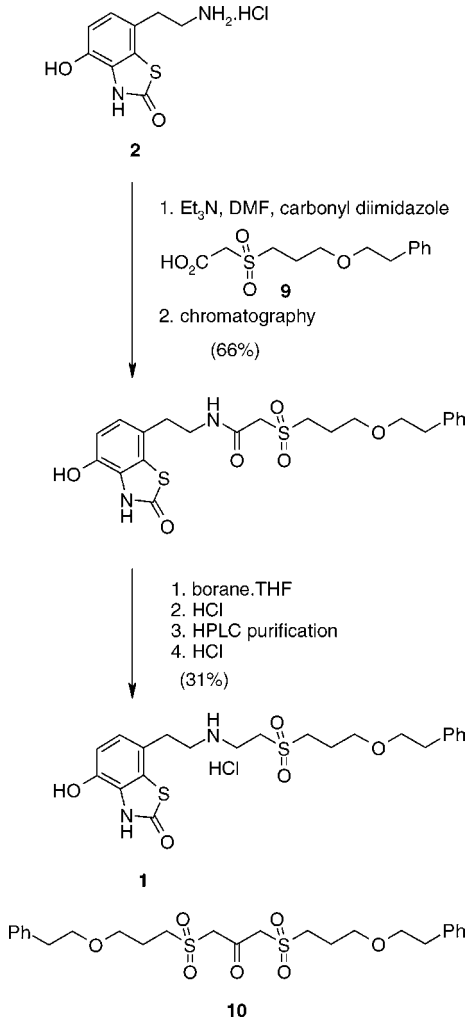
These processing stages were run successfully at pilot plant scale providing multikilogram quantities of hydrochloride **2**.

Route Selection for Synthesis of Sibenadet Hydrochloride: The Amide Route. With a supply route secured for benzothiazolone amine hydrochloride **2**, the definition of robust downstream chemistry for conversion of **2** to sibenadet hydrochloride was required. The early small quantities prepared during the discovery phase employed a route utilizing an amide intermediate that was subjected to borane-mediated reduction, outlined in Scheme 2.[2] To trial this chemistry in the laboratory, a supply of the requisite acid **9** was needed, previously synthesized from the known oxathiane **11**[6] via thiol **12**[2] within the medicinal chemistry department (Scheme 3).

The experience gained from running this sequence in the laboratory suggested that it was not ideal as the basis of a supply route to **9**, even on the laboratory scale. Two disadvantages were the use of the unstable phenylacetaldehyde as starting material, which is prone to polymerization, and the supply of 3-mercaptopropanol, which was not available in bulk quantities. In addition, the calcium/liquid ammonia reductive cleavage[5] of oxathiane **11** was unreliable, sometimes giving very low yields of thiol **12**.

We were able to eliminate these concerns by implementing an alternative route based on a thiyl radical addition reaction[7] after minimal process research effort. Addition of the thiyl radical derived from mercaptoacetic acid to the allyl ether **14**,[8] readily prepared by phase transfer mediated alkylation of 2-phenyl ethanol, gave the thioether acid **13** together with regioisomer **13a** as a byproduct (~10 mol %). Subsequent oxidation and purification by recrystallization from toluene yielded the pure acid **9** in around 60% overall yield, and this route was found to be suitable for the preparation of **9** in ~50 g quantities in the laboratory. Although a number of development issues remained to be addressed should this route become adopted in the longer term (e.g., conditions for the oxidation of **13**), it represented a considerable improvement over the initial sequence. Moreover, the thiyl radical addition tactic not only proved useful within medicinal chemistry in their ongoing analogue synthesis programme but would also feature in the final sequence to sibenadet hydrochloride.

Scheme 2. **Initial route to 1 via the amide intermediate derived from 2**



Having prepared sufficient quantities of the acid **9**, we turned our attention to the formation of the amide and its subsequent reduction. It soon became clear that the performance of these reactions was hampered by a number of drawbacks. First, activation of the acid **9** was required in order to form the amide upon reaction with the amine;

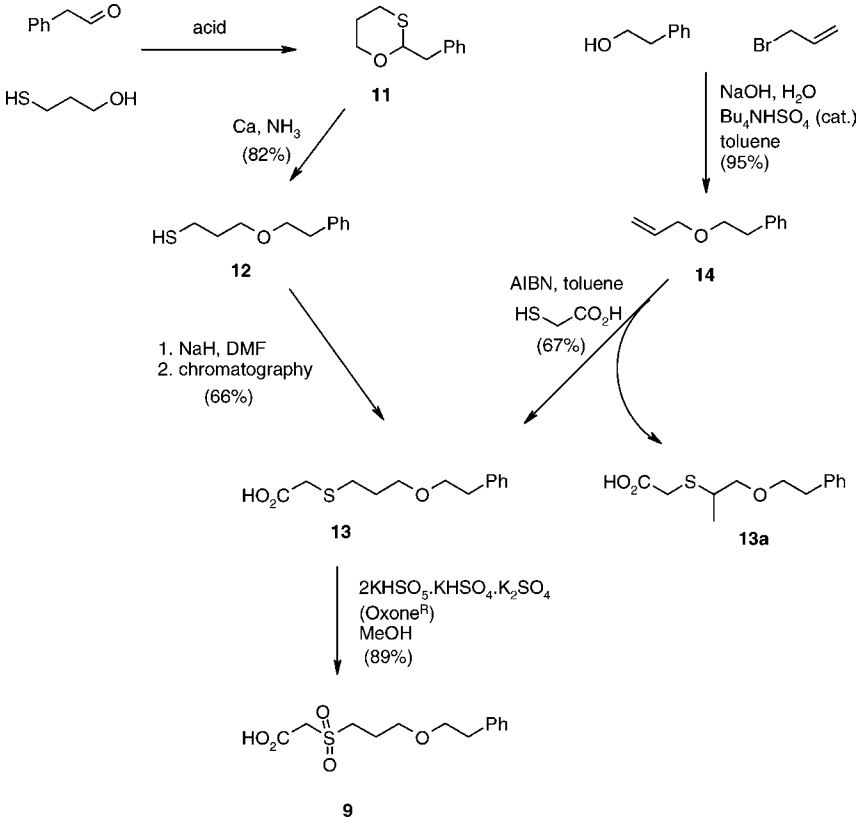
(5) (a) Kurth, M. J.; Tahir, S. H.; Olmstead, M. M. *J. Org. Chem.* **1990**, *55*, 2286. (b) Newman, B. C.; Eliel, E. L. *J. Org. Chem.* **1970**, *35*, 3641.

(6) Fuji, K.; Ueda, M.; Sumi, K.; Kajiwara, K.; Fujita, E.; Iwashita, T.; Miura, I. *J. Org. Chem.* **1985**, *50*, 657. This paper describes a low-yielding preparation of **11** by alkylation of 2-lithio-1,3-oxathiane with benzyl bromide. We have found that condensation of phenylacetaldehyde with 3-mercapto-1-propanol under standard acid-catalyzed Dean−Stark distillation conditions gives **11** in good yield.

(7) (a) Meltzer, P. C.; Liu, S.; Blanchette, H. S.; Blundell, P.; Madras, B. K. *Bioorg. Med. Chem.* **2002**, *10*, 3583. (b) Buskas, T.; Soederberg, E.; Konradsson, P.; Fraser-Reid, B. *J. Org. Chem.* **2000**, *65*, 958. (c) Curci, M.; Schneider, M.; Mieloszynski, J. L.; Paquer, D. *Sulfur Lett.* **1992**, *15*, 169. (d) Hazato, A.; Tanaka, T.; Watanabe, K.; Bannal, K.; Toru, T.; Okamura, N.; Manabe, K.; Ohtsu, A.; Kamimoto, F.; Kurozumi, S. *Chem. Pharm. Bull.* **1985**, *33*, 1815. (e) Smith, B.; Hernestam, S. *Acta Chem. Scand.* **1954**, *8*, 1111.

(8) Hill, C. M.; Simmons, D. E.; Hill, M. E. *J. Am. Chem. Soc.* **1955**, *77*, 3889.

Scheme 3. **Initial route and the first radical addition based route to acid 9**



however, whilst a number of methods yielded the desired product, the reaction was usually accompanied by the formation of the symmetrical ketone **10** as a major impurity. Clearly, this impurity arises from condensation of 2 molecules of a derivative of the acid **9**, such as the active ester or derived ketene, followed presumably by a decarboxylation. Another troublesome impurity was the *N*,*O*-diacyl derivative formed by acylation of both the amino and phenol hydroxy functions, observed in most of the coupling methods screened. There were a number of other impurities observed, some specific to the coupling method employed, but in all cases after workup and during isolation, the amide proved reluctant to solidify, and isolated yields and purities were low.

The reduction stage proved no less problematic, even when the input amide had been purified by chromatography. Borane-mediated reactions were characterized by over-reduction, involving the benzothiazolone carbonyl function, resulting in several impurities which were difficult to remove and appeared to inhibit crystallization of the hydrochloride **1** after workup. Preparative chromatography was required to obtain pure material and crystallization of the hydrochloride salt from methanol was then facile but in an overall yield of only 20% from **2**. Although elimination of the chromatography may have been possible with extended optimization studies to give material of acceptable quality, we took the view that the low yields and volume efficiencies associated with these stages would render long-term throughput requirements unattainable using this route.

Route Selection for Synthesis of Sibenadet Hydrochloride − the Alkylation Route: An alternative route to sibenadet hydrochloride from **2** was required, and a straightforward disconnection across the carbon−nitrogen bond led us to consider a direct *N*-alkylation of the free amine **2b** (Scheme 4). Since the side chain of sibenadet contains a β-amino sulfone moiety, an obvious choice of electrophile for the alkylation of **2b** is the vinyl sulfone **15** which should act as acceptor in a conjugate addition reaction.[9] It was our hope that an electron-withdrawing inductive effect associated with the beta disposed sulfone group, once appended, would counteract the usual increase in nucleophilicity associated with secondary amine products in such alkylations and minimize formation of tertiary amine byproducts that often hampers this method as a preparative technique.[10]

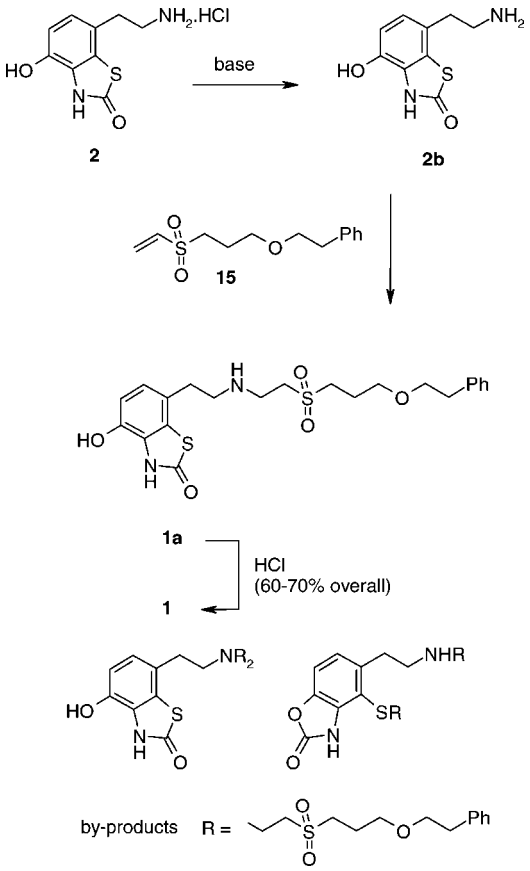
Initial model studies using phenyl vinyl sulfone[11] as electrophile for amine **2b** were encouraging, and a rapid entry to the vinyl sulfone **15** was sought in order to explore this route. We took advantage of the existing laboratory supplies of acid **9** as a precursor (Scheme 5) by reducing to the alcohol, converting this to the chloride in situ and eliminating

(9) (a) Teyssot, M.-L.; Fayolle, M.; Philouze, P.; Dupuy, C. *Eur. J. Org. Chem.* **2003**, 54. (b) Bashford, K. E.; Cooper, A. L.; Kane, P. D.; Moody, C. J.; Muthusamy, S.; Swann, E. *J. Chem. Soc., Perkin Trans. 1* **2002**, *14*, 1672. (c) Evans, B. E.; Lundell, G. F.; Gilbert, K. F.; Bock, M. G.; Rittle, K. E.; Carroll, L. A.; Williams, P. D.; Pawluczyk, J. M.; Leighton, J. L.; Young, M. B.; Erb, J. M.; Honns, D. W.; Gould, N. P.; DiPardo, R. M.; Hoffman, J. B.; Perlow, D. S.; Whitter, W. L.; Veber, D. F.; Pettibone, D. J.; Clineschmidt, B. V.; Anderson, P. S.; Freidinger, R. M. *J. Med. Chem.* **1993**, *36*, 3993. (d) Schoeberl, A.; Biedermann, M. *Justus Liebigs Ann. Chem.* **1968**, *716*, 37. (e) Friedman, M.; Romersberger, J. A. *J. Org. Chem.* **1968**, *33*, 154.

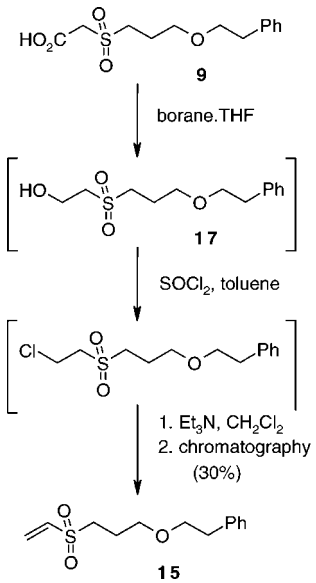
(10) Srivastava, S. K.; Chauhan, P. M. S.; Bhaduri, A. P. *Synth. Commun.* **1999**, *29*, 2085 and references therein.

(11) Rosenmund, P.; Brandt, B.; Flecker, P.; Hoffmann, E. *Liebigs Ann. Chem.* **1990**, 857.

Scheme 4. **Alkylation route to 1: addition of 2b to a vinyl sulfone**



Scheme 5. **Initial route used to prepare vinyl sulfone 15**



HCl to give **15** as a low melting solid. Initial reactions of **15** with **2** in the presence of triethylamine in both DMF and methanol demonstrated the feasibility of the approach, with reasonable conversion to **1a**, and in the case of the methanol reactions, product of good quality could be isolated as the filterable solid hydrochloride **1** by acidification with hydrochloric acid in 60−80% yield. A number of impurities were observed in the crude reaction mixtures, including two byproducts shown in Scheme 4 derived from over-alkylation, the expected tertiary amine and, interestingly, the *S*-alkylated isomer (∼10 mol % in total). The tertiary amine was characterized initially by HPLC-MS and subsequently confirmed by NMR experiments run on a sample isolated by chromatography that demonstrated the existence of two equivalent side chain units. The structure of the *S*-alkylated isomer was originally misassigned as the *N*,*N*′-bis-alkylated derivative but ^{1}H, ^{13}C, and several 2-D NMR experiments confirmed that the thiazolone ring had been replaced by an oxazolone ring and the sulfur atom had become alkylated. Nevertheless, the levels of these impurities were reduced upon isolation of **1** in an initial crystallization, and attempted purification by recrystallization indicated that methanol appeared to be a suitable solvent, yielding material that should be acceptable from a quality viewpoint.

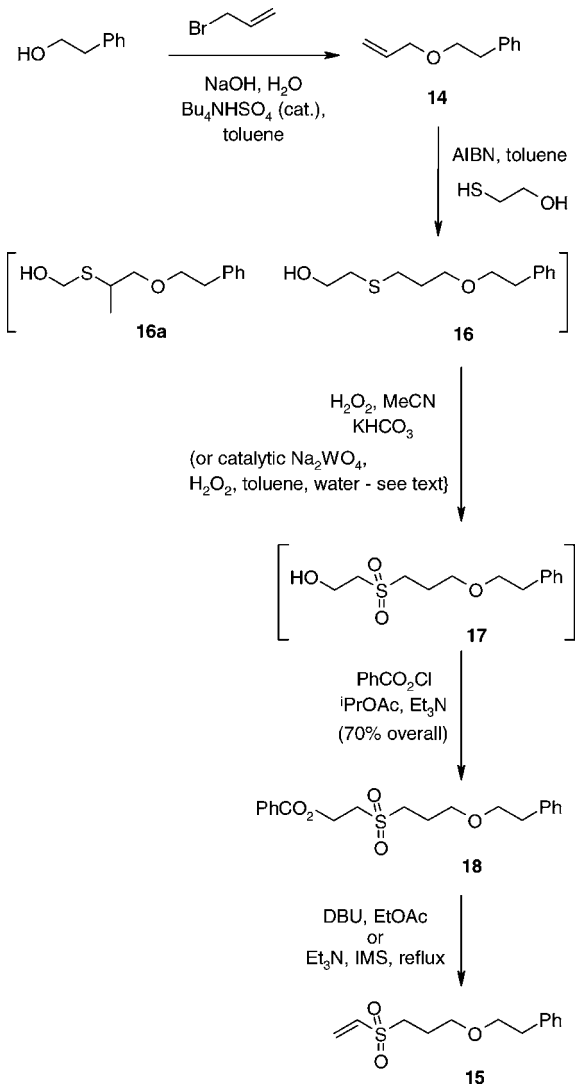
These results demonstrated some major advantages of this method over the amide route, cutting out a synthetic step and at the same time removing the need for preparative chromatography. We believed that this approach should deliver a long-term manufacturing process and set about process research towards an improved synthesis of vinyl sulfone **15**, subsequent scale-up work, and further development and scale-up of the alkylation process to give **1**.

Route Selection for Synthesis of Vinyl Sulfone 15: The Final Synthetic Route for 1. The overall method employed to prepare vinyl sulfone **15** (Schemes 3 and 5) was not particularly efficient, since it incorporated what appeared to be an unnecessary reduction of acid **9**. Therefore, a strategy based upon analogous radical addition chemistry early on using 2-mercaptoethanol instead of mercaptoacetic acid was examined (Scheme 6).

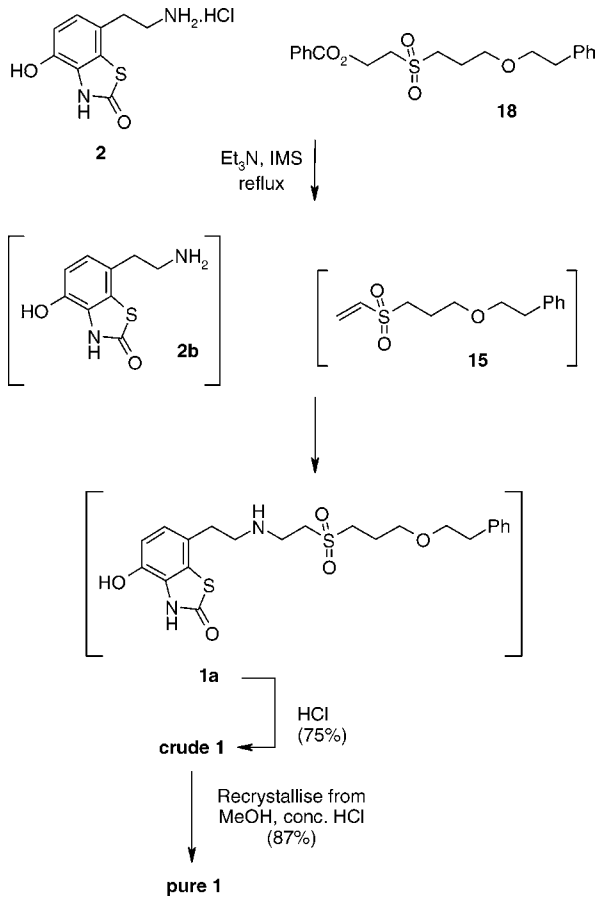
This thiyl radical addition reaction worked in a similar mode to its predecessor, resulting in good conversion to give thioether **16** along with around 10 mol % of the regioisomeric addition product **16a**. The radical reaction could be initiated by light, air, or chemical initiator, and azobisisobutyronitrile was found to be most suitable. The thioether could be oxidized smoothly to the sulfone **17** using hydrogen peroxide and acetonitrile under basic conditions.[12] We envisaged that conversion of **17** to the vinyl sulfone **15** should be possible by converting the hydroxy group into a good nucleofuge for a β-elimination reaction. A variety of derivatives were made, and it was found that under the right conditions esters were reactive enough toward β-elimination to allow facile preparation of **15**.[13] An example, the benzoate ester **18**, was also found to be highly crystalline, and this greatly enhanced the route as a potential manufacturing process, since all the preceding intermediates were oils. Suitable conditions for the elimination included DBU in ethyl acetate at ambient temperature and, most conveniently, triethylamine in industrial methylated spirit (IMS; ethanol denatured with ∼4% methanol) at reflux. The crude benzoate **18** was derived from 2-phenyl ethanol in what was essentially a telescoped process, and once it was established that **18** could be crystallized in a highly pure state, free from the regioisomer

(12) Ando, T.; Cork, D. G.; Kimura, T. *Chem. Lett.* **1986**, *5*, 665.
(13) Eyley, S. (AstraZeneca AB). WO 00/50413 A1.

Scheme 6. **Final route to 15 and conditions used for large-scale production of 18**



Scheme 7. **Production process used for manufacture of 1 from 2**



derived from **16a**, we felt that this route was an appropriate choice as the final synthetic sequence.

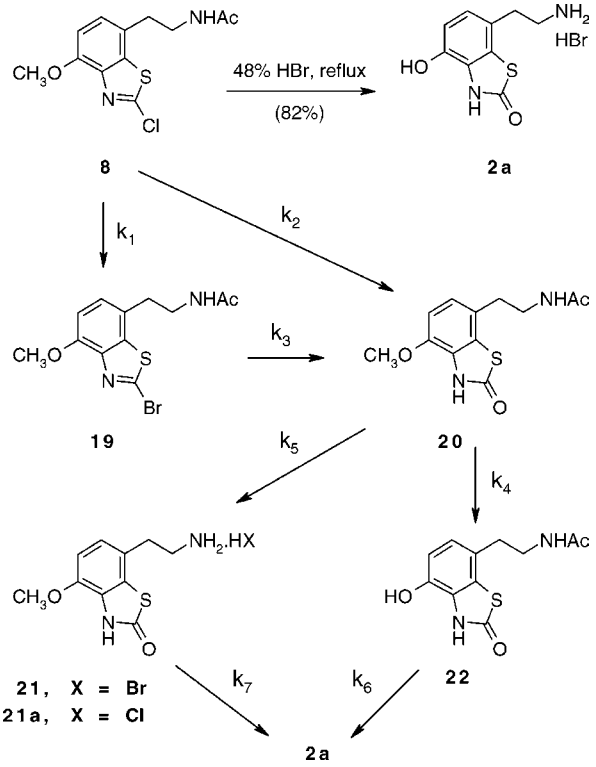
Process Development: The Final Manufacturing Process. Having demonstrated that elimination of benzoate from **18** to give the vinyl sulfone **15** could be achieved by heating with triethylamine in IMS, the same solvent type as that used for the subsequent alkylation of **2b**, it seemed logical to attempt both these transformations in the same reaction vessel. This would offer a reduction in the number of processing stages and obviate the need to isolate **15** (Scheme 7). This was reduced to practice in the laboratory by mixing stoichiometric quantities of **18** and **2** in ethanol, adding triethylamine, heating to reflux for several hours, cooling, and acidifying with hydrochloric acid. Crude **1** was found to crystallize out in a reproducible process. The crude material obtained was converted to the pure drug substance by means of a single recystallization from methanol giving material with an acceptable impurity profile (no significant contamination by benzoic acid was observed). This represented a major improvement, and the process, now deemed suitable for long-term supply of **1**, was transferred to the pilot plant and used to supply drug substance for Phase II and Phase III clinical trials and carcinogenicity studies.

Commercial Process

Benzothiazolone Amine Hydrochloride 2. The nine-stage process for manufacture of benzothiazolone hydrochloride **2** outlined in Scheme 1 was transferred to external supply manufacturers for further development and scale-up to production where process improvements were introduced. In addition to the enhanced nitration procedure already discussed, another significant change was made in the deprotection of the benzoyl thiourea **5**, where alternative conditions were employed, involving use of catalytic sodium methoxide in methanol with an acetic acid quench. This proved more robust than the hydroxide process, which required tight control in the acidifying quench, and furnished material at least as good if not better in terms of quality. It was later established that either set of conditions could be used at this processing stage without giving rise to significant differences in impurity profile at intermediate **2** or at the drug substance itself.

At this stage, preparation was underway for validation of the processing stages downstream of intermediate **4**, our proposed registered starting material, and appropriate process ranges for the key parameters were established along with suitable specifications for the intermediates. As part of this, key batch data were taken into account and any anomalous runs were carefully considered. For the deprotection stage yielding **2a**, investigation of a failed batch showed that the

Scheme 8. **Intermediates involved in the HBr mediated deprotection of 8 to give 2a**



strength of the hydrobromic acid solution was important. A kinetic study revealed that the reaction pathway was related to the acid concentration, and the mechanistic pathway outlined in Scheme 8 was elucidated, where k_{1-7} represent rate constants.

The first step is a simple rapid displacement of chloride by bromide (the 2-bromo benzothiazole **19** could be isolated from low conversion runs), and this in turn undergoes fast hydrolysis to the benzothiazolone **20**. The deprotection pathway then diverges through two intermediates **21** and **22**, each of which is converted to the final product **2a**.

Only those steps whose products have been detected in time courses of the reaction at reflux temperatures were included in this analysis (i.e., downstream from **20**). The concentration of HBr was varied between 42 and 57% w/w, at reflux temperature, using purified **20** as starting material. Samples were removed at specified time-points and analyzed by HPLC to determine molar concentrations. The kinetic parameters, based on the above reaction scheme describing pseudo-first-order reactions, were determined by fitting experimental data using RATE in BatchCAD.

Variation of rate constants with HBr concentration revealed that the rate of the deacetylation was essentially invariant over the acid concentration range studied. However, the rate of the demethylation stages showed a strong dependency on acid concentration (Figure 3).

The profile for the intermediate **21** is therefore sensitive to the concentration of HBr as depicted in Figure 4, derived from calculations based on the fitted rate constants. This indicates that, at lower HBr concentrations, the level of this compound peaks at much higher values and persists longer throughout the reaction.

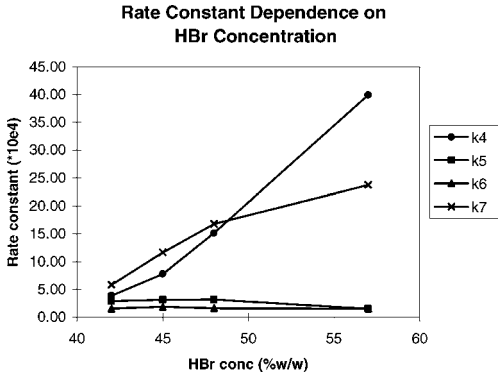


Figure 3. **Rate constants k_4-k_7 as a function of HBr concentration.**

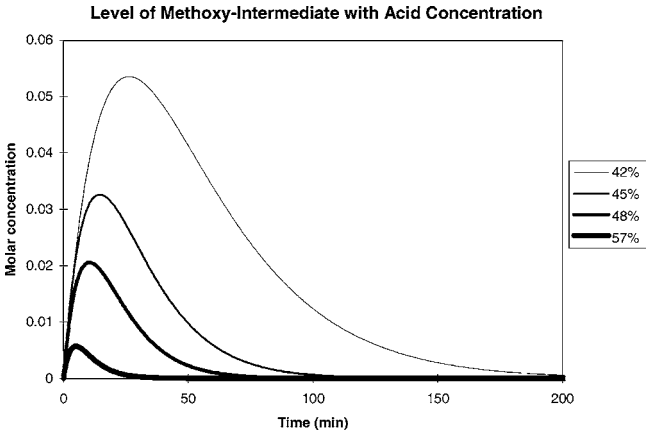


Figure 4. **Molar concentration profiles of intermediate 21 calculated from rate constants derived from fitting experimental data.**

Isolation and analysis of the product mixtures from these small-scale reactions were not carried out; therefore, these data do not support a specific lower limit for HBr concentration. However, it is worth noting that a concentration of 5×10^{-4} M for **21** at the end of the reaction would lead to at least 0.26% w/w of this impurity in the batch of **2** (this assumes proportionate cocrystallization of **21** with **2a** and no reduction in the recrystallization stages for conversion of **2a** to **2**, which is consistent with data from several laboratory and pilot plant batches). It had been established that **21** was converted to the corresponding methoxy-derivative of **1** in the final stages of drug substance manufacture, an impurity that we wished to control. These results led to the introduction of drying of precursor **8**, isolated from an aqueous quench, and the incorporation of a lower limit for HBr concentration (46% w/w) as a key parameter for robustness.

Another important operational parameter was the type of filter used to remove the charcoal from the recrystallizations during conversion of **2a** into **2**, since physical separation of the highly insoluble dihydrochloride impurity **Bis-2** occurred during this filtration. It was important to control the level of this impurity at this stage since it was found to react, not unexpectedly, in the downstream alkylation chemistry to give derivatives that would contaminate the final product **1**. Using filters that were rated capable of removing particulates down to 1 micron reduced the level of **Bis-2** present in **2** to within

acceptable specified limits.

Ultimately the manufacturing processes downstream of **4** were fully validated at two commercial suppliers, with an output batch size of approximately 70 kg for **2**, and over 1 tonne of material was produced using the validated process. Although these process changes were introduced after the batches of **2** used for Phase III drug substance manufacture were produced, we were able to demonstrate equivalence at intermediate **2** and also later confirmed that the drug substance made from these supplies of **2** was also equivalent to the Phase III drug substance in terms of both impurity profile and physical form.

Benzoate Ester 18. The synthesis of allyl ether **14** from 2-phenyl ethanol under phase transfer conditions with portionwise addition of tetrabutylammonium hydrogen sulfate catalyst proceeded smoothly and was scaled up to a 105 kg batch size (input of 2-phenyl ethanol). After an aqueous wash and a distillation, the product was isolated as a toluene concentrate. The next three synthetic transformations were performed on this concentrate in a telescoped sequence. After the radical addition, again run in toluene, the product solution was submitted to the oxidation process. Here, our outsourcing partner introduced a notable modification, involving a tungstate-catalyzed hydrogen peroxide oxidation[14] in a two-phase aqueous toluene solvent system. This gave a much improved volume efficiency compared to the original acetonitrile-mediated process. In addition, since the organic solvent was common to the previous stage, a simple aqueous workup and azeodrying protocol could be employed giving the sulfone alcohol **17** as a toluene concentrate. This was subjected to acylation using benzoyl chloride in isopropyl acetate as cosolvent, and after a solvent swap, the crude benzoate **18** crystallized upon seeding. A routine recrystallization gave highly pure **18** in around 70% overall yield from 2-phenyl ethanol. This process was fully validated and provided 230 kg output batch sizes for **18**. Over 1 tonne of material was produced using the validated process.

Sibenadet Hydrochloride 1. The process defined for manufacture of the batches for Phase III clinical trials (Scheme 7) was transferred successfully to the production facility with a 3-fold increase in scale. As part of this, the following process improvements were made: (i) seeding was introduced for crystallization of the crude drug substance, and the wash solvent was changed from two portions of 2-propanol to a single methanol wash, improving filterability considerably; (ii) the pure drug substance was also washed with methanol instead of 2-propanol, again improving filterability and facilitating subsequent drying. These changes were predicated on technical trial batches run in the pilot plant prior to full technology transfer to production, and on laboratory based process range work, and confirmation was obtained during commissioning in production that the changes had no significant impact of quality whilst improving the overall cycle time.

Control of Physical Form. During preparation of drug substance for Phase II clinical trials, it was discovered that sibenadet hydrochloride could exist in more than one polymorphic form. Two forms relevant to the manufacturing process were identified, characterized, and designated Form I and Form II. We were able to demonstrate that Form I was thermodynamically more stable and that Form II was meta-stable with respect to Form I and was converted to Form I in differential scanning calorimetry recycling experiments. This interconversion also translated to the recrystallization process where we found that batches contaminated with Form II could be converted to Form I on recrystallization. However, sometimes more than one recrystallization was required to effect complete conversion. Since we believed that the ideal process for isolation and purification of **1** should be limited to a crystallization of the crude followed by a single recrystallization, we set about optimization with respect to control of the polymorphic form, without compromising the impurity profile.

In an earlier process for recrystallization of **1**, a distillation step was employed to concentrate the methanol solution prior to final recrystallization. It was observed that this distillation would often lead to the formation of a crust of **1** that formed on the surfaces of the hot reaction vessel during solvent removal. Batches prepared in this way were comprised of mixtures of Form I and Form II with Form II often predominating. Further laboratory studies showed that the majority of recrystallizations where deliberate crust formation was allowed to occur yielded mixtures of the two forms. In addition, an extensive series of laboratory recrystallizations with seeding and low cooling rate (of the order of 0.1 °C min^{-1}) gave predominantly Form I material. Laboratory experiments using a turbidiometric method indicated that **1** has a very wide meta-stable zone width in the solubility curve for this recrystallization system. Since this implied that a state of high supersaturation was likely to be long-lived, especially with slow cooling rates, we adopted seeding routinely for all scale runs in an attempt to avoid uncontrolled spontaneous crystallization. Unfortunately, the corrosive nature of the recrystallization system precluded on-line particle size monitoring with the equipment available at the time, and so we were unable to determine unequivocally whether seeding was indeed controlling the crystallization through secondary nucleation.

During manufacture of the drug substance for Phase III clinical trials, based on these empirical data, the following control measures were adopted: transfer of the hot solution from dissolution vessel to recrystallization vessel (via a polishing filter) under conditions that avoided evaporation and adventitious crystallization, addition of seed (minimum of 3.1% w/w) between 50 and 60 °C, and a cooling rate of 0.1 °C min^{-1}. These parameters were formally transferred to the commercial manufacturing facility during commissioning. All scale runs using this recrystallization protocol afforded Form I material. The final two stages giving crude and pure sibenadet hydrochloride were successfully validated at a 40 kg batch output scale.

Conclusions

A process for manufacture of initial launch quantities of sibenadet hydrochloride **1** has been developed based on a

(14) (a) Stec, Z.; Zawadiak, J.; Skibinski, A.; Pastuch, G. *Polish J. Chem.* **1996**, *70*, 1121. (b) Bortolini, O.; Di Furia, F.; Modena, G.; Seraglia, R. *J. Org. Chem.* **1985**, *50*, 2688.

convergent synthesis involving key intermediates **2** and **18**. It was estimated that the validated batch scale would supply sufficient drug substance annually for three years postlaunch with further process efficiency improvements. Projected peak annual demand four years postlaunch of around 3 tonnes could, if necessary, be met through increasing the batch scale.

Experimental Section

General. Melting points were recorded on a capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 300, 360, or 400 MHz in $CDCl_3$ or DMSO-d_6. ^{13}C NMR spectra were recorded at 75, 100, or 125 MHz in DMSO-d_6 (resonances coincident with those of the solvent are not quoted). Mass spectra were recorded on a variety of instruments using electron impact (EI), attached proton chemical ionisation (APCI), or fast atom bombardment (FAB) ionisation techniques.

For compounds **1**, **2**, **4**−**8**, **14**, **17**, and **18**, the procedures described represent the manufacturing scale processes that have been fully validated.

***N*-[4-Methoxyphenyl)ethyl]acetamide.**[15] A suitable reaction vessel was charged with acetic anhydride (103.5 kg, 1014 mol), and 2-(4-methoxyphenyl)ethylamine (143.4 kg, 948 mol) was added from a head tank holding the temperature at less than 30 °C (range 20 to 30 °C). After the addition was complete, the reaction mixture was stirred for 1 h. A suitable quench vessel was charged with 32% sodium hydroxide (352 kg, 2816 mol) and water (399 L). The reaction mixture was added to the sodium hydroxide solution keeping the temperature at less than 20 °C. The quench slurry was cooled to 0−5 °C, and the precipitated product was isolated on a centrifuge and washed with water (497 L). The product was obtained as a water-wet cake and used directly in the next stage.

***N*-[3-Nitro-4-methoxyphenyl)ethyl]acetamide. Method A.** A suitable dissolution vessel was charged with acetic acid (87 kg), *N*-[4-methoxyphenyl)ethyl]acetamide (29.0 kg dry weight equivalent, 150 mol) was added, and the contents of the vessel were warmed to 30−35 °C. The resulting solution was cooled to 15−25 °C and charged to a head tank connected to a suitable reaction vessel. Concentrated nitric acid (70%, 135 kg, 1500 mol) was charged to the reaction vessel, and the solution of acetamide was added from the head tank keeping the temperature in the range 15−25 °C. After the addition was complete, the reaction mixture was stirred for 30 min at 15−25 °C and cooled to 0−5 °C and then added to a solution of 20% sodium hydroxide (591 kg, 2955 mol) in a suitable quench vessel keeping the temperature in the range 0−20 °C. The quench slurry was cooled to 0−5 °C, and the precipitated product was isolated on a centrifuge and washed with water (123 L). The product was obtained as a water-wet cake. Yield 17.9 kg, 50% from 2-(4-methoxyphenyl)ethylamine (corrected for moisture).

Method B (Employed Using *N*-[4-Methoxyphenyl)-ethyl]acetamide That Had Been Dried to <2% w/w Moisture). A suitable dissolution vessel was charged with acetic acid (460 kg), *N*-[4-methoxyphenyl)ethyl]acetamide (115 kg, 595 mol), acetic anhydride (102 kg, 999 mol), and 98% sulfuric acid (11 kg, 110 mol). To this mixture was added 98% nitric acid (56 kg, 871 mol) in 5 kg aliquots maintaining a reaction temperature of 15−20 °C during the addition. The reaction mixture was stirred for 1 h and then added to water (1150 L), and the mixture stirred for 16 h. 20% Sodium hydroxide solution (2200 L) was added to the stirred mixture over 6 h keeping the temperature below 25 °C, and the product was collected by filtration, washed with water, and dried in a vacuum tray oven. This gave *N*-[3-nitromethoxyphenyl)ethyl]acetamide (99.1 kg, 70% yield corrected for moisture) as a solid that contained approximately 5% w/w moisture which was suitable for processing in the next stage. An analytically pure sample was obtained by recrystallization from two volumes of ethyl acetate (53% recovery) giving yellow crystals, mp 88−89 °C, GC purity 99.1%; MS (EI) *m*/*z* 238 ($M^+ + H$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.67 (d, J = 2.2 Hz, 1H), 7.39 (dd, J = 8.6, 2.2 Hz, 1H), 7.04 (d, J = 8.6 Hz, 1H), 5.66 (br s, 1H), 3.94 (s, 3H), 3.49 (q, J = 7.1 Hz, 2H), 2.82 (t, J = 7.1 Hz, 2H), 1.96 (s, 3H). Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.56; H, 6.05; N, 11.81.

***N*-[2-(3-Amino-4-methoxyphenyl)ethyl]acetamide, Hydrohloride (4).** A suitable vessel was charged with 2-propanol (2244 L) and *N*-[3-nitromethoxyphenyl)ethyl]acetamide (375 kg, 1574 mol), and then a slurry of 5% palladium on charcoal (31 kg, 50% water wet) in 2-propanol (100 L) was added and washed in with 2-propanol (100 L). Hydrogen was introduced to the stirred mixture allowing the temperature to rise to 62−68 °C and the pressure to rise to 2.5−3.0 bar. When the theoretical charge of hydrogen has been added (∼9.5 kg), the reaction mixture was filtered at ∼65 °C into a suitable vessel to remove the catalyst which was washed on the filter with 2-propanol (298 L). To the combined, stirred filtrate was added 33% hydrochloric acid (261 kg, 2363 mol) at 17−23 °C over ∼1 h. The mixture was stirred for at least 4 h at 17−23 °C, the precipitated product was isolated on a centrifuge in four loads, and each load was washed with 2-propanol (3 × 67 L). The damp product was dried under vacuum at up to 80 °C to give **4** (310 kg, 80%) as an off-white solid, HPLC purity 99.2%; MS (APCI +ve) *m*/*z* 209 ($M^+ + H$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.06 (br m, 3H), 8.02 (br t, J = 5.4 Hz, 1H), 7.30 (d, J = 1.8 Hz, 1H), 7.21 (dd, J = 8.4, 1.8 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 3.86 (s, 3H), 3.24−3.16 (m, 2H), 2.65 (t, J = 7.2 Hz, 2H), 1.79 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.1, 150.6, 132.1, 129.1, 123.9, 120.4, 112.4, 56.1, 34.1, 22.6. Anal. Calcd for $C_{11}H_{16}N_2O_2$.HCl: C, 53.99; H, 7.00; N, 11.45. Found: C, 53.72; H, 6.95; N, 11.34.

***N*-{2-(4-Methoxy-3-[3-(1-phenylmethanoyl)thioureido]-phenyl)ethyl}acetamide (5).** Reaction vessel A was charged with water (2380 L), **4** (485 kg, 1982 mol), and methyl isobutyl ketone (1905 kg). 30% Sodium hydroxide was added at 15−25 °C until the pH of the aqueous layer was >12 (approximately 340 kg). The contents of the reactor were heated to 50−55 °C, and the two layers that had formed were allowed to separate. The organic layer was retained,

(15) (a) Yamada, S.; Fujii, T.; Takagi, K.; Gomi, Y.; Matsushita, S. *Chem. Pharm. Bull.* **1963**, *11*, 258. (b) Walpole, G. S. *J. Chem. Soc.* **1910**, *97*, 941.

and the aqueous layer was further extracted with methyl isobutyl ketone (1575 kg) at 50−55 °C. The organic layers were combined and retained in reaction vessel A at 50−55 °C. Reaction vessel B was charged with methyl isobutyl ketone (1540 kg), ammonium thiocyanate (182 kg, 2391 mol), and benzoyl chloride (311 kg, 2212 mol), maintaining the temperature at 35−40 °C, stirred for 1 h, and then cooled to 15−25 °C. The resulting solution of benzoyl isothiocyanate was transferred, via a filter to remove ammonium chloride, into reaction vessel A (containing the solution of free base of **4)** at 50−55 °C. The filter cake was washed with methyl isobutyl ketone (230 kg), and this washing added to reaction vessel A. The mixture was stirred for a minimum of 2 h at 50−55 °C and cooled to 15−25 °C, and the product was isolated by filtration and washed with methyl isobutyl ketone (645 kg) and water (1320 kg). The damp product was dried under vacuum at up to 65 °C to give **5** (663 kg, 90%) as an off-white solid, HPLC purity >97.5%. An analytically pure sample was obtained by slurrying in 20 volumes of refluxing acetonitrile, cooling, and filtering to afford a white solid (96% recovery), HPLC 98.9%; MS (APCI +ve) *m*/*z* 372 ($M^+ + H$); IR (neat, cm^{-1}) 3300, 1640, 1560, 1523; ^1H NMR (300 MHz, DMSO-d_6) δ 13.00 (s, 1H), 11.55 (s, 1H), 8.50 (s, 1H), 8.00−7.97 (m, 2H), 7.89 (t, J = 5.4 Hz, 1H), 7.70−7.64 (m, 1H), 7.57−7.51 (m, 2H), 7.07 (s, 2H), 3.87 (s, 3H), 3.27−3.20 (m, 2H), 2.67 (t, J = 7.2 Hz, 2H), 1.80 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 177.7, 169.0, 168.4, 149.0, 132.0, 130.9, 128.7, 128.4, 126.6, 126.5, 123.4, 111.2, 56.1, 34.6, 22.7. Anal. Calcd for $C_{19}H_{21}N_3O_3S$: C, 61.43; H, 5.70; N, 11.31. Found: C, 61.36; H, 5.68; N, 11.29.

***N*-[2-(4-Methoxy-3-thioureidophenyl)ethyl]acetamide (6).** A suitable vessel was charged with methanol (2160 kg) and **5** (550 kg, 1481 mol), and the mixture was heated to 40−45 °C. Sodium methoxide in methanol (21%, 83 kg, 323 mol) was added, and the reaction mixture was stirred at 40−45 °C for 45−60 min. Acetic acid (22 kg, 366 mol) was added, the vessel contents were cooled to 15−20 °C and stirred for 30 min, and the precipitated product was collected by filtration and washed with methanol (470 kg) followed by water (590 kg). The damp product was dried under vacuum at up to 80 °C to give **6** (399 kg, 90%) as an off-white solid, HPLC purity >99%; MS (APCI +ve) *m*/*z* 268 ($M^+ + H$); IR (neat, cm^{-1}) 3435, 1615, 1523; ^1H NMR (300 MHz, DMSO-d_6) δ 8.97 (s, 1H), 7.83 (t, J = 5.4 Hz, 1H), 7.80−7.00 (br m, 3H), 7.00−6.93 (m, 2H), 3.78 (s, 3H), 3.24−3.17 (m, 2H), 2.63−2.57 (m, 2H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.2, 169.0, 150.3, 131.0, 127.0, 125.9, 111.4, 55.6, 34.5, 22.6. Anal. Calcd for $C_{12}H_{17}N_3O_2S$: C, 53.91; H, 6.40; N, 15.71. Found: C, 53.67; H, 6.39; N, 15.52.

***N*-[2-(2-Amino-4-methoxybenzothiazol-7-yl)ethyl]acetamide (7).** A suitable vessel was charged with methanesulfonic acid (1825 kg) and acetic acid (367 kg), and **6** (290 kg, 1085 mol) was added portionwise to the stirred mixture keeping the temperature of the mixture below 30 °C. The resulting mixture was cooled to 5−10 °C, and a freshly prepared solution of *N*-bromosuccinimide (184 kg, 1034 mol) in methanesulfonic acid (590 kg) was added at 5−10 °C over 30 min. The reaction mixture was stirred for 30−40 min at 5−10 °C, warmed to 45−50 °C, and stirred for a further 60−70 min and then cooled to 20−25 °C. The mixture was added to a cold 21% sodium hydroxide solution (9600 kg, prechilled to 5−10 °C), keeping the temperature below 30 °C during the addition. The temperature of the mixture was adjusted to 20−25 °C, and the product was isolated by filtration and washed with water until the pH of the washings was in the range 6−8 (approximately 2900 kg). The damp product was dried under vacuum at up to 75 °C to give **7** (265 kg, 92%) as an off-white solid, HPLC purity >97%; MS (APCI +ve) *m*/*z* 266 ($M^+ + H$); IR (neat, cm^{-1}) 3405, 3317, 1661, 1629, 1540, 1501; ^1H NMR (400 MHz, DMSO-d_6) δ 7.94−7.91 (m, 1H), 7.42 (s, 2H), 6.80−6.76 (m, 2H), 3.81 (s, 3H), 3.28 (q, J = 7.2 Hz, 2H), 2.69 (t, J = 7.2 Hz, 2H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.1, 164.9, 148.5, 141.9, 132.0, 124.4, 121.2, 108.6, 55.8, 35.0, 22.7. Anal. Calcd for $C_{12}H_{15}N_3O_2S$: C, 54.32; H, 5.70; N, 15.84. Found: C, 54.28; H, 5.68; N, 15.87.

***N*-[2-(2-Chloro-4-methoxybenzothiazol-7-yl)ethyl]acetamide (8).** A suitable vessel was charged with copper(I) chloride (29 kg, 293 mol), copper(II) chloride dihydrate (50 kg, 293 mol), ethanol (8 kg), and 33% hydrochloric acid (1991 kg, 1800 mol). **6** (155 kg, 584 mol) was added portionwise, with the temperature kept below 28 °C during the addition. The resulting suspension was cooled to 2−8 °C, and 28% sodium nitrite solution (432 kg, 1753 mol) was added over 1.75−2.0 h keeping the temperature at 2−8 °C and held within this temperature range for a further 90 min. The reaction mixture was added to a mixture of water (6098 L) and methyl isobutyl ketone (430 kg) at 20−25 °C, and the resulting mixture was stirred for 17.5 h at 20−25 °C. The precipitated product was isolated by filtration and washed with water (1860 L). The damp product was dried under vacuum at up to 50 °C to give **8** (107 kg, 64%) as a red-brown solid, HPLC purity >94%. An analytically pure sample was obtained by slurrying the crude material in 16 volumes of ethyl acetate, refluxing for 3 h, and filtering hot to remove **Bis-8**. Addition of charcoal to the hot solution (50% w/w relative to crude **8**), refluxing for a further 1 h, hot filtration, and cooling overnight yielded **8** as yellow-orange crystals (51% recovery), HPLC purity 99.7%; MS (APCI +ve) *m*/*z* 285 and 287 ($M^+ + H$), 251 ($M - Cl$); IR (neat, cm^{-1}) 3364, 1673; ^1H NMR (300 MHz, DMSO-d_6) δ 7.97−7.93 (m, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.08 (d, J = 8.1 Hz, 1H), 3.93 (s, 3H), 3.37−3.29 (m, 2H), 2.83 (t, J = 7.2 Hz, 2H), 1.77 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.2, 151.2, 149.5, 140.0, 137.5, 126.9, 124.7, 108.8, 56.0, 38.3, 34.5, 22.6. Anal. Calcd for $C_{12}H_{13}ClN_2O_2S$: C, 50.61; H, 4.60; N, 9.84. Found: C, 50.57; H, 4.59; N, 9.78.

7-(2-Aminoethyl)-4-hydroxy-1,3-benzothiazol-2(3*H*)-one, Hydrochloride (2). A suitable vessel was charged with 48% hydrobromic acid (2805 kg) and **8** (170 kg, 597 mol). The mixture was heated to 115 °C and then held at reflux (115−125 °C) for 7.0−7.5 h before cooling to 0−10 °C and stirring for about 1 h. The hydrobromide salt **(2a)** was isolated and washed with 2-propanol (total 268 kg). The damp hydrobromide salt (∼160 kg damp weight) was

charged to a suitable vessel containing water (1632 kg), charcoal (Norit SX1-G carbon, 14 kg), and filter aid (Vitacel FAC200, 7 kg). The mixture was warmed to 65−75 °C and held for at least 30 min and then filtered hot through a polishing filter capable of removing particles down to at least 1 micron in size. The filtrate was held at 65−75 °C, and the filter and pipe work were rinsed through with hot water at 65−75 °C (68 kg). To the stirred filtrate was added 33% hydrochloric acid (302 kg, 2733 mol) at 60−70 °C, and then the mixture was cooled to 5−15 °C. The slurry was held at 5−15 °C for at least 30 min, and the product was isolated by filtration and washed with 2-propanol (total 217 kg). This material (∼135 kg damp weight) was recrystallized once more in the same way using water (1233 kg), charcoal (10 kg), filter aid (7 kg), wash water (51 kg), and 33% hydrochloric acid (225 kg, 2037 mol). The recrystallized material was isolated by filtration, washed with 2-propanol (total 170 kg), and dried under vacuum at up to 70 °C to give **2** (93 kg, 63%), as a light yellow crystalline solid, HPLC purity >98.5%; MS (APCI +ve) *m/z* 211 ($M^+ + H$); IR (neat, cm^{-1}) 3127, 3062, 1665; ^1H NMR (400 MHz, DMSO-d_6) δ 11.80 (br s, 1H), 10.19 (br s, 1H), 8.14 (br s, 3H), 6.87 (d, $J = 8.2$ Hz, 1H), 6.79 (d, $J = 8.2$ Hz, 1H), 2.98 (br m, 2H), 2.79 (t, $J = 7.8$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.1, 141.8, 124.7, 123.6, 123.0, 121.1, 112.8, 38.2, 31.1. Anal. Calcd for $C_9H_{10}N_2O_2S.HCl$: C, 43.81; H, 4.49; N, 11.35; Cl, 13.00; S, 14.37. Found: C, 44.22; H, 4.53; N, 11.47; Cl, 13.37, S, 14.63.

[2-(2-Propenyloxy)ethyl]benzene (14). A suitable vessel was charged with toluene (470 L), stirring was started, and sodium hydroxide (micropearls, 103 kg, 2575 mol) followed by tetrabutylammonium hydrogen sulfate (TBAH) (3.15 kg) was added. 2-Phenylethanol (105 kg, 860 mol) and allyl bromide (135 kg, 1116 mol) were added and rinsed in with toluene (30 L). The vessel was heated to 65−75 °C, and the contents were maintained at 65−75 °C for 2−4 h with efficient stirring. A solution of TBAH (2.10 kg) in water (5.3 L) was charged to the vessel, and stirring continued at 65−75 °C for 1−2 h. A further portion of TBAH (1.05 kg) in water (2.6 L) was added to the vessel, and stirring continued at 65−75 °C for up to 16 h. The mixture was cooled to 35−40 °C, water (210 L) was added, and the resulting mixture stirred for 15 min. Stirring was stopped, and the phases were allowed to separate at 35−40 °C. The aqueous phase was run to waste, and the organic phase was washed with water (55 L). This wash was repeated, and the organic phase was separated and concentrated by distillation of the solvent (approximately 530 L of solvent was removed; if necessary distillation was continued until allyl bromide content was ≤0.1% by GC) with a final vessel temperature of 145 °C. The mixture was cooled to 20 °C and filtered to give **14** as a toluene concentrate (approximately 95 mol % **14** by GC; equivalent to 135 kg, 97%).

{**[3-(2-Phenethyloxy)propyl]sulfonyl**}**ethanol (17).** To a solution of mercaptoethanol (72 kg, 921 mol) in toluene (80 L) at 65−70 °C was added AIBN solid (0.8 kg) in one portion followed by **14** (toluene concentrate 135 kg weight equivalent) added over approximately 1 h (mixture held at 65−70 °C during addition). A solution of AIBN (2.7 kg) in toluene (140 L) was added at 65−70 °C over 3−5 h and rinsed in with toluene (20 L). The resulting mixture was stirred at 65−70 °C for a further 2−3 h and then cooled to 35−45 °C giving a solution of crude thioether **16** used without further purification. A solution of sodium tungstate dihydrate (1.4 kg, 4.2 mol) in water (10 L) was added, and to the resulting stirred mixture was added 35% hydrogen peroxide (185 L, 2100 mol) at a rate that maintained the temperature at 40−55 °C during the addition. The resulting mixture was stirred for 4−6 h at 35−55 °C, stirring was stopped, and the phases were allowed to separate over 30−60 min keeping the temperature 35−55 °C. The lower aqueous layer was separated, extracted with isopropyl acetate (200 L) by stirring for 15−30 min at 35−55 °C, and the isopropyl acetate extract combined with the remaining organic mixture. To the combined organic phases was added a solution of sodium sulfite (21 kg) in water (200 L), with the temperature maintained at 35−45 °C during the addition. The mixture was stirred for 15−30 min at 35−45 °C, stirring stopped, and the phases were allowed to separate over 30−60 min. The aqueous layer was run to waste, and the organic phase was diluted with isopropyl acetate (150 L) and washed at 40−60 °C with sodium carbonate solution (10% w/v, 7 kg sodium carbonate + 70 L water). This wash was repeated, and the organic phase was finally washed with sodium chloride solution (5% w/v, 3.5 kg sodium chloride + 70 L water) at 40−60 °C. The organic phase was dried by azeotropic distillation under Dean−Stark conditions collecting approximately 20 L of water with a final vessel temperature of 92−102 °C. Isopropyl acetate (70 L) was distilled off, and the reaction mixture was diluted with isopropyl acetate (200L) and sampled for water content by Karl−Fisher assay (if water content was >0.3% w/w, azeotropic distillation was continued). The reaction mixture was cooled to 15−25 °C and filtered to give a solution of crude **17** as a toluene/isopropyl acetate solution (yield approximately 215 kg including regioisomer, approximately 870 kg total weight of solution) used directly in the next stage.

Benzoic Acid, 2-{[3-(2-phenethyloxy)propyl]sulfonyl}-ethyl Ester (18). To the toluene/isopropyl acetate solution of **17** (approximately 870 kg) was added triethylamine (96 kg, 948 mol) and isopropyl acetate (330 L). The mixture was cooled to 15−30 °C, and benzoyl chloride (134 kg, 953 mol) added over 3−6 h while maintaining the vessel contents at 15−30 °C during the addition (residual benzoyl chloride was washed in with isopropyl acetate (50 L)). The resulting mixture was stirred for 1−2 h at 15−30 °C and then sampled for conversion by HPLC. If required, a further portion of triethylamine (8 kg, 79 mol) and benzoyl chloride (11 kg, 78 mol) was added, and the mixture stirred for a further 1−2 h. Water (410 L) was added, and the mixture stirred for 15−30 min and was then allowed to settle for 30−60 min. The lower aqueous layer was run to waste, and the organic phase was washed with a solution of sodium bicarbonate (25 kg of sodium bicarbonate + 410 L of water) by stirring for 1−2 h and allowing the phases to separate over 30−60 min. The

aqueous layer was run to waste, and this wash was repeated. The organic phase was concentrated by distillation at atmospheric pressure until the vessel temperature reached 90−95 °C and then further concentrated under progressive vacuum without allowing the vessel temperature to fall below 60 °C until the vessel temperature reached 90−95 °C at 20−50 mmHg pressure (a total distillate of approximately 1100 L was collected). The mixture was cooled to 60−70 °C, warm (approximately 50 °C) 2-propanol (950 L) added, and the resulting mixture was reheated, if necessary, to 50−55 °C and then cooled to 38−42 °C. Seed crystals of **18** (0.5−1.5 kg) were added, and the mixture was stirred for 1−2 h at 35−40 °C and then cooled to 10−20 °C over 2−4 h and stirred 1−2 h. The crystalline product was isolated by filtration on a centrifuge, washing with cold (5−15 °C) 2-propanol (2 × 50 L per centrifuge load) to give damp crude **18** (approximately 244 kg dry weight equivalent). A suitable vessel was charged with damp crude **18** (approximately 244 kg dry weight equivalent) and 2-propanol (980 L), and the mixture heated to approximately 80 °C to effect dissolution. The solution was filtered hot into a second vessel, the first vessel was charged with 2-propanol (120 L) that was then heated to approximately 80 °C, and this was also passed through the filter into the second vessel. The resulting solution in the second vessel was cooled to 42−46 °C and held at that temperature for at least 1 h. The solution was then cooled further to 10−20 °C over at least 2 h and held at 10−20 °C for at least 1 h. The recrystallized product was collected by pressure filtration, and the filter cake was washed with prefiltered (0.5 micron cartridge) 2-propanol (240 L) at 10−20 °C and was dried at 35−45 °C to give pure **18** (226 kg, 70% from 2-phenylethanol) as a white crystalline solid, mp 65−66 °C, HPLC purity >99.7%; MS (APCI +ve) *m*/*z* 377 ($M^+ + H$); IR (neat, cm^{-1}) 2938, 1726, 1277, 1107, 711; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00−7.97 (m, 2H), 7.70−7.66 (m, 1H), 7.54 (t, J = 6.2 Hz, 2H), 7.29−7.25 (m, 2H), 7.22−7.16 (m, 3H), 4.64 (t, J = 4.6 Hz, 2H), 3.65 (t, J = 4.6 Hz, 2H), 3.56 (t, J = 5.6 Hz, 2H), 3.48 (t, J = 5.0 Hz, 2H), 3.21−3.17 (m, 2H), 2.77 (t, J = 5.6 Hz, 2H), 1.96−1.92 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.3, 138.9, 133.5, 129.2, 128.7, 128.1, 125.9, 70.8, 67.8, 58.1, 51.1, 50.4, 35.4, 21.7. Anal. Calcd for $C_{20}H_{24}O_5S$: C, 63.81; H, 6.43; S, 8.52. Found: C, 63.89; H, 6.39; S, 8.39.

4-Hydroxy-7-{2-[(2-{[3-(2-phenylethoxy)propyl]-sulfonyl}ethyl)amino]ethyl}-1,3-benzothiazol-2(3*H*)-one Hydrochloride (1). Ethanol (473 kg), **18** (50.4 kg, 134 mol), and **2** (30.0 kg, 122 mol) were charged to a suitable reaction vessel with vigorous stirring. Triethylamine (43.1 kg, 435 mol) was added, and the mixture was refluxed (75 °C or above) for around 4.5 h. The reaction mixture was cooled to approximately 65 °C, and 36% hydrochloric acid (55.5 kg, 549 mol) was added at a controlled rate keeping the temperature of the mixture below 72 °C during the addition. Residual hydrochloric acid was washed in with ethanol (15 kg), and the temperature of the mixture was adjusted to 65−69 °C. Seed crystals of **1** (approximately 0.90 kg) were added, and the stirred mixture was allowed to cool to 10−20 °C using a cooling rate of 0.2 °C/min and stirred for at least 1 h. The crystalline product was collected by filtration, washed with methanol (105 kg), and dried at up to 55 °C to give crude **1** (46 kg, 75%) as a light yellow crystalline solid, HPLC purity >97%.

Recrystallization of 1. Crude **1** (46 kg, 92 mol) was charged to a dissolution vessel, and methanol (736 kg) was added with vigorous stirring. The mixture was heated to reflux (the boiling point was about 65 °C) and held at reflux for 30 min. Hydrochloric acid (36%, 18.3 kg) was added, and the mixture was held at reflux for 20 min and then transferred to a receiving vessel via a polishing filter, ensuring that crystallization of the product caused by either overcooling or solvent evaporation was avoided during the transfer. The vessel contents were allowed to cool to around 55 °C, and seed crystals of **1** (2.28 kg, 4.55 mol) were added. The mixture was stirred for 90 min at around 55 °C, cooled to around 8 °C using a cooling rate of 0.1 °C/min, and stirred for at least 1 h. The solid product was isolated on a centrifuge in as many loads as necessary, and each load was washed with methanol (total amount of methanol used for the washing was 75−120 kg). The product was dried at around 55 °C (approximately 16 h) to give pure **1** (42.3 kg, equivalent to 40 kg, 87% from crude **1**) as a pale yellow crystalline solid, mp 219−223 °C (dec), HPLC purity >99%; MS (FAB +ve) *m*/*z* 465 ($M^+ + H$); IR (neat, cm^{-1}) 3328, 3184, 1655, 1314, 1136, 1117, 606; ^{1}H NMR (360 MHz, DMSO-d_6) δ 11.81 (s, 1H), 10.19 (s, 1H), 9.43 (br s, 2H), 7.32−7.15 (m, 5H), 6.88 (d, J = 8.2 Hz, 1H), 6.79 (d, J = 8.2 Hz, 1H), 3.63−3.55 (m, 4H), 3.60 (t, J = 6.1 Hz, 2H), 3.41−3.30 (br m, 2H), 3.24−3.19 (m, 2H), 3.19−3.11 (br m, 2H), 2.91−2.85 (m, 2H), 2.81 (t, J = 7.0 Hz, 2H), 1.92 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.1, 141.8, 138.9, 128.8, 128.2, 126.0, 124.8, 123.8, 123.0, 120.8, 112.7, 70.9, 67.7, 49.5, 47.8, 46.1, 35.4, 29.8, 21.8. Anal. Calcd for $C_{22}H_{29}N_2O_5S_2$·HCl: C, 52.74; H, 5.83; N, 5.59; S, 12.80. Found: C, 52.58; H, 6.07; N, 5.75; S, 12.77.

Preparation of Acid 9 from Allyl Ether 14. To a toluene concentrate of **14** (85 mol % by GC, 11.8 g, 67.5 mmol) was added mercaptoacetic acid (8.8 g, 95.5 mmol) in a flask open to the atmosphere, and the mixture was stirred for 16 h (an initial exotherm occurs raising the internal temperature of the mixture to approximately 60 °C) giving crude **13** (20.6 g, approximately 73 mol % **13** by HPLC; 19:1 mol ratio of **13:13a**). A portion of this product (17.9 g) was suspended in water (50 mL), and a solution of potassium carbonate (96.8 g, 700 mmol) in water (240 mL) slowly added. To the resulting stirred mixture was added a solution of potassium peroxymonosulfate (OXONE, 130 g, 211 mmol) in water (450 mL) over a 2 h period (the internal temperature rose to 45 °C). The suspension was stirred for 16 h, water (300 mL) was added to give a solution, and this was washed with diethyl ether (2 × 200 mL, these washings were discarded) and acidified by slow addition of 3 M sulfuric acid (approximately 300 mL). The mixture was then extracted with diethyl ether (2 × 200 mL), and the combined extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated to give a clear oil. After

dissolution in toluene (150 mL) and concentration (rotary evaporator, water bath 50 °C, water pump), the oil was dissolved in toluene (150 mL) at 60 °C, and the solution was left to stand for 16 h. The product that had crystallized was collected by filtration and dried to give **9**[1] (10.3 g, 61%) as a white solid, HPLC purity 99.3%.

Preparation of Vinyl Sulfone 15 from Acid 9. To a solution of **9** (2.86 g, 10 mmol) in THF (10 mL) was added 1 M borane·THF solution (14 mL, 14 mmol) resulting in effervescence which subsided over 10 min. The mixture was stirred at ambient temperature for 3 h and then a solution of sodium hydroxide (1.63 g) in water (5 mL) was added (effervescence). After the mixture was stirred for 30 min, saturated brine (3 mL) was added, and the mixture was extracted with diethyl ether (50 mL). The organic phase was separated, dried over anhydrous sodium sulfate, and concentrated to give crude **17** as a clear oil (2.22 g). A portion of this product (2.0 g) was dissolved in toluene (2 mL), thionyl chloride (0.9 mL, 12.3 mmol) was added, and the mixture was heated at 95−100 °C for 1.5 h. After cooling, the reaction mixture was concentrated to give an oil which was dissolved in dichloromethane (10 mL) and added dropwise to a solution of triethylamine (2.1 mL, 15 mmol) in dichloromethane (1.5 mL). The resulting mixture was stirred for 2 h, then washed with 2 M hydrochloric acid (20 mL) and brine (10 mL), dried over anhydrous sodium sulfate, and concentrated to give the crude product as an oil which was purified by chromatography on silica gel eluting with 10% ethyl acetate/90% dichloromethane. This afforded pure **15** (0.68 g, 30%) as a clear oil which crystallized on standing, mp 28−28.5 °C, HPLC purity 99.5%; MS (FAB +ve) *m*/*z* 255 ($M^+ + H$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.30 (t, J = 7.0 Hz, 2H), 7.25−7.14 (m, 3H), 6.57 (dd, J = 16.6, 9.7 Hz, 1H), 6.42 (d, J = 16.6 Hz, 1H), 6.14 (d, J = 9.7 Hz, 1H), 3.64 (t, J = 7.0 Hz, 2H), 3.52 (t, J = 5.9 Hz, 2H), 3.02 (m, 2H), 2.87 (t, J = 7.0 Hz, 2H), 2.01 (m, 2H).

***N*-[2-(2-Bromo-4-methoxybenzothiazol-7-yl)ethyl]acetamide (19).** To 48% HBr solution (44 mL) at 22 °C with stirring was added **8** (12.0 g, 0.042 mol), and the resulting red-brown solution was heated to 100 °C (internal temperature) over a 55 min period using controlled heating on a jacketed vessel. The reaction mixture was quenched by addition of water (500 mL) with stirring giving a precipitate, and the mixture was cooled in an ice bath and neutralized by portionwise addition of 28% ammonia solution. The resulting mixture was stirred in an ice bath for 30 min resulting in formation of a brown solid that was isolated by filtration and washed with 2-propanol to give crude **19** as a brown solid (9 g). This material was dissolved in ethyl acetate (160 mL) by refluxing for 2 h and filtered hot, and the filtrate was allowed to cool to ambient temperature with stirring. The recrystallized product was collected by filtration, washed with 2-propanol, and dried under vacuum for 16 h giving **19** (4.8 g, 34% overall), HPLC purity 90%; MS (APCI +ve) *m*/*z* 329 and 331 ($M^+ + H$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, J = 8.1 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 5.47 (br s, 1H), 4.02 (s, 3H), 3.58 (d, J = 6.9 Hz, 2H), 2.95 (t, J = 6.9 Hz, 2H), 1.95 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.2, 151.1, 141.6, 138.6, 136.0, 126.8, 124.6, 108.6, 56.0, 38.7, 34.6, 22.6.

***N*-[2-(4-Methoxy-2-oxo-2,3-dihydrobenzothiazol-7-yl)-ethyl]acetamide (20).** A stirred suspension of **8** (42.3 g, 0.149 mol) in 36% hydrochloric acid (212 mL) was heated to reflux giving a red-brown solution. The solution was refluxed for 2 h 20 min during which time a precipitate had formed. The mixture was allowed to cool, and the precipitated product was collected by filtration, air-dried, and then dried further under vacuum for 16 h affording crude **20** (20.3 g, 51%) as a yellow solid, HPLC purity 87%. This material was dissolved in ethanol (160 mL) and water (160 mL) at 76−80 °C, and the resulting solution was filtered hot and allowed to cool with stirring for 16 h. The recrystallized product was collected by filtration, washed with 2-propanol, and dried under vacuum for 16 h to give **20** (15.1 g, 38% overall) as a yellow solid, HPLC purity 96%; MS (APCI +ve) *m*/*z* 267 ($M^+ + H$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.85 (s, 1H), 7.93 (m, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 3.85 (s, 3H), 3.25 (q, J = 6.8 Hz, 2H), 2.63 (t, J = 6.8 Hz, 2H), 1.77 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.5, 169.1, 143.4, 125.3, 125.2, 123.4, 122.8, 108.8, 55.9, 38.7, 33.5, 22.6.

7-(2-Aminoethyl)-4-methoxy-1,3-benzothiazol-2(3*H*)-one, Hydrochloride (21a). A suspension of trifluoroacetamide **3**[3] (10 g, 0.029 mol) in a mixture of ethanol (100 mL), water (50 mL), and 36% hydrochloric acid (50 mL) was heated to reflux and refluxed for 4 h. The resulting brown solution was concentrated on a rotary evaporator (water bath at 40 °C), removing most of the ethanol to initiate crystallization of the product. The resulting mixture was cooled at 0−4 °C for 35 min, and the product was isolated by filtration, washed with diethyl ether (around 60 mL), and dried under vacuum at 50 °C for 16 h to give **21a** (5.48 g, 71%) as a fine yellow powder, HPLC purity 95%; MS (FAB +ve) *m*/*z* 225 ($M^+ + H$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.24 (br s, 3H), 7.03 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 3.86 (s, 3H), 3.08−2.93 (br m, 2H), 2.91−2.82 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.3, 144.0, 125.8, 123.4, 122.9, 108.9, 56.0, 38.0, 31.1.

***N*-[2-(4-Hydroxy-2-oxo-2,3-dihydrobenzothiazol-7-yl)-ethyl]acetamide (22).** To a suspension of **2** (20.4 g, 0.082 mol) in DMF (100 mL) was added triethylamine (27.5 mL, 0.196 mol) at 10 °C, and the mixture was stirred for 10 min. Acetyl chloride (7.0 mL, 0.098 mol) was added dropwise over 30 min at 10−20 °C, and the mixture was allowed to warm to ambient temperature and stirred for 3 h. The mixture was cooled to 10 °C and water (100 mL) was added over a 10 min period resulting in the formation of a precipitate. The suspended solid was stirred for 30 min, then collected by filtration, washed with water (200 mL), and dried under vacuum at 45 °C for 16 h to give crude **22** (15.6 g, 75%) as a yellow solid. Purification could be achieved by recrystallization from methanol/water (75/25 v/v, 43% recovery for the first crop) to afford **22** as an off-white solid, HPLC purity 96.1%; MS (EI) *m*/*z* 252 ($M^+ + H$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.50 (br s, 1H), 9.94 (br s, 1H), 7.92 (m, 1H),

6.78 (d, $J = 8.4$ Hz, 1H), 6.70 (d, $J = 8.4$ Hz, 1H), 3.23 (m, 2H), 2.58 (t, $J = 7.2$ Hz, 2H), 1.98 (s, 3H).

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Supporting Information Available

Table summarizing critical parameters and activities associated with the registered processing stages of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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