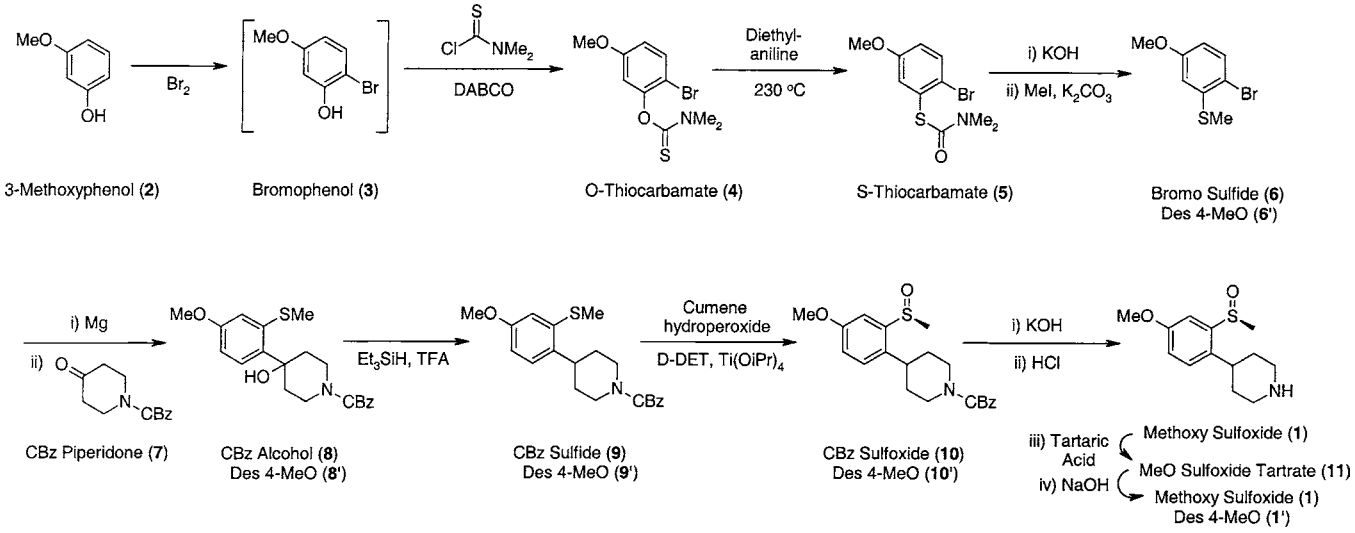
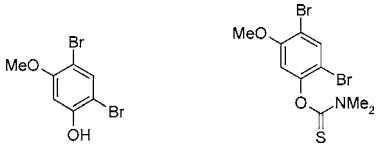
Scheme 1



and could in fact be run in the more acceptable dichloromethane at 20 °C with the exotherm controlled by the bromine addition rate. The distillation was avoided by successful telescope into the following crystalline O-thiocarbamate stage, as discussed below.



The main challenge of this bromination process was to control the ratio of the desired bromophenol (**3**) to the dibromide (**12**) (and other multiple bromination products), whilst achieving adequate conversion of **2**. The Research conditions gave a 12:1 ratio in favour of the product with some residual **2** (which is an oil and is lost in the mother liquors at the next stage). Our change to dichloromethane gave a slightly worse but still acceptable ratio.[8] We briefly investigated alternative conditions (standard electrophilic bromination,[9] NBS in acetonitrile,[10] and NBS in aqueous base[11]), but all gave much higher levels of regioisomeric di- and tribrominated products as determined by LC−MS.

To establish that we were working in a robust region of reaction space,[1] and possibly to optimize the reaction further, particularly the ratio, we conducted a factorial experimental design (FED) using a four-cell HEL Automate reactor. We investigated five parameters at two levels in eight experiments, resulting in a quarter factorial. The parameters investigated with their high and low levels are shown in Table 1; however, the fast addition rate and low-temperature combinations were deliberately excluded from the design as being unsuitable. The FED showed that longer addition times moderately favoured better selectivity, whilst other factors had little effect. Thus, we chose the lower temperature to control the exothermic addition, and 0.85 equiv of bromine as a compromise between unreacted **2** and dibromide (**12**). However, larger scale trials showed that the lower charge of bromine at 0.75 equiv with stirring at room temperature for several hours gave a moderately improved solution yield of **3**. No other work specific to this stage was undertaken as it was successfully telescoped into the *O*-thiocarbamate stage.

Table 1. **FED parameters for bromophenol stage**

parameter	low level	high level
bromine charge (equiv)	0.75	0.95
dichloromethane charge (volumes)	6	8
addition temperature (°C)	5	20
addition time (min)	15	60
reaction temperature (°C)	5	20

***O*-Thiocarbamate Stage (4).** The Research process redissolved the distilled bromophenol (**3**) in DMF to which DABCO and dimethylthiocarbamoyl chloride (DMTCC) were added sequentially in portions, to acylate the free phenol. After an overnight hold, the crude *O*-thiocarbamate was precipitated by the addition of a large volume of water (25 volumes), and the crude dried solid then recrystallised from hot methanol in 44% overall yield for the two stages. We were concerned about the potential toxicity of DMTCC by comparison with the *O*-analogue, dimethyl carbamoyl chloride, a known animal carcinogen[12] generated at low levels during the preparation of other NK compounds.[1,4] The advice from our occupational health department was that the risk from the nonvolatile *S*-analogue was much lower and could be used under standard precautions for lab work and Large Scale Lab (LSL)[13] manufacture.

(7) Under Article 2E of the Montreal Protocol (United Nations Environment Programme, 1988), production and use of 1,1,1-trichloroethane, which is an ozone-depleting chemical, should have been phased out in developed countries by 1996.
(8) We also tried chloroform which gave a marginally better ratio than that with dichloromethane, but not sufficiently so in our view to justify its usage.
(9) Sandin, R. B.; McKee, R. A. In *Organic Syntheses;* Blatt, A. H., Ed.; John Wiley and Sons: New York, 1943; Collect. Vol. 2; pp 100−101.
(10) Carreno, M. C.; Garcia Ruano, J. L.; Sanz, G.; Toledo, M. A.; Urbano, A. *J. Org. Chem.* **1995**, *60*, 5328.
(11) Auerbach, J.; Weissman, S. A.; Blacklock, T. J.; Angeles, M. R.; Hoogsteen, K. *Tetrahedron Lett.* **1993**, *34*, 931.
(12) Irving Sax, N. *Dangerous Properties of Industrial Materials*, 5th ed.; Van Nostrand Reinhold Company: New York, 1979.

We had few other concerns with this stage but felt that several worthwhile improvements could quickly be assessed. The first of these was to prove the reaction could be performed in dichloromethane, which allowed us to telescope from the previous stage, hence avoiding the distillation of the bromophenol. We cut down the equivalents of both DABCO (2.4 to 1.25) and DMTCC (2.4 to 1.03) without compromising the result. DMTCC also had much higher solubility in dichloromethane and so could be added as a solution, thus avoiding solid charging of a key reagent. A change to triethylamine from DABCO gave a gelatinous precipitate (presumably $Et_3N{\cdot}HCl$) so that we retained the more efficient DABCO. An attempt to avoid the aqueous wash with dilute HCl to remove DABCO·2HCl (now possible with dichloromethane in place of DMF) led to the precipitation of a white solid during subsequent processing and low-strength product, presumably both due to the presence of DABCO·2HCl. The reaction was notably faster in DMF compared to dichloromethane (4 h versus 18 h at 20 °C), but the product form was poor and required drying before recrystallisation. Using NMP as a cosolvent (7% v/v with dichloromethane) did not improve the reaction rate and resulted in high losses to liquors. Finally, a solvent swap after the aqueous wash into methanol and distillation of the dichloromethane was successful, which avoided isolation and drying of the crude *O*-thiocarbamate. The product crystallized well from methanol, as noted by our Research colleagues, but was often slow to initiate. Seeding or self-seeding at ~30 °C proved to be robust in the lab, and during manufacture only the first batch required seeding, the second two crystallising spontaneously.

Three batches were manufactured in the LSL. Quality was typically >96% with the dibromo analogue (**13**) being the major impurity (untypically higher in the last batch). High product strengths indicated that UV−invisible inorganic and DABCO·2HCl residues had been successfully removed. DSC analysis of the product **4** showed that there was no thermal instability at operational temperatures, and no further hazard testing was judged necessary in this case. The overall yield was ~45%, effectively the same as the Research process but with simplified operations; about 15% product remained in the liquors which could not be isolated.

Overall, we were able to apply standard process development improvements to these two stages and combine them into one telescope. Although the yield was moderate, we were able to produce adequate quantities of material in three batches. The processes had proved both safe and robust in manufacture and so had met the project remit, and further improvements were passed over in favour of working on later, more challenging stages as discussed below.

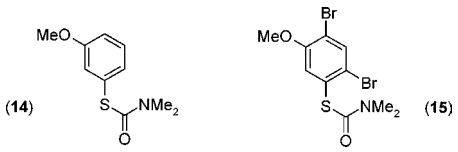
(13) The Macclesfield LSL is a cGMP manufacturing facility for synthesis of bulk drug for clinical studies and uses all glass vessels. It is typically where the first significant scale-up of a process occurs, and commonly delivers tens of kilograms of intermediates and kilograms of bulk drug. It consists of a range of glass reactors 10−100 L in scale, fully contained with other ancillary equipment in fume cupboards. Operating ranges vary from −78 to +130 °C. Atmospheric hydrogenations can be performed, and a 20-L rotary evaporator is available for distillations if required. Product is generally isolated as a solid on Nutsches. AstraZeneca has several other LSLs at different sites which operate in a similar fashion.

***S*-Thiocarbamate Stage (5).** This stage provided the first real test of applying the Research chemistry approach to this target molecule, as mentioned in our introductory paper.[1] Formation of the *S*-thiocarbamate is achieved from the *O*-thiocarbamate precursor by a Newman−Kwart rearrangement[14] using the method of Tímár[15] in refluxing *N*,*N*-diethylaniline (bp 218 °C). This could only be achieved in the LSL in a heating mantle, and that limited it to 20 L maximum. Previously for ZD6021 we had decided not to use a heating mantle for the cyano ester stage, although in part this was due to the presence of cyanide.[3] That reaction had ideally required 180 °C, but only 130 °C could be achieved in a jacketed vessel, attenuating reaction times from 4 to 48 h. Necessity forced a rethink for the *S*-thiocarbamate process for which the higher temperature was essential. Fortunately, the process received from Research was also very concentrated, so that the manufacture could be comfortably completed in the 20-L flask in three batches, one of which was a smaller-scale proving batch.

The Research process heated the *O*-thiocarbamate in degassed diethylaniline at reflux for 3−4 h; the solvent was distilled off by short-path distillation, and the residue was precipitated in ice-cold 6 M HCl, extracted with diethyl ether, dried, and concentrated to a brown solid which was recrystallised as a white solid from methanol in ~60% overall yield. Aside from the operational use of the heating mantle which was new to the LSL at the time, we were concerned about the need for degassing the reaction solution, and its effectiveness in the LSL versus the lab. Lab preparations showed that degassing to remove oxygen was indeed necessary; without it, a lower yield of sticky-brown product higher in impurities resulted. Both evacuation/purging and sparging techniques were shown to be acceptable in the lab. In the LSL both methods were used in combination and were found to be successful without issue. If the impurity profile was good, it was found that a straightforward drown-out of the reaction mixture directly into an excess of ice-cold 6 M HCl could be used in place of the extractive procedure. This yielded the *S*-thiocarbamate as a light-brown solid which was washed with water and dried. Typical lab yields had been around 60% as for the Research process. In fact, the combined yield in the LSL for the 3 batches was 88%, well above the planning yield of 59%. Quality was also good, being typically 96% by LC area and >95% by strength. The major impurities were residual starting material (**4**), dibromo-*O*-thiocarbamate (**13**), des-bromo-*S*-thiocarbamate (**14**), and dibromo-*S*-thiocarbamate (**15**), of which **4** and **15** were the two major ones (up to 3%, but only one predominated). Batch three had an untypically high level of **15** at 9.3%; all other impurities were below 1% by HPLC.

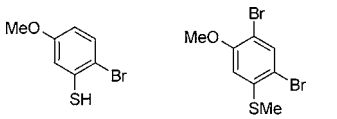
Finally, preliminary hazard work of a DSC on the product **5** revealed a possible concern from 181 °C, well below the proposed reaction temperature. A more thorough, larger-scale Carius tube test revealed a prolonged double exotherm from 228 °C, quite possibly the heat of reaction since this is close to the temperature of the rearrangement. Although this was

(14) Newman, S.; Karnes, H. A. *J. Org. Chem.* **1966**, *31*, 3980 and Kwart, H.; Evans, E. R. *J. Org. Chem.* **1966**, *31*, 410.
(15) Sebök, P.; Tímár, T.; Eszenyi, T.; Patonay, T. *Synthesis* **1994**, 837.



judged acceptable on the 20-L scale, additional hazard testing would have been required for further scale-up. Fortunately, this did not present us with a capacity issue due to the concentrated nature of the process.

Bromosulfide Stage (6). This stage was inherited as a partial telescope from Research and was already relatively simple. Hydrolysis of the *S*-thiocarbamate in methanol with 7.6 equiv of KOH gave the intermediate thiol (**16**) as an oil after an acidic workup, which was redissolved in DMF and treated with K_2CO_3 and methyl iodide to give the desired bromosulfide. The quantity of base seemed excessive, and this was readily reduced to 2.2 equiv, whilst the methyl iodide charge was cut down from 1.7 to 1.1 equiv (1.0 being just insufficient). The solvent swap to DMF also seemed unnecessary, so that the alkylation reaction was also conducted successfully in methanol. On completion, water was added and the product extracted into MTBE and concentrated to an oil. Hazard studies (Carius tube) showed that, although the hydrolysis phase was essentially an "all-in" process, there were no exotherms of concern; the alkylation reaction was effectively under process control by the methyl iodide addition.

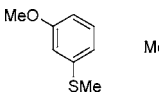


Thiol (**16**) Dibromo sulfide (**17**)

This process was developed for manufacture in only 2 weeks, well inside our 4−6 week target. Other than the changes noted above, dimethyl sulfate was investigated as an alternative alkylating agent. However, methyl iodide gave a slightly faster, cleaner reaction so that this was retained, other safety and health issues being considered well controlled in the LSL environment. Quality was as good (>98% by HPLC), except for that of batch three where the high level of dibromo-(*S*)-thiocarbamate carried through as the dibromosulfide (**17**) at 6% by HPLC. Crude yield of the concentrated oil for each of the three batches was >100%, but with quality so high, we assumed this was residual MTBE. The product was an oil, and we had no initial standard with which to compare it. Unfortunately, the first batch of the following Grignard reaction was partially quenched, and we assumed from this that the residual solvent was, in fact, methanol. Azeotroping the bromosulfide batches from toluene under vacuum distillation reduced the yield to a more plausible 90% each and allowed the CBz alcohol stage to proceed smoothly. Our rapid development had been too rapid in this case.

CBz Alcohol Stage (8). This stage proved to be the most demanding test of the new strategy on scale-up, since purification by chromatography was required. Initially, Grignard conditions were used in coupling bromosulfide (**6**) with CBz piperidone (**7**), by analogy with the nearly identical Grignard coupling of ZD7944 bromosulfide (**6′**) with CBz piperidone.[6] Using 1.35 equiv of **6** in 1:1 toluene:THF gave a poor conversion of **6** to CBz alcohol (**8**) in only 30% yield after chromatography after several attempts. As noted in our introductory report,[1] we used Kepner−Tregoe analysis for problem solving at critical points, and this proved to be effective here. Several potential causes for the low yield were proposed, but most were readily eliminated as being inconsistent with other experimental data. As discussed above, it was quickly shown by this methodical approach that residual solvent (methanol) in bromosulfide (**6**) was the cause of the problem (by partially quenching out the Grignard reagent). Azeotroping **6** with toluene removed the residual methanol, improving the yields significantly in the subsequent reaction.

Whilst investigations had quickly been proving this hypothesis, we had also tried the harsher direct lithiation of bromosulfide with butyllithium at −78 °C, which appeared to work better. With the toluene-azeotroped bromosulfide, the lithiation reaction was quickly optimized in the lab. Neat anhydrous THF was found to be better than the toluene−THF mixtures we had started with. Using a 1.2 equiv excess of **6**, a 65−70% yield of **8** could be obtained after chromatography. These lithiation conditions were used for the first batch in the LSL, but unfortunately a troublesome unknown impurity was produced in this batch at 15% which had previously only been seen at <5% in lab work. Because of the concern that this had not scaled up well, we reverted to the more well-known (in our hands) Grignard conditions. With the other improvements and changes now made, the next three batches all performed well under the Grignard conditions, to give the crude product after workup as a viscous brown/red oil.



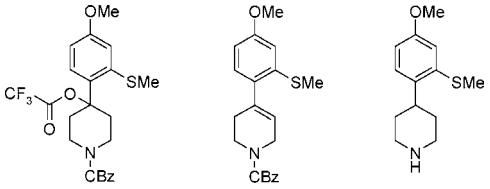
Methoxy sulfide (**18**)

Chromatography was required to remove the residual quenched Grignard reagent product methoxy sulfide (**18**), which always contaminated the product due to the excess of **6** used. Yields were much poorer without an excess of ∼1.2−1.3 equiv of **6**, and this was the best compromise. Residual CBz piperidone (**7**) was a lesser contaminant which was also removed by chromatography, although in this case crystallization could also be effective. For the LSL, a loading of 14:1 silica gel:crude CBz alcohol was used on a Nutsche filter, eluting with ethyl acetate/hexane combinations. This performed well in the LSL, giving product of 80−85% by NMR strength. A further crystallization/trituration in 3 volumes of ethyl acetate/hexane gave an overall yield of 75% for the two purification steps of **8** with 100% strength. After the first few pure column fractions had been concentrated to dryness, further purifications were found to be unnecessary, as the pure fractions seeded the new liquors on standing. This also avoided the need to concentrate all the liquors, saving considerable time.

Neither process (lithiation or Grignard) was formally hazard-assessed in this case, as they were deemed to be

similar to the analogous ZD7944 stage which had been fully assessed previously. The lithiation was run at −78 °C which was judged low enough to control any potential exothermic addition. The Grignard reaction was initiated by a small charge of bromosulfide (**6**) (12% maximum) and controlled by dropwise addition over several hours only after the initial exotherm had subsided, keeping the temperature below 30 °C at all times. This worked well for all three batches. Overall, a yield of 60−65% for the three Grignard batches was achieved, with quality in the range 96−99%, the only significant impurity being residual **7** at <0.5%, with the mass balance being accounted for by solvent. Output was of necessity very poor, due to the large volumes of solvent required for the chromatography. This also took 3−4 weeks just for the purification alone. However, accommodating a lithiation and then a Grignard reaction, with chromatographic purification of an intermediate halfway through a synthesis, were within the new project remit and were judged a success.

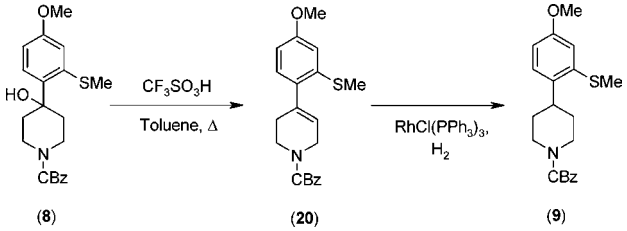
CBz Sulfide Stage (9). This was another process that was used without major changes direct from Research. The alcohol is activated as the TFA ester (**19**) and this is displaced by hydride transfer from triethylsilane (TES) to give the desired reduced product, CBz sulfide (**9**). Some of the elimination product, CBz alkene (**20**) is also formed as an impurity. A further competing reaction is deprotection of the CBz group to give piperidine (**21**).



The Research method had used 2.0 equiv of both TFA and TES. A similar reaction for ZD7944 had used 10.0 equiv of each, and on discussion with Research, it transpired that their yields had been highly variable without obvious explanation. On scaling up to several grams (without solvent), we observed three phases using this combination (assumed to be TFA, TES, and substrate); thus, it is possible that uneven agitation may have accounted for some of these differences. We investigated solvents to overcome this potential problem and found that both dichloromethane and isohexane gave good selectivity for **9** over alkene (**20**) (∼50:1). Unfortunately, whilst the ratio between these components was good, there was also extensive degradation in addition. Other solvents tried (toluene, ethyl acetate, and NMP) all gave the alkene as the major product. We therefore persevered with the solvent-free reaction. Reducing the temperature to −10 °C also improved the selectivity for formation of **9** over alkene formation or CBz deprotection. However, lower temperatures led to higher levels of the postulated intermediate TFA ester (**19**), which in turn led to higher levels of alkene again.

Given these problems, we attempted an FED to investigate other possible factors, but the results were not reproducible when scaled up. We suspected that physical factors such as agitation and addition rate were not well controlled on the small scale (we were very short of material for lab work at this point in the sequence, and the solvent-free system was of necessity highly concentrated). We decided to investigate the effect of fast and slow TFA additions rates. The fast addition (<5 min) gave low levels of the alkene (∼1%), but the exotherm was uncontrolled. The slow addition gave a relatively high level of alkene to product, whilst unreacted **8** was still present during the first hour, but the level of alkene did not increase during the second hour of the addition. Given the three phases we had already observed, we suspected the solubility characteristics of the reaction were changing and thus affecting the reaction kinetics. We also tried addition of TES to the other two components, but formation of alkene predominated in all these cases. From this we deduced that addition of **8** to a rapidly stirred solution of TFA and TES should give us the best outcome. Since we could not use solvent, **8** had to be added in portions to these reagents. Some alkene was observed after the first portion, but this was found not to increase with subsequent portions, and the level by the end of the reaction was acceptably low. This procedure was adopted for the LSL, and after a somewhat tedious workup, the product CBz sulfide could be isolated after crystallization of the crude oil from ethyl acetate/hexane as a white solid in typically 70% yield for three batches. Final quality was 99% with any residual CBz alkene removed by the crystallization; isohexane washes were needed to remove siloxane byproducts resulting from the bicarbonate quench of excess TES. This was another stage that had less than 4 weeks' development time spent on it; it was also severely hampered by lack of starting material **8**, due to problems with the previous stage and from being several steps into a lengthy synthesis.

Scheme 2

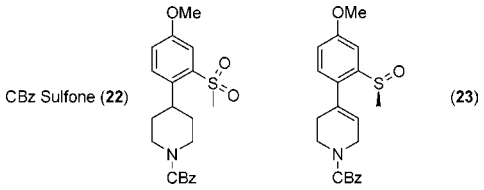


Alternative Hydrogenation Process. An alternative two-step hydrogenation process was also briefly investigated for the CBz sulfide stage, based on a similar approach used for the analogous ZD7944 stage (Scheme 2). Dehydration of alcohol **8** with catalytic 10 mol % methane sulfonic acid in toluene under Dean−Stark conditions proceeded very quickly (<1 h) and cleanly to give CBz alkene in effectively quantitative yield. Reduction of the trisubstituted alkene with Wilkinson's catalysts proved less facile, however. There was very little reaction at room temperature and pressure with 5 mol % catalyst, although at 60 °C with this loading, a lab sample of **9** contaminated with 20% alkene was usefully converted cleanly to the desired product. This procedure had worked well for ZD7944, but there was not time to develop it further for ZD2249 CBz sulfide since fortunately, the TFA/TES procedure was successful before further study was required (e.g., higher H_2 pressures, lower catalyst loadings).

CBz Sulfoxide Stage (10). Kepner−Tregoe potential problem analysis had identified this stage as potentially one of the more technically challenging ones due to the asymmetric oxidation of the sulfide to the (*S*)-sulfoxide. The Research process took place at −30 °C over a period of 6 days, which was deemed to be unacceptably long. Again, a previous process had been developed for ZD7944 CBz sulfoxide (**10′**), and this was found to be suitable for manufacture in this case with only minor modifications.

The key aspect of this reaction was in achieving a high enantiomeric excess (ee). Factors affecting the ee were known from the literature,[16] the related ZD7944 process and the ZD3638 project, which included an extensively studied asymmetric sulfoxidation reaction.[17] The literature indicates that a 2:1:1:1 ratio of diethyl tartrate (DET):Ti(O-*i*Pr)$_4$:sulfide:water gives the optimum ee. An FED performed on ZD7944 CBz sulfide had shown that a range of 0.5−1.5 equiv of water was ideal. Reliable water analysis was critical, but unfortunately it was found that CBz sulfide was not compatible with the Karl Fischer reagent. We therefore had to assume the CBz sulfide was dry and analysed the water content of the DET/dichloromethane solution, assuming that the solvent would be the biggest source of moisture. The critical water charge could then be made up to 1.0 equiv on the basis of this result.

The temperature was also known to be critical. In this case, oxidation at −5 °C gave product with an ee of 85%; decreasing it to −15 °C improved the ee to 94%, which was judged to be an acceptable compromise between reaction rate and ee. The addition of the cumeme hydroperoxide (used as the oxidant) was exothermic, which also affected the ee. The addition rate had to be adjusted to so that the internal temperature of the vessel could be controlled, since any increase would erode the final ee of the product. The cumene hydroperoxide charge was also studied. The reaction was completed overnight at −15 °C with a slight excess (1.05 equiv) of hydroperoxide, with only 1.3% of the sulfone (**22**) being formed. On using 1.2 equiv of hydroperoxide, the reaction could be completed in just 2 h, but the level of this impurity rose significantly. The overnight hold with the lower charge was therefore preferred.



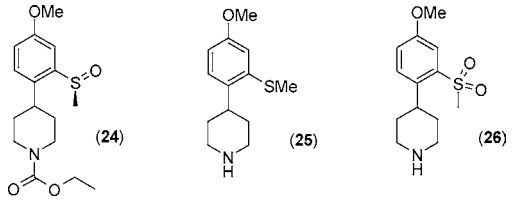
The workup for this reaction required treatment of the reaction mixture with HCl to dissolve the insoluble titanium oxide residues. However, the product would not crystallize (the Research generated sample was a solid); GC showed the presence of DET residues, but neither cumene alcohol or hexaethyldisiloxane (from quenched TES) was present. It was assumed the DET residues were enough to hinder the crystallization. Refluxing the product-containing dichloromethane solution with NaOH in the presence of *n*-Bu$_4$NOH removed the DET residues to <0.1% by GC determination; without the *n*-Bu$_4$NOH, the procedure was less successful, and although beneficial, an oil still resulted. However, since the DET did not cause a problem with the following stages and given the proximity of the manufacturing deadline, we decided not to introduce a new reagent with unknown consequences for the impurity profile so late in the development process. CBz sulfoxide was therefore concentrated to a viscous yellow oil of 60−70% strength against an analytically pure standard, giving a corrected yield of 70−85%.

The following methoxy sulfoxide stage was an apparently simple hydrolysis of the CBz carbamate group with KOH. We therefore attempted to combine the previous alkaline hydrolysis of the CBz sulfoxide stage (during its workup) with this reaction hydrolysis step. However, these attempts were unsuccessful in the time available. Product-related quality was typically 96% by LC (i.e. allowing for solvents and DET residues), with 1.3% of the sulfone (**22**) and no residual CBz sulfide. Sulfated ash analysis showed <0.1% inorganic residues, indicating that the titanium oxide/salts had been successfully removed. The ee was determined by chiral LC and was consistently around 94%, which was satisfactory, given known improvements in quality in later steps. Unfortunately, both the CBz sulfone (**22**) and the unsaturated sulfoxide (**23**) coeluted with the required (*S*)-enantiomer of **10**, which made accurate determinations of ee difficult. A good assessment of these impurities from achiral LC was required to generate useful results. No formal hazard assessment was conducted in this case, again because of the close similarity with the previous ZD7944 process. Overall, two batches were successfully manufactured, the first a smaller proving trial, with 88% overall yield and 94.4% ee in both cases. Manufacture was surprisingly trouble-free, which we attributed to good understanding of this type of process from previous projects.

Methoxy Sulfoxide Stage (1). The last stage in the synthesis of this fragment of ZD2249 proved to be the most problematic, although chemically one of the simplest. It was again a stage for which the development was severely curtailed by lack of starting material, which of necessity reduced the development time and compressed it to a few weeks just before the planned manufacture. Once again, experience from a related ZD7944 stage, Pip sulfoxide (**1′**), formed the basis of the process and undoubtedly saved some time. Using 10 equiv of KOH in industrial methylated spirits (IMS) required a total of 6 h compared to only 3 for ZD7944; increasing the KOH charge to 14 equiv halved the reaction time, but other impurities started to become significant. The reaction was known to proceed partly via the intermediate ethyl carbamate (**24**) (formed by partial solvent hydrolysis), which seemed unusually stable in this case, and required prolonged heating with an increase in reaction times for completion.

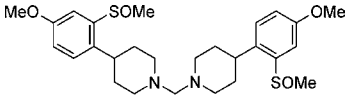
(16) For reviews, see: Zhao, S. H.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135−5144 and Kagan, H. B. Asymmetric Oxidation of Sulphides. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp 203−226.

(17) Hogan, P. J.; Hopes, P. A.; Moss, W. O.; Robinson, G. E.; Patel, I. *Org. Process Res. Dev.* **2002**, *6*, 225−229.



An acid−base extraction procedure as for ZD7944 was then used for the purification and isolation, which gave a dichloromethane solution of the product which was concentrated to an oil. This procedure appeared satisfactory, but the final crystallization solvent combination of toluene/isohexane was less than ideal, with the product often oiling out and recovery being disappointing despite ∼95% observed solution yields. A range of alternative solvents was rapidly screened, but none of these offered any significant advantage. A 3:1 isohexane:toluene solvent ratio was used to improve recovery (to about 70% yield with 88% strength), although the physical form remained poor. Unreacted **10** and carbamate **24** remained in the neutral toluene phase during the aqueous extractions. The deprotected sulfide **25** was seen, but at <0.1%, whilst the deprotected sulfone **26** was seen at up to 5% in reaction liquors. This was puzzling as no more than 1.5% was carried through from **10**, which indicated that the oxidation was occurring during the hydrolysis, more so with the higher equivalents of KOH. Fortunately the crystallization reduced this impurity to <1% in the isolated product.

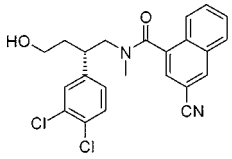
No other work could be undertaken in the time, and so methoxy sulfoxide was manufactured in the LSL in a single batch in unexpectedly high yield of 99%, corrected for strength as determined by LC of 89%. Unfortunately, NMR analysis showed that it contained 20 mol % of a dimeric compound (i.e., 40% w/w). The impurity could not be detected by LC (or it coeluted with the product peak) despite much effort, but NMR analysis (^{1}H and ^{13}C experiments) tentatively assigned the structure as the methylene-bridged dimer (**27**). An analogous impurity had been assigned from the equivalent ZD7944 stage, albeit at only a 5% level. The assumption in both cases was that a prolonged hold, possibly exacerbated by heating during the distillation of the dichloromethane solution, in the presence of basic residues (NaOH) had effected double substitution by the piperidine NH group on dichloromethane to result in the methylene-bridged dimer (**27**), a not uncommon occurrence when using this solvent.[18]



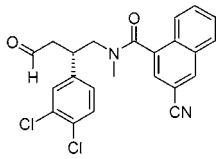
Methylene-bridged Dimer (**27**)

Attempts to use this contaminated material directly in the next stage (reductive amination coupling to the amidealcohol via the aldehyde) on the assumption that the proposed dimer should be inert in this reaction were unsuccessful. The dimer gave rise to another impurity at ∼20% in this penultimate stage which could not be removed. A re-treatment procedure was therefore required at the methoxy sulfide stage. Our Research colleagues had recrystallised **1** with tartaric acid to improve the ee. This was a step we had been hoping to avoid, but although we did not need to improve the ee, we found this procedure, when modified, to be effective at removing dimeric impurity (**27**). The Research procedure had sacrificed yield for homochiral quality; when we reduced the ethanol solvent for the crystallization from 13.5 volumes down to just 3.5 volumes, we achieved a 55% yield. This was a good result as it was estimated that there was only 66% methoxy sulfoxide present by mass in the sample. The free base of **1** was then obtained by treatment of the tartrate salt **11** with aqueous NaOH and extraction into hot toluene at 80 °C. In the LSL the tartrate salt failed to crystallize from 3.5 volumes of ethanol, but on increasing the volume to 5.5 and adding a seed of tartrate salt, the product precipitated as required. Attempts to completely re-extract the purified methoxy sulfoxide into toluene from an aqueous NaOH solution were however unsuccessful. Ethyl and butyl acetates were also unsuccessfully examined as extraction solvents. Fortunately, and somewhat surprisingly, it was found that the aqueous solution of **1** could be used directly in the reductive amination step that followed. This concluded the manufacture of ZD2249 methoxy sulfoxide.[19]

Final Assembly Stages of ZD2249. The coupling of ZD6021 cyano acid with ZD6021 *N*-methylamine was achieved with EDCI to give the amide alcohol (**28**) which was oxidized to the amide aldehyde (**29**) by Swern oxidation and used without isolation as described previously.[4] The reductive amination conditions of coupling aldehyde (**29**) with methoxy sulfoxide (**1**) to give crude ZD2249 are worth a separate comment, however, as they were untypical of the standard conditions used for the other compounds in the NK series.



Amide Alcohol (**28**)



Amide Aldehyde (**29**)

The amide aldehyde (**29**) was used as a dichloromethane solution, which had already been successfully telescoped from the Swern oxidation directly into the coupling stage for ZD6021, using borane−pyridine complex as the reducing agent in the presence of methoxy sulfoxide (**1**). Early lab samples of **1** were relatively free of dimeric impurity (**27**). Identification in later samples of ZD2249 Crude was delayed because this impurity coeluted with an expected monochloro impurity (derived from dehalogenation), which was assumed to be the major problem. At 30 °C, 0.5 equiv of BH_3 had been sufficient to drive the reaction to completion; however, once **27** was identified, it was noted that **27** also increased in this reaction with temperature. A lower temperature with 1.0 equiv of BH_3 were required to complete the reaction.

(18) Lee, S. A.; Robinson, G. E. *Process Development: Fine Chemicals from Grams to Kilograms*; Oxford University Press: Oxford, 1995.

(19) Several other potentially shorter routes to methoxy sulfoxide that were briefly investigated may also be reported at a later date.

An acidic quench followed by base and brine washes removed other impurities and gave crude ZD2249 in ~80% strength, if the dimer was not present in **1**.

Since the dimer **27** was present in the manufactured batch of **1**, a recrystallisation as the tartrate salt (**11**) was developed to remove it, as discussed above. The tartrate salt was then neutralized with NaOH, and in the lab, **1** had been re-extracted into toluene. In the LSL, this was only moderately successful, with most of **1** remaining in the aqueous phase. It was decided to attempt a two-phase reductive amination using the aqueous phase containing **1** diluted with methanol and the dichloromethane solution of **29**. (Dichloromethane did not give rise to the dimer **27** under these reaction conditions.) These solutions were stirred together for 2 h before adding 1.0−1.2 equiv of BH_3 and leaving to stir overnight. Despite the potential for quenching the BH_3 reagent with water (water sensitivity had been shown for ZD6021),[4] a good conversion to ZD2249 crude was achieved, and the impurity profile was even improved compared to the mono-phasic reaction. Two batches were prepared in the LSL in 79% yield, the second larger batch using 1.2 equiv of **29** as this was the material available in greater excess at the time. Quality was moderate at only 75%, with amide alcohol (**28**) the major impurity at 10.5%, but this was readily removed on forming the ZD2249 hydrogen fumarate salt.

Overall, this was a highly pleasing result; the use of a two-phase reductive amination with an apparently water-sensitive reagent was a significant and surprising bonus at this phase of the project. The hazard issues were not considered serious in this case, since a full assessment had already been performed for the ZD6021 crude stage using similar methodology. The resulting final quality of ZD2249 hydrogen fumarate salt was 94.8%, which was just on the acceptable limit we had set ourselves. The final yield of 0.95 kg was somewhat down on the planned 1.3 kg, but was still sufficient to support the required clinical trials.

Conclusions

ZD2249 methoxy sulfoxide manufacture provided another good exemplification of our new project strategy,[1] in particular, our revised approach to traditional long-term manufacturing factors. Chemical safety remained our first concern, and early discussions with the Process Hazards Section once again proved beneficial. Hazards work was less than for ZD6021 cyano acid,[3] in part because the chemistry was judged less hazardous, but we were undoubtedly fortunate that several similar transformations had been fully hazard assessed for pilot-plant manufacture for ZD7944. Health hazards were also generally lower than for ZD6021 cyano acid.

We also repeated our aim of demonstrating that Research-type processes could successfully be operated on up to 100-L scale with minimal developments to deliver 1 kg of bulk drug. This included the high-temperature Newman−Kwart rearrangement (*S*-thiocarbamate) where high temperatures had not been possible previously,[1,3] the Grignard/lithiation reaction (CBz alcohol), and the Kagan asymmetric oxidation reaction (CBz sulfoxide). Large-scale chromatography was also used to purify 7.5 kg of CBz alcohol which it was not possible to purify any other way.

If the safety and health issues were less for ZD2249 compared to ZD6021, the quality issues were much greater and required additional attention. Fortunately, we had learnt from experience that greater analytical support was required, which was especially useful in identifying impurities and for developing more demanding chiral LC methods. More analytical resource was made available for this project, and this is reflected in the acknowledgments.

We attempted to address the material supply issue by removing 100-g samples from the manufacturing supply at key stages to facilitate later lab work (these quantities had been included in the materials plan). Unfortunately, stages 4 and 8 were chosen, and these were the two with the most significant manufacturing issues; therefore, this strategy was only partially successful. This remains an issue in any long synthesis that is developed at a fast rate.

The FED approach was again used extensively on this project, maximizing learning from a small number of small-scale reactions. Kepner−Tregoe techniques were also applied, not just to problem-solving and decision-making, but also for potential problem analysis, which was conducted right at the start of this project, having learnt from experience on ZD6021.

Overall, against our target rate of developing each stage in 4 weeks, we found that ZD2249 had taken slightly longer, although the majority of stages were developed in 5 weeks, with the average being 6 weeks. A couple of stages took significantly longer. As with ZD6021, safety and robustness had been the key factors, although quality had also required some effort. Other factors such as environment, health, operability, output, and yield had received some attention, but no work was driven by cost at this early stage (although raw materials were generally cheap, 10 equiv of TES and TFA would not be acceptable for a manufacturing process!).

ZD2249 manufacture proved to be probably the most challenging example of the four compounds undertaken on this new project strategy, certainly from a delivery point of view if not from a technical one, and this was almost entirely due to the difficulties of the methoxy sulfoxide fragment manufacture. Even so, we delivered the desired quality of bulk drug within the demanding 6−7 month deadline, although the delivery was slightly down on the target mainly due to the quality issues at the methoxy sulfoxide stage. That we were able to manufacture ZD2249 without any hazard incident and with only one intermediate batch out of 20 batches manufactured[20] being unsuitable for use, again supports the conclusion that this new project approach was both safe and robust.

Experimental Section

General Procedures. Reaction mixtures and products were analysed by reverse phase HPLC on Hewlett-Packard 1050 or 1100 instruments according to the following condi-

(20) Manufacture of the methoxy sulfoxide portion required 20 batches in total, being generally three batches per stage for the early stages and one to two for the later ones. No batches were lost from either repeat manufactures of the cyano acid or *N*-methylamine portions.

tions. **Method A (general):** column, Waters Spherisorb S5 ODS-2, 250 mm × 4.6 mm i.d.; eluent, 550:450 acetonitrile: water with 0.1% v/v TFA; flow rate 1.0 mL/min; wavelength 230 nm; injection volume 5−10 μL. Typical retention times were the following: methoxyphenol (**2**) 3.7; bromophenol (**3**) 5.1; *O*-thiocarbamate (**4**) 11.2; dibromo-*O*-thiocarbamate (**13**) 18.8; *S*-thiocarbamate (**5**) 9.2; bromosulfide (**6**) 9.9; CBz piperidone (**7**) 3.8; CBz alcohol (**8**) 7.9; methoxy sulfide (**18**) 7.0; CBz sulfide (**9**) 37.0; CBz alkene (**20**) 34.0; CBz sulfoxide (**10**) 7.8; DET 2.7; CBz sulfone (**22**) 10.5; methoxy sulfoxide (**1**) 3.1 min. **Method B (general):** column, Waters Spherisorb S5 ODS-1, 250 mm × 4.6 mm i.d.; eluent, 550: 450 acetonitrile:water with 0.1% v/v TFA; flow rate 1.5 mL/ min; wavelength 230 nm; injection volume 5 μL. Typical retention times were the following: *S*-thiocarbamate (**5**) 7.0; bromothiol (**16**) 8.3; bromosulfide (**6**) 9.4; CBz piperidone (**7**) 3.6; CBz alcohol (**8**) 8.8; CBz alkene (**20**) 20.2; CBz sulfide (**9**) 21.7 min. **Method C (determination of ee):** column, Chiralpak AD, 250 mm × 4.6 mm i.d.; eluent, 80: 20 hexane:absolute ethanol; flow rate 1.0 mL/min; wavelength 230 nm; injection volume 10 μL. Typical retention times were: CBz sulfide (**9**) 14.6, (*R*)-CBz sulfoxide (**R-10**) 27.1, (*S*)-CBz sulfoxide (**10**) 31.5 min. **Method D (determination of ee):** column, Chiral CBH, 150 mm × 4.0 mm i.d.; eluent, 10:90 2-propanol:aqueous buffer (0.013 M aqueous KH_2PO_4 adjusted to pH 7 with KOH); flow rate 1.2 mL/min; wavelength 220 nm; injection volume 10 μL. Typical retention times were the following: (*R*)-methoxy sulfoxide (**R-1**) 5.4; (*S*)-methoxy sulfoxide (**1**) 13.3 min. HPLC purities/strengths are area % normalized, except where noted otherwise. Melting points were determined using a Griffin melting point apparatus (aluminium heating block) and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 400 spectrometer at 400 and 100.6 MHz respectively with chemical shifts given in ppm relative to TMS at $\delta = 0$. Electrospray (ES^+) mass spectra were determined on a Micromass LCT with time-of-flight and electron impact (EI^+) mass spectra were determined on a Micromass Autospec. Analytical TLC was carried out on commercially prepared plates coated with 0.25 mm of self-indicating Merck Kieselgel 60 F_{254} and visualised by UV light at 254 nm. Preparative scale silica gel flash chromatography (for lab work) was carried out by standard procedures using Merck Kieselgel 60 (230−400 mesh). Where not stated otherwise, assume standard practices have been applied. Note well: Yields and strengths given in the text above are those which can be expected from the processes operated under normal conditions; figures below are quoted for individual experiments and may vary from those quoted in the text.

Preparation of ZD2249 *O*-Thiocarbamate (4) via Bromophenol (3). A solution of 3-methoxyphenol (**2**) (96.3 g, 0.78 mol) in dichloromethane (600 mL) was cooled to 5 °C in a vessel connected to a sodium hydroxide scrubber under a slow purge of nitrogen. A solution of bromine (107.6 g, 0.67 mol, 0.87 equiv) in dichloromethane (200 mL) was added evenly over 90 min, and the solution allowed to warm to 20 °C. The reaction mixture was quenched with a solution of sodium bicarbonate (67.2 g, 0.78 mol) in water (800 mL) added over 10 min with increased agitation. An effervescence and mild exotherm of a few degrees, easily controlled by water-cooling on this scale, resulted initially, which subsided after the first third of this solution had been added. The mixture was agitated for 1 h and allowed to stand; the dichloromethane solution of crude bromophenol (**3**) was separated and returned to a clean, dry vessel. DABCO (110 g, 0.98 mol, 1.26 equiv) was added as a solid in one portion, again resulting in a modest exotherm (2−3 °C on this scale), easily controlled by water cooling. A solution of DMTCC (98.7 g, 0.80 mol, 1.03 equiv) in dichloromethane (600 mL) was added evenly over 90 min. There was no detectable exotherm. The resulting solution was agitated for 16 h at 20 °C, during which time some gelatinous solid may form (thought to be DABCO·2HCl), but which readily dissolved during the aqueous workup. A solution of HCl (2.0 M, 480 mL) was added with rapid agitation, the resulting layers were allowed to settle and were separated, with the upper aqueous phase being discarded. The dichloromethane solution was washed twice more with HCl (2 × 480 mL) and returned to a dry vessel. The dichloromethane was removed by distillation at atmospheric pressure until no more distillate was observed (4.5 h on this scale; the temperature of the resulting dark-orange oil rose to 58 °C). Methanol (480 mL) was added evenly over 30 min to the crude concentrate with slow agitation, maintaining the internal temperature. The resulting solution was cooled at 10 °C/h and then held at 20 °C with stirring for 3 h. A white solid usually crystallized during the cooling phase, or occasionally during the addition of the methanol. If after the hold time at 20 °C no solid had appeared, addition of a pure seed of *O*-thiocarbamate or self-seeding of the solution was always successful in crystallising the product. The solid was isolated by vacuum filtration, and the displacement was washed with ice-cold methanol (80 mL) and dried in a vacuum oven at 50 °C to yield the title compound as a white crystalline solid (84.2 g, 37.4%). HPLC purity 99.5%, t_R 11.2 min (method A); mp 103−105 °C; ^{1}H NMR (400 MHz, $CDC1_3$) δ 7.45 (1H, dt, $J = 8.0$, 1.1 Hz), 6.73 (1H, s), 6.72 (1H, dd, $J = 9.9$, 2.9 Hz), 3.79 (3H, s), 3.47 (3H, s), 3.39 (3H, s); ^{13}C NMR (100.6 MHz, $CDC1_3$) δ 186.14, 159.55, 151.64, 132.98, 113.53, 111.12, 107.52, 55.68, 43.45, 38.93; MS (ES^+) 290/292 (MH^+, 1:1, 100%), 210 ($(MH - Br)^+$, 42%).

Preparation of ZD2249 *S*-Thiocarbamate (5). A slurry of *O*-thiocarbamate (**4**) (30.2 g, 104 mmols) in *N*,*N*-diethylaniline (75.5 mL) was stirred in a vessel which was evacuated by water-pump pressure for 20 min. The slurry was then purged with either nitrogen or argon at atmospheric pressure for 20 min. The evacuation was then repeated, but the slurry was then purged overnight with stirring. The reaction mixture was then heated to reflux (218 °C) for 7 h to give a yellow solution which after this period was allowed to cool freely to 20 °C overnight with stirring. In a separate vessel, hydrochloric acid (6.0 M, 173 mL, 1.04 mol, 10.0 equiv) was cooled to 5 °C, and the reaction mixture was added to it evenly over 30 min with rapid stirring. A brown solid was immediately precipitated with a 7 °C exotherm

on this scale, easily controlled by the rate of addition. The resulting suspension was stirred for a further 30 min at 5 °C before being isolated by vacuum filtration. The filter cake was displacement-washed with water (90.6 mL), pulled dry for 20 min, and then dried in a vacuum oven at 35 °C to yield the title compound as an off-white or buff-coloured crystalline solid (24.0 g, 65.7%). HPLC purity 96%, t_R 9.2 min (method A); mp 66−68 °C; ^{1}H NMR (400 MHz, $CDC1_3$) δ 7.54 (1H, d, J = 8.8 Hz), 7.18 (1H, d, J = 3.0 Hz), 6.82 (1H, dd, J = 8.8, 3.0 Hz), 3.79 (3H, s), 3.08 (6H, s); ^{13}C NMR (100.6 MHz, $CDC1_3$) δ 165.16, 158.82, 133.65, 131.03, 123.01, 120.93, 117.44, 55.60, 37.03; MS (ES^+) 290/292 (MH^+, 1:1, 100%).

Preparation of ZD2249 Bromosulfide (6). *S*-Thiocarbamate (**5**) (3.0 g, 10.3 mmol) was added in one portion to a slurry of potassium hydroxide (1.5 g at 85% strength, 22.6 mmol, 2.2 equiv) in methanol (18 mL) and heated to reflux (65 °C) for 2 h. The reaction mixture was then cooled to 5 °C, and methyl iodide (1.60 g, 11.3 mmol, 1.1 equiv) in methanol (3.0 mL) was added evenly over 10 min. After complete reaction, water (18 mL) was added to the reaction mixture and stirred for 5 min to allow a cream precipitate to redissolve. MTBE (18 mL) was added, and the mixture stirred for 10 min; then the resulting layers were allowed to settle and separate, and the lower aqueous layer was extracted again with MTBE (18 mL). The combined MTBE layers were washed with brine (9 mL) and then allowed to settle and separate, and the MTBE layer was concentrated to dryness by distillation at reduced pressure to yield the title compound as a dark-coloured, crude oil (2.50 g, ∼100%). An analytically pure sample was obtained by purification with silica gel flash chromatography eluting in 4:1 hexane: dichloromethane (R_f 0.34, SiO_2) with 91% recovery. For plant manufacture, azeotropic drying from a toluene solution was required to remove residual methanol, bring the typical yield down to ∼90%. HPLC purity (of crude oil) >98%, t_R 9.4 min (method B); mp (light oil); ^{1}H NMR (400 MHz, $CDC1_3$) δ 7.39 (1H, d, J = 8.6 Hz), 6.69 (1H, d, J = 2.8 Hz), 6.56 (1H, dd, J = 8.7, 2.8 Hz), 3.80 (3H, s), 2.46 (3H, s); ^{13}C NMR (100.6 MHz, $CDC1_3$) δ 159.42, 140.70, 133.12, 112.41, 112.27, 110.80, 55.54, 15.81; MS (EI^+) 232/234 (M^+, 1:1, 100%), 217/219 ($M - CH_3^+$, 1:1, 14%), 199/201 ($M - SH^+$, 1:1, 23%), 138 ($M - CH_3Br^+$, 62%); and 310/312/314 (dibromosulfide (**17**) M^+, 1:2:1, 8%).

Preparation of ZD2249 CBz Alcohol (8) by Grignard Reaction. Magnesium turnings (625 g, 25.68 mol, 1.28 equiv) were charged to a thoroughly dried vessel under an inert atmosphere, followed by anhydrous THF (25 L) with agitation. The agitation was stopped, and bromosulfide (**6**) (702 g, 3.01 mol, 0.12 equiv) was added neat over several minutes followed by iodine (0.5 g). Occasional stirring was started to allow initiation of the reaction to occur, as detected by an exotherm of up to 30 °C. Once initiation had occurred, the remaining bromosulfide (5.146 kg, 22.07 mol, 0.88 equiv) was added neat over 2.5 h, keeping the temperature below 30 °C. A final charge of THF (1 L) was added to wash in residual bromosulfide, and the reaction mixture was stirred for 16 h. A filtered solution of CBz piperidone (**7**) (4.681 kg, 35.75 mol, 1.0 equiv) in anhydrous THF (15 L) was added evenly to the Grignard reagent over 2.5 h, keeping the temperature below 30 °C, during which time an orange-coloured solution formed, with some precipitation towards the end of addition. After complete reaction, a solution of ammonium chloride (16.8 kg) in water (42 L) was added evenly over 2 h and the resulting suspension stirred at ∼20 °C for 15 h (there was a 10 °C exotherm initially on addition). The layers were separated, and the lower aqueous phase was extracted twice with ethyl acetate (15 L, then 10 L). All three organic portions were combined and dried over magnesium sulfate (4 kg) in a dry vessel. The drying agent was filtered off and washed with ethyl acetate (13 L), and the combined organic portions were concentrated under reduced pressure to yield the crude title compound as a red/brown viscous oil (8.657 kg, 111%). HPLC purity 61.2% giving a strength-corrected yield of 67.9% (5.88 kg). Complete analytical data is reported in the chromatographic purification section below.

Preparation of ZD2249 CBz Alcohol (8) by Lithiation Reaction. Bromosulfide (**6**) (10.0 g, 42.9 mmol, 1.20 equiv) and THF (77 mL) were cooled to −78 °C under an inert atmosphere. *N*-Butyllithium (2.5 M in hexanes, 17.2 mL, 42.9 mmol, 1.20 equiv) was added dropwise over 30 min, maintaining the temperature below −70 °C, followed by THF (3 mL). A slurry of partially dissolved CBz piperidone (**7**) (8.34 g, 35.75 mmol 1.0 equiv) in anhydrous THF (25.3 mL) was added evenly to the lithiated reagent over 1.0 h, keeping the temperature below −70 °C, followed by THF (3 mL). During the addition the solution became darker. The reaction mixture was stirred at −78 °C for ∼45 min. After complete reaction, the reaction mixture was allowed to warm to 20 °C and quenched by the addition of a saturated solution of ammonium chloride (65 mL) added evenly over 15 min. The resulting layers were separated, and the aqueous phase was extracted once with ethyl acetate (25 mL). The organic portions were combined and concentrated to dryness under reduced pressure to give the crude title compound (heavily contaminated with product-related impurities) as a yellow, viscous oil, 17.8 g (127%). HPLC purity 70.3% giving a strength-corrected yield of 89% (12.5 g). Complete analytical data is reported in the chromatographic purification section below.

Purification of Crude ZD2249 CBz Alcohol (8) by Large-Scale Chromatography. Chromatography was performed on a 42-cm diameter polypropylene Nutsche, extended to 70-cm depth and specially manufactured for this purpose. The base of the Nutsche had a paper filter covered in a layer of sand onto which the silica "column" was loaded as a slurry in 1:1 ethyl acetate:isohexane (eluent), with another layer of sand on top. Standard flash chromatography silica gel (230−400 mesh) was used at 14 times the mass of the crude material to be purified. The crude CBz alcohol was dissolved in an equal mass of eluent and loaded onto the column. Aliquots of eluent were pulled through the column by vacuum, using the dry flash technique, collecting fractions containing pure CBz Alcohol; clean eluent fractions were recycled on this scale. The product containing fractions

were concentrated on a 20-L rotary evaporator to give the purified title compound as a viscous yellow oil initially, which crystallized on standing and eventually seeded other column fractions directly before concentration. Typical yields and purity are given in the text. HPLC, t_R 7.9 min (method A); TLC (SiO_2, 1:1 ethyl acetate:isohexane; methoxy sulfide R_f 0.82; CBz alcohol R_f 0.33; CBz piperidone R_f 0.29); mp 90−91 °C; ^{1}H NMR (400 MHz, $CDC1_3$) δ 7.28−7.38 (5H, m), 7.24 (1H, d, J = 8.8 Hz), 6.95 (1H, d, J = 2.7 Hz), 6.70 (1H, dd, J = 8.7, 2.7 Hz), 5.14 (2H, s), 4.10 (2H, bs), 4.05 (1H, s), 3.80 (3H, s), 3.38 (2H, bs), 2.51 (3H, s), 2.10 (2H, bd, J = 12.3 Hz), 1.99 (2H, bs); ^{13}C NMR (100.6 MHz, $CDC1_3$) δ 158.82, 155.35, 138.28, 137.00, 136.68, 128.48, 127.92, 127.88, 127.84, 126.49, 117.51, 110.88, 72.05, 67.01, 55.35, 39.96, 37.01, 36.91, 19.09; MS (ES^+) 410 ($M + Na^+$, 12%), 370 ($MH^+ - H_2O$, 65%), 326 (16%), 278 (21%), 201 (48%).

Preparation of ZD2249 CBz Sulfide (9). Triethylsilane (56.5 mL, 354 mol, 10.0 equiv) and trifluoroacetic acid (27.3 mL, 348 mol, 10.0 equiv) were mixed with stirring and cooled to 10 °C. CBz alcohol (**8**) (13.7 g, 35.4 mmol, 1.0 equiv) was added as a solid in 10 equal portions at 10 min intervals over a period of 1.5 h. After a further 30 min, the reaction mixture was cooled to 0 °C and added to a cooled saturated solution of sodium bicarbonate (440 mL) with vigorous stirring. The addition rate was adjusted to control some effervescence and a mild exotherm, but slow addition was only necessary at the beginning. Dichloromethane (68 mL) was added with vigorous stirring for 10 min, the layers were allowed to separate, and the pH was checked to be in the range 7−8 (more sodium bicarbonate was added, if not). The lower organic phase was separated and the solvent removed under reduced pressure to give a crude oil which was then dissolved in acetonitrile (82 mL). Isohexane (68 mL) was added with vigorous stirring, and after standing the phases were separated. The lower acetonitrile phase was washed twice more with isohexane (2 × 68 mL) and then concentrated under reduced pressure to give a crude oil. This was dissolved in ethyl acetate (14 mL) and heated to reflux, and isohexane (56 mL) was added slowly. The solution was cooled evenly to 20 °C over 3 h during which time a white solid appeared and then was stood over ice for a further 2 h. The solid was isolated by filtration, washed with isohexane (15 mL), and dried in vacuo at 40 °C to yield the title compound as a white solid (10.24 g, 78%). HPLC purity 99%, t_R 37.0 min. (method A) or t_R 21.7 min. (method B); mp 84−85 °C; ^{1}H NMR (400 MHz, $CDC1_3$) δ 7.30−7.39 (5H, m), 7.05 (1H, d, J = 8.5 Hz), 6.76 (1H, d, J = 2.7 Hz), 6.67 (1H, dd, J = 8.5, 2.7 Hz), 5.16 (2H, s), 4.32 (2H, bs), 3.79 (3H, s), 3.07 (1H, tt, J = 12.0, 3.3 Hz), 2.91 (2H, bt, J = 11.7), 2.45 (3H, s), 1.82 (2H, bd, J = 12.7 Hz), 1.57 (2H, bm); ^{13}C NMR (100.6 MHz, $CDC1_3$) δ 158.38, 155.34, 137.89, 136.98, 135.41, 128.49, 127.87, 126.45, 112.25, 109.95, 67.05, 55.31, 44.83, 38.03, 32.41, 16.00; MS (ES^+) 372 (MH^+, 100%), 328 ($(MH-CO_2)^+$, 41%).

Preparation of ZD2249 CBz Sulfoxide (10). (−)-Diethyl D-tartrate (12.04 g, 58.4 mmol, 2.00 equiv) was dissolved in dichloromethane (109 mL, 10.1 volumes) and the water content of the resulting clear solution determined by Karl Fischer titration. This solution was transferred to a thoroughly dried reaction vessel containing CBz sulfide (10.85 g, 29.2 mmol, 1.00 equiv) under an inert atmosphere and stirred to give a pale yellow solution. Titanium isopropoxide (8.96 mL, 29.2 mmol, 1.00 equiv) was added, followed by distilled water (0.50 mL, 27.8 mmol, 0.95 equiv) sufficient to make up the total water content of the reaction mixture to 1.00 equiv. The reaction mixture was cooled to −15 °C and cumeme hydroperoxide (5.56 mL of an 80% w/w solution, 30.7 mmol, 1.05 equiv) added dropwise over 60 min, maintaining the temperature at −15 °C. After 5−16 h the reaction was complete, and a solution of 3 M HCl (60 mL, 200 mmol, 6.84 equiv) was added, allowing the mixture to warm to 20 °C. (Note well. This addition is strongly exothermic.) This was stirred at 20 °C for 1 h after which the pale-yellow lower dichloromethane phase was separated from the bright-orange upper aqueous phase and returned to the reaction vessel. A solution of 4 M NaOH (66 mL, 264 mmol, 9.04 equiv) was added and the mixture heated to 40 °C for 1 h before cooling back to 20 °C. (Note well. This addition can be exothermic at first if there is residual HCl left in the organic phase.) The phases were separated, and the lower dichloromethane phase was washed twice with water (66 mL each, 6.1 volumes) before concentration under reduced pressure to give the crude title compound as a pale-yellow oil (15.55 g, 137.4%; 10.34 g, 91.4% corrected for strength). HPLC purity, 96% by area, 66% against a standard; t_R 7.8 min. (method A); ee 93.6% (method C); mp (oil); ^{1}H NMR (400 MHz, $CDC1_3$) δ 7.52 (1H, d, J = 2.8), 7.48 (1H, m), 7.31−7.38 (4H, m), 7.17 (1H, d, J = 8.6 Hz), 6.96 (1H, dd, J = 8.6, 2.8 Hz), 5.16 (2H, s), 4.33 (2H, vbs), 3.86 (3H, s), 2.78−2.93 (3H, bm), 2.69 (3H, s), 1.60−1.94 (∼4H, bm); ^{13}C NMR (100.6 MHz, $CDC1_3$) δ 159.54, 155.23, 144.17, 136.75, 133.87, 128.51, 128.19, 128.05, 127.94, 124.36, 118.56, 106.85, 67.22, 55.56, 44.51, 43.84, 36.86, 31.75; MS (ES^+) 387 (MH^+, 100%), 344 ($(MH - CO_2)^+$, 21%).

Preparation of ZD2249 Methoxy Sulfoxide (1). CBz sulfoxide (15.2 g @ 66.5%, 26.0 mmol, 1.0 equiv), IMS (76 mL, 5.0 volumes) and KOH (19.7 mL of 48/50% w/w solution, 260 mmol, 10.0 equiv) were heated together at reflux for 6 h, after which time the hydrolysis was complete. The reaction mixture was concentrated to an oil, then toluene was added (30.4 mL, 2.0 volumes) and re-concentrated to ensure all the IMS had been removed. Fresh toluene (91 mL, 6.0 volumes) and water (38 mL, 2.5 volumes) were added, and the mixture was cooled to 5 °C with stirring. Concentrated HCl (21.3 mL of 37% w/w solution, 260 mmol, 10.0 equiv) was added dropwise over 30 min, keeping the temperature below 18 °C. (Note well. Some CO_2 is liberated during this addition, which is also exothermic; higher temperatures may racemise the sulfoxide under these conditions.) Water was added (30.4 mL, 2.5 volumes) and the pH adjusted to 1 with additional HCl if necessary to reduce losses of product to the toluene phase. After 15 min, the phases were separated, and the lower product-containing aqueous phase was washed with toluene (30.4 mL, 2.5 volumes) and separated again. A solution of NaOH (2.5 mL

of 46/48% w/w solution, 44.0 mmol, 1.7 equiv) in water (7.4 mL, 0.6 volumes) was added carefully to the aqueous phase at 20 °C (a modest exotherm is observed on this scale). After stirring for a few minutes, the pH was adjusted to >11 with additional NaOH if required to reduce product losses to the aqueous phase in the following extractions. The aqueous phase was extracted twice with dichloromethane (91 mL each, 6.0 volumes) and the combined dichloromethane portions concentrated to dryness to give the crude title compound as a pale-yellow viscous oil or white solid (depending on quality and strength) (6.39 g, 96.9%). HPLC purity 100%, t_R 3.1 min (method A); ee 94.4% (method D); mp 128−132 °C (sinters ∼120 °C); ^{1}H NMR (400 MHz, $CDC1_3$) δ 7.51 (1H, d, J = 2.8 Hz), 7.27 (1H, d, J = 8.5 Hz), 7.00 (1H, dd, J = 8.6, 2.8 Hz), 3.87 (3H, s), 3.18 (2H, bt, J = 12.1 Hz), 2.70−2.79 (3H, m), 2.69 (3H, s), 1.57−1.85 (∼5H, m); ^{13}C NMR (100.6 MHz, $CDC1_3$) δ 159.30, 144.00, 135.08, 127.93, 118.46, 106.52, 55.69, 47.09, 43.85, 37.43, 35.03, 33.85; MS (ES^+) 254 (MH^+, 100%).

Preparation of ZD2249 Methoxy Sulfoxide Tartrate Salt (11). Methoxy sulfoxide (1.616 kg @ 85%, 5.45 mol, 1.0 equiv) was heated to reflux in absolute ethanol (2.75 L, 2.0 volumes) to give a clear colourless solution. In a separate vessel, L-(+)-tartaric acid (868 g, 5.723 mol, 1.05 equiv) was heated to reflux in absolute ethanol (2.06 L, 1.5 volumes) to give a clear colourless solution. Both solutions were allowed to cool slightly, and the tartaric acid solution was transferred by vacuum to the methoxy sulfoxide solution to give a turbid solution which was heated back to reflux for 1 h. The clear solution was allowed to cool to 20 °C overnight, but there was no crystallization. The solution was cooled to 3 °C over 3 h to give an oily emulsion. Further absolute ethanol (2.75 L, 2.0 volumes) was added and the solution heated back to reflux. A 10-mL portion was taken and induced to crystallize in a clean beaker by scratching to provide a seed which was added back to the main reaction vessel. After a further 2 h at reflux, the solution was allowed to cool to 20 °C overnight, during which time significant crystallization occurred. The solution was cooled further to 0 °C for 2 h and then isolated by filtration on a Nutsche and deliquored thoroughly. The product was washed with chilled absolute ethanol (1374 mL, 1.0 volume) and then chilled MTBE (2748 mL, 2.0 volumes) and dried in vacuo at 40 °C to give the title compound as a white solid. HPLC and MS data as for methoxy sulfoxide. Mp 181−182 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.36 (1H, d, J = 2.8 Hz), 7.32 (1H, d, J = 8.4 Hz), 7.10 (1H, dd, J = 8.4, 2.8 Hz), 3.98 (2H, s), 3.81 (3H, s), 3.4−4.8 (vb), 3.33 (2H, bd, J = 11.6 Hz), 2.89−3.05 (3H, m), 2.69 (3H, s), 1.91−2.01 (1H, dq, J = 13.2, 2.8 Hz), 1.80−1.88 (2H, m), 1.74 (1H, bd, J = 13.2 Hz); ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 174.56, 158.84, 145.02, 133.31, 127.81, 117.43, 107.17, 71.78, 55.37, 43.49, 43.30, 43.22, 33.58, 30.09, 28.66.

Acknowledgment

We thank Steve Hallam and Paul Gillespie (Process Hazards Section, Macclesfield) for the hazard studies; Steve Baldwin, Nathalie Roberts, and Matt Young (Avlon) and later Kate Arnot and Anne Williams (Macclesfield) for analytical support; and Claire Ancell and Sophie Prottey for additional experimental work. We also benefited from excellent cooperation on this project with our Research colleagues in Wilmington, DE, and in particular from Daniel Hill.

Received for review September 1, 2003.

OP030039Z