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Application of an Enantiomerically Pure Bicyclic Thiolactone in the Synthesis of a Farnesyl Transferase Inhibitor

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Abstract:

An efficient manufacturing route to a novel farnesyl transferase inhibitor is described. The target molecule is a pro-drug, and its synthesis is complicated by the presence of labile functionality. The Medicinal Chemistry synthesis required trityl mercaptan to introduce a thiol group stereospecifically. An important objective of a new route was avoidance of such an atom-inefficient protecting group, and this was achieved by use of a bicyclic thiolactone. Reduction of the thiolactone with DIBAL afforded a masked aldehyde which participated cleanly in the key reductive amination step without loss of stereochemical integrity. The reported procedure for making the thiolactone was found to give inconsistent results. Development work resulted in a telescoped process that was operated successfully and reproducibly on the large scale. Removal of an N-Boc protecting group in the final step of the drug synthesis required careful choice of conditions to avoid cleaving other ester groups in the molecule. An impurity formed in the deprotection step was identified as the S-*tert*-butyl analogue arising from attack of the *tert*-butyl cation on the methionine residue; its identity was confirmed by independent synthesis.

Introduction

AZD3409 is a novel, orally active antiproliferative agent with potential application in the treatment of breast cancer and other tumours.[1] It acts by inhibiting farnesyl transferase and geranylgeranyl transferase, two enzymes which prenylate ***Ras*** proteins in cells. These proteins are involved in signaling processes. Mutant forms of ***Ras*** protein are found in many types of cancers where they cause uncontrolled cell division independent of external signals. Prenylation leads to modification of the protein structure by addition of a lipid chain to the carboxy-terminus, thus allowing the protein to dock into the cell membrane and initiate further biological activity. AZD3409 is unusual in being a double pro-drug with the active species being the thiol acid. The nicotinoyl group is rapidly cleaved in the gut to release the thiol which is detected in plasma and is able to pass into cells. The isopropyl ester is removed by the action of an intracellular esterase. This article describes the development of an efficient synthetic route capable of being operated on a commercial scale.

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(1) (a) Stephens, T. C.; Wardleworth, M. J.; Matusiak, Z. S.; Ashton, S. E.; Hancox, U. J.; Bate, M.; Ferguson, R.; Boyle, T. *Proc. Am. Assoc. Cancer Res.* **2003**, *44*, R4870. (b) Bell, I. M. *J. Med. Chem.* **2004**, *47*, 1869.

Results and Discussion

Medicinal Chemistry Synthesis. The synthetic route to AZD3409 used in Medicinal Chemistry was long, linear and involved several unsatisfactory features, notably use of trityl mercaptan to introduce the protected thiol and use of the Weinreb amide **2** as a precursor for the reductive amination (Scheme 1). Additionally, the presence of two labile groups in the molecule posed problems on scale-up. This synthetic route was used to make Campaigns 1 and 2 which delivered a total of 20 kg of drug substance. There were significant quality issues. Increased levels of impurity in the penultimate intermediate affected the performance of the next stages, proving that the crystallization processes were far from robust. An attempt to improve the quality of the crude product by chromatography on alumina was unsuccessful and merely resulted in loss of one-third of the material on the stationary phase.

Synthetic Strategy. Trityl mercaptan is not readily available in bulk and is a very atom-inefficient way of introducing a sulfur atom. A more efficient way of generating the thiol at C-4 was sought. *N*-Protected bicyclic thiolactones have found utility in the synthesis of carbapenems such as meropenem.[2,3] In this case, the protected thiolactone is reacted with an amine to give a proline amide containing the thiol at C-4. It occurred to us that it should be possible to reduce thiolactone **11** to thiolactol **12**. The latter is a masked aldehyde which should be capable of undergoing the required reductive amination whilst at the same time liberating the thiol at C-4 (Scheme 2).

Manufacture of Amine 10. Stilbene **9** was prepared in 90% yield by a Heck reaction between 4-fluorostyrene and methyl 2-chloro-5-nitrobenzoate. Catalytic reduction of the nitro and alkene groups occurred in the same process, affording ester **6a** which was hydrolysed to acid **6b** in 82% yield over the two steps. The coupling between acid **6b** and methionine isopropyl ester required mild conditions to avoid racemisation or hydrolysis of the isopropyl ester. Several amide-coupling procedures were screened, and the method using EDCI/HOBT/NMM in NMP gave the best results. Reaction conditions had to be defined carefully due to the risk of competition between the two different amino groups. In particular, at low pH values the rate of the desired reaction is reduced by protonation of the methioninate amino group. Byproduct **13** from the reaction of acid **6b** first with itself and then with methionine isopropyl ester (or from the reaction between amine **10** and acid **6b**) was observed, but its level in the product was controlled at about

(2) Brands, K. M. J.; Marchesini, G.; Williams, J. M.; Dolling, U.-H.; Reider, P. J. *Tetrahedron Lett.* **1996**, *37*, 2919.
(3) Matsumura, H.; Bando, T.; Sunagawa, M. *Heterocycles* **1995**, *41*, 147.

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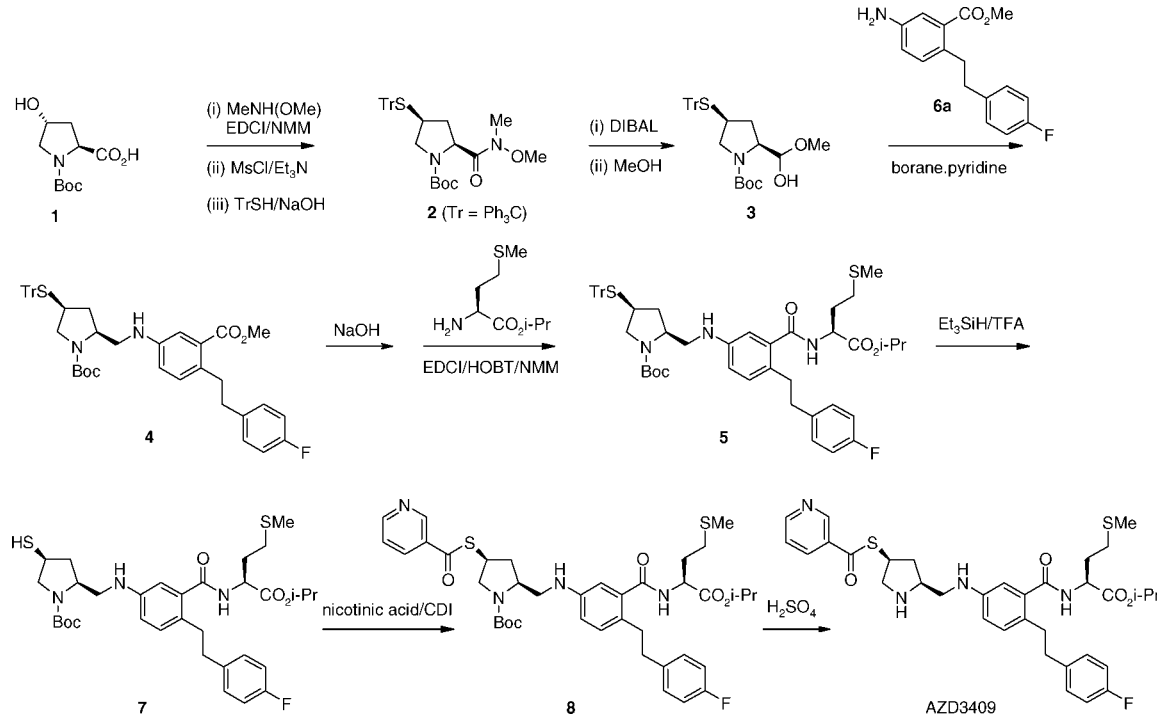
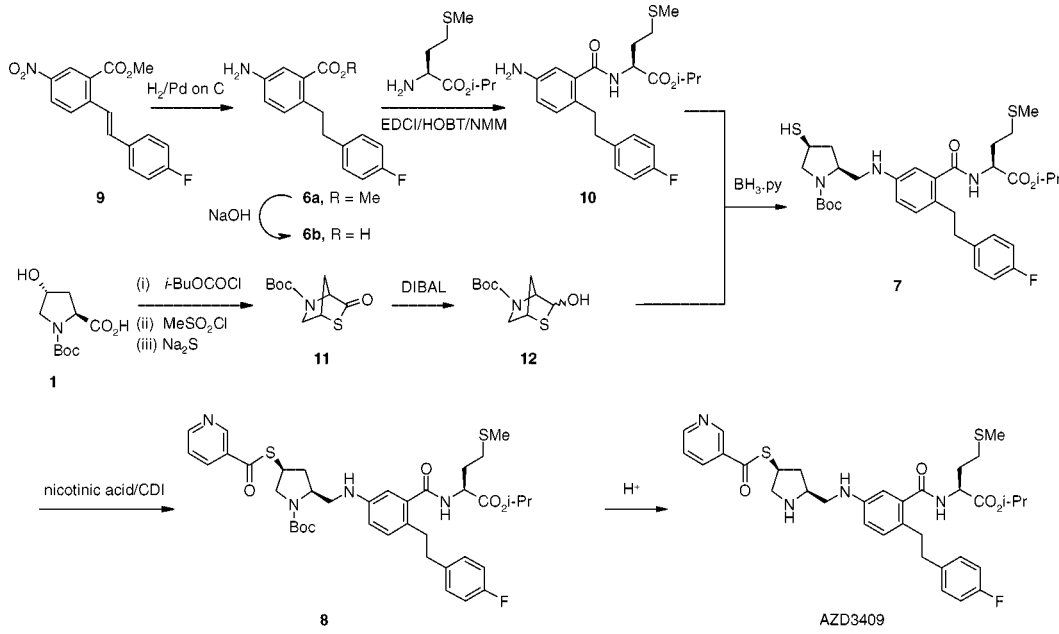
Scheme 1. **Medicinal Chemistry Route to AZD3409**



Scheme 2



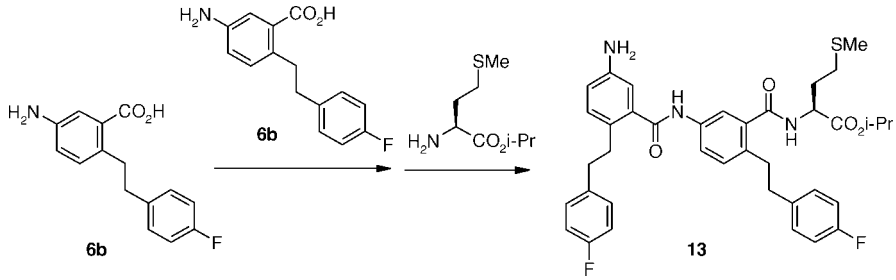
1% with the final process (Scheme 3). The kinetics of the process were studied and have been reported elsewhere.[4] The first process to be scaled up suffered from a lengthy workup involving multiple extractions and washes. In a subsequent improvement, crystalline amine **10** was isolated in 89% yield simply by adding water to the reaction mixture in a carefully controlled manner to avoid the problem of oiling out. The batch cycle time was dramatically reduced.

It was necessary to confirm the retention of stereochemical integrity in the methionine residue throughout the synthesis. This posed a significant analytical challenge. Reference samples of intermediates were prepared from D-methionine isopropyl ester. The L-and D-isomers of amine **10** could not be separated using a range of chiral HPLC systems. Despite a considerable amount of work, isomer separation in the downstream compounds proved impossible using standard methodology. Eventually, capillary electrophoresis (CE) provided a way forward by demonstrating that amine **10** manufactured on the plant scale had >99.6% ee.

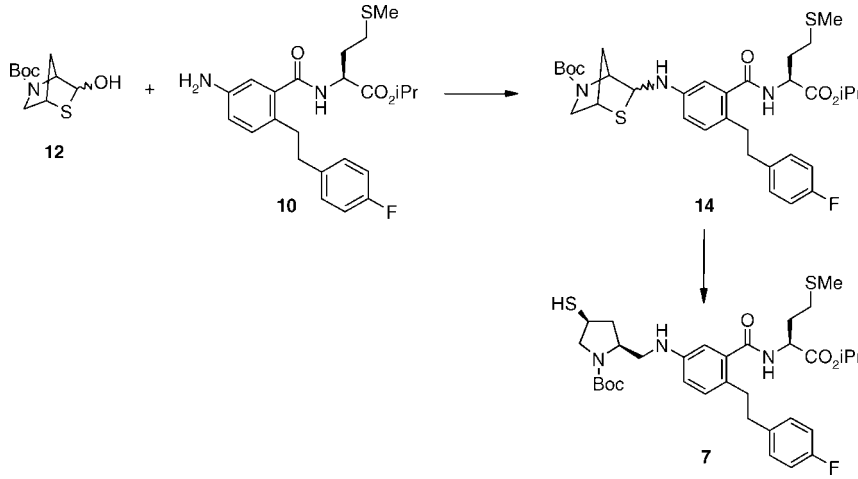
Reductive Amination. Several reagents were investigated in the reductive amination step, and 8 M borane·pyridine complex was chosen for plant-scale operation. An acid catalyst is necessary to achieve an acceptable rate of reduction, and

(4) Chan, L. C.; Cox, B. G. *J. Org. Chem.* **2007**, *72*, 8863.

Scheme 3



Scheme 4



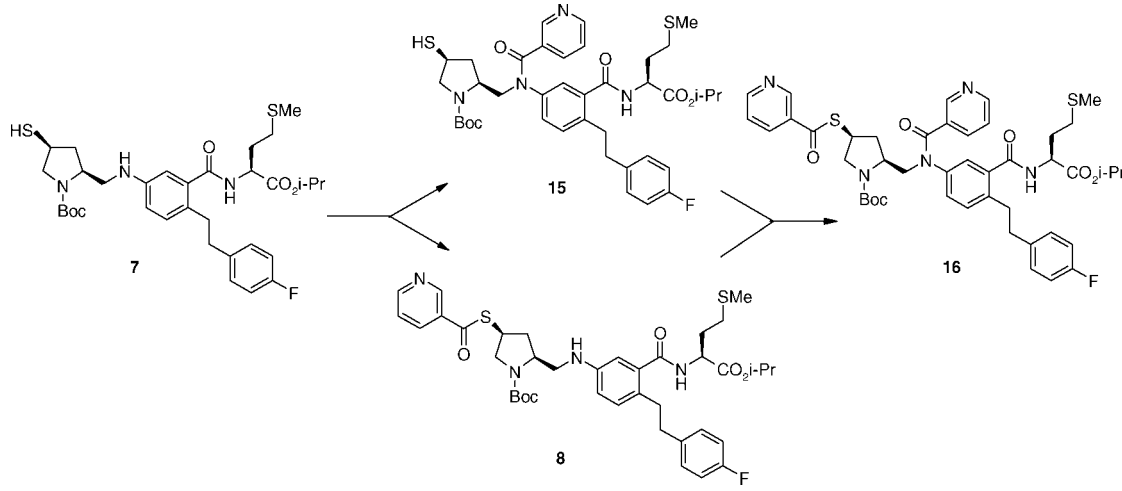
chloroacetic acid was used to good effect in initial experiments. Later this was discarded in favour of HCl in isopropanol due to the possibility of carry-over into the next step and the risk of transesterification between chloroacetic acid and the nicotinoyl ester (or formation of an activated amide with excess CDI). Thiol **7** is an oil and likely to be susceptible to oxidation on storage so there was no benefit in isolating the product from the reductive amination. Instead, thiol **7** was reacted *in situ* with the active amide prepared from nicotinic acid and CDI to give thioester **8** which was isolated as a crystalline solid in 76% yield from thiolactol **12**. It had been assumed that thiolactol **12** would react via the open-chain aldehyde form. In view of the acidity of protons alpha to a carbonyl or imino group, there was concern that epimerisation would occur at C-2 of the pyrrolidine ring during the reductive amination. In the event and to our surprise, none of the *trans*-diastereomer was found in the product (limit of detection <0.05%) (samples of both *trans*-isomers were prepared by independent synthesis from the appropriate *cis*-*N*-Boc-4-hydroxyproline using the route shown in Scheme 1).

Mixing thiolactol **12** and amine **10** at room temperature leads to rapid formation of cyclic thioaminal **14** (this conversion can be monitored by HPLC canlysis) followed by slow and pH-dependent reduction to thiol **7** (Scheme 4). Presumably, existence of the intermediate in a cyclic form rather than the open-chain imine protects it against epimerisation.

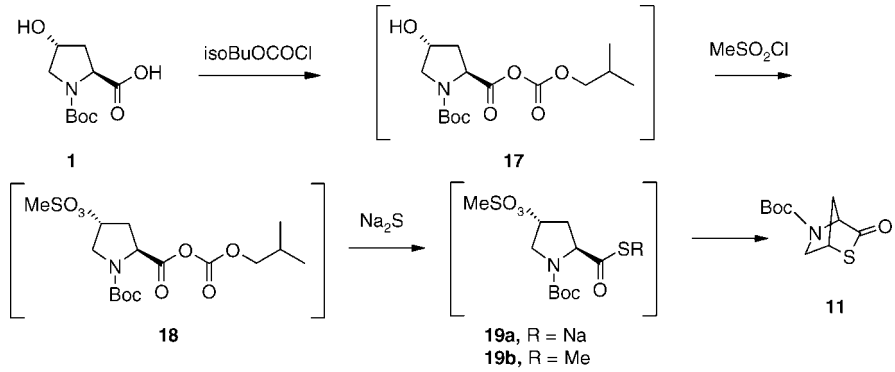
Regioselectivity of Acylation. Typical preparations of thioester **8** afforded up to 1% of an impurity **16** containing an additional nicotinoyl group on the aniline nitrogen. The impurity can be produced by either of two pathways: acylation on N followed by acylation on S or vice versa (Scheme 5). During a programme of work aimed at synthesising key impurities, it became apparent that the impurity cannot be prepared by acylation of thioester **8**; several attempts with different amide coupling reagents (CDI, EDCI etc) failed to produce any of the required compound. The importance of understanding the origin of this impurity in the process was highlighted during a manufacturing campaign when the second plant batch (73 kg scale) generated 6% of the impurity. Although the impurity was removed during downstream processing, its presence at such a high level had a significant impact on the overall yield. The unusually high level of impurity was attributed to an extended addition time for the nicotinoyl imidazolide solution (2.5 h versus the desired 1 h or less) which was caused by a blocked orifice plate. This effect was simulated in the laboratory. Conversely, an experiment in which the nicotinoyl imidazolide solution was added quickly produced only 0.04% of the impurity.

A possible explanation for this phenomenon involves general base catalysis. The pK_a values for the aniline and thiol groups of **7** in water are estimated to be ~4 and ~10, respectively. However, there appears to be relatively little information on the ionisation of thiols in acetonitrile. A pK_a value of 19 is reported for 2-mercaptophenol in acetonitrile[5a] (this is due to the weakly solvating effect of acetonitrile), and the figure for the thiol group in **7** is likely to be even higher. The pK_a value for the aniline group in **7** is predicted to be ~10.[5b] It seems highly unlikely that the thiol function in **7** reacts via the ionised form under the process conditions. Imidazole has the potential to influence the selectivity of the reaction by acting as a general base catalyst. It is reasonable to expect imidazole to catalyze acylation of the thiol rather than the aniline due to their very

Scheme 5



Scheme 6



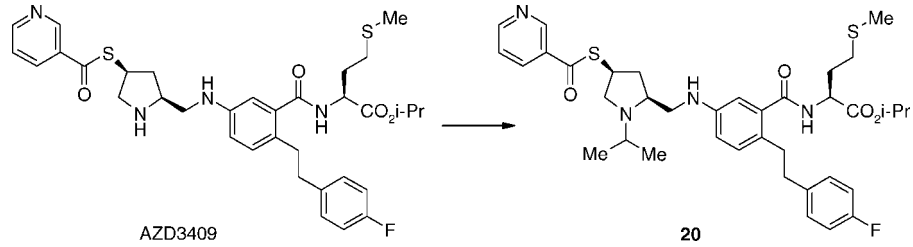
different pK_a values. The abnormally long addition time that occurred on the plant scale led to an extended period of time where the reaction mixture was deficient in imidazole, resulting in more of the impurity **16** being produced through nonselective acylation; a low level of monoacyl compound **15** was also detected during analysis of the product. Further experimental evidence concerning the influence of imidazole was obtained. When the acid charge in the reaction was increased, the amount of impurity **16** also increased. On the other hand, when one molar equivalent of imidazole was added to the reaction mixture prior to the addition of nicotinoyl imidazolide, impurity **16** was not produced. Addition of imidazole to the reaction mixture would be a suitable precautionary measure in the event of equipment failure.

Manufacture of Thiolactone 11. The published procedure for making thiolactone **11** involves a multistage telescoped process starting from *N*-Boc-4-hydroxyproline **1** (Scheme 6).[2] Much experimental work was carried out within AstraZeneca in an attempt to develop a process that could be scaled up reliably. Initial investigations were hampered by the lack of a robust quantitative analytical method (due to the relative instability of the intermediates), and attempts to carry out the preparation on any scale above 20 g resulted in greatly diminished yields. Significant amounts (about 20%) of methyl thioester **19b** were observed when methyl chloroformate was used to activate the carboxylic acid. Although the level of this impurity was reduced to <5% in isolated thiolactone **11**, the yield loss was considered unacceptable. Ethyl chloroformate gave poor-quality product (purity about 70% by HPLC) in variable yield. Benzyl and phenyl chloroformate gave little or none of the required product.

Finally, isobutyl chloroformate was chosen in place of the methyl or ethyl analogues for activation of the acid group. This had two advantages: the greater stability of the mixed anhydride allowed the reaction to be monitored reliably by HPLC analysis, and unwanted transfer of the alkyl group from the chloroformate to give the isobutyl analogue of **19b** was avoided.

Analytical monitoring of preparations which gave a poor yield of thiolactone **11** indicated loss of product during the workup. The stability of thiolactone **11** in toluene solution was tested. Exposure to aqueous hydrochloric acid, sodium bicarbonate, sodium hydroxide, or sodium sulfide at 45 °C for 3 h caused varying degrees of decomposition and generated predictable byproduct resulting from cleavage of the thiolactone group (including disulfides). However, this did not explain the observation that virtually complete disappearance of product sometimes occurred even when significant levels of the expected impurities were not detected. In these cases, disappearance of thiolactone **11** was accompanied by precipitation of a very fine, white solid which proved difficult to analyse as it was virtually insoluble in most solvents. An NMR spectrum showed the solid to be closely related to thiolactone **11**, and MS analysis showed a spread of high molecular weights indicative of a polymer.

Scheme 7



Anionic polymerization of thiolactones (e.g., induced by *n*-butyl lithium) has been reported.[6] To test whether this could explain the observed phenomena in the present case, a solution of thiolactone **11** in THF was exposed to *n*-butyl lithium (2.5 mol %) in hexane at room temperature. The substrate disappeared, but no degradation products were observed by HPLC analysis. Similar results were seen with some of the ingredients used in the thiolactone process, for example diisopropylethylamine hydrochloride (1 mol equivalent) and sodium sulfide (5 mol %) in water.

To reduce the risk of capricious and potentially catastrophic polymerisation, key changes were made to the process: the charge of sodium sulfide was reduced from 1.15 to 1.05 mol equivalent, the reaction mixture was quenched with an aqueous solution of citric acid, and additions of aqueous hydrochloric acid and aqueous sodium bicarbonate were omitted from the workup. This minimised the exposure of thiolactone **11** to any residual sulfide or chloride anions, particularly during the distillation stages. The improved process was successfully scaled up (at a contract manufacturer) to produce over 1000 kg of thiolactone **11** in an average yield of ~76% (99.6% ee, total organic impurities <1% w/w by GC) (an authentic sample of the enantiomeric thiolactone was prepared for use as an analytical reference standard).

DIBAL Reduction of Thiolactone 11. In early development work, the reduction of thiolactone **11** with DIBAL was performed at −70 °C to avoid the expected over-reduction of the tautomeric aldehyde. Further investigation led to the conclusion that thiolactol **12** is resistant to over-reduction as similar yields (70–75%) and quality are obtained at −70 °C and at around 0 °C with approximately 10% of product lost to the crystallisation mother liquors. A satisfactory mass balance was not obtained with the process; neither HPLC nor GC analysis revealed significant amounts of any other components. It is presumed that some loss of the Boc group occurred during the workup. On scale-up, the reduction step was carried out at 0–5 °C, and it was beneficial to add the reaction mixture to a warm aqueous solution of Rochelle salt rather than vice versa as this allowed the two liquid phases to be separated more easily. Crystallisation from toluene/*n*-heptane afforded dense, crystalline product of high purity. The average yield in plant manufacture was 73%.

Boc Deprotection to Generate AZD3409. Use of the Boc protecting group in drug synthesis is commonplace. Numerous methods for its removal have been described, but there does not appear to be a single method of choice for scale-up. Early manufacturing campaigns of AZD3409 used sulfuric acid (5 mol equivalents) in a mixture of toluene and isopropanol (35–40 °C for 6 h), but this generated 6–9% of an *N*-*tert*-butyl impurity, resulting in a crude product that was difficult to purify. A publication from Pfizer prompted us to develop a process using 85% phosphoric acid in 2-methyltetrahydrofuran (35 °C for 1 h) that afforded crude AZD3409 in 88% yield.[7] Whilst this process worked well on the kilo scale, there were significant issues when it was operated in the pilot plant. Use of a very large excess (34 mol equivalents) of phosphoric acid and a correspondingly large amount of aqueous base during the workup resulted in long addition times because of the need to control exotherms. The problems were exacerbated by severe foaming that occurred whilst the batch was being diluted with water. As a consequence of the extended processing times, significant degradation of the product occurred through hydrolysis of the labile ester groups; impurity levels in the isolated product totalled 10% (HPLC area). Further experiments showed that a significant reduction in phosphoric acid usage could only be achieved at the expense of very long reaction times. The environmental burden of the process was also considered unacceptable for long-term use, and it was necessary to re-examine the alternatives.

Hydrogen chloride (5 N) in isopropanol was selected for further evaluation. Conditions were chosen to minimise cleavage of other sensitive ester groups in the molecule. A simple and efficient process was developed which scaled up successfully in the pilot plant, affording crude AZD3409 in about 80% yield. The product was purified through conversion to its malate salt.

Formation of an Unexpected Impurity during Deprotection. The identity of an impurity present at levels of 0.1–0.3% in pure AZD3409 HCl salt prepared by the phosphoric acid deprotection process was puzzling. LC−MS indicated a mass of 694 which is 42 units higher than that of AZD3409. Initially, the impurity was thought to be an *N*-acetyl derivative of AZD3409, but its HRMS suggested that incorporation of an isopropyl group was more likely. However, this suggestion was disproved when an authentic sample of the isopropyl compound **20** was prepared by reductive amination with acetone and sodium triacetoxyborohydride (Scheme 7).

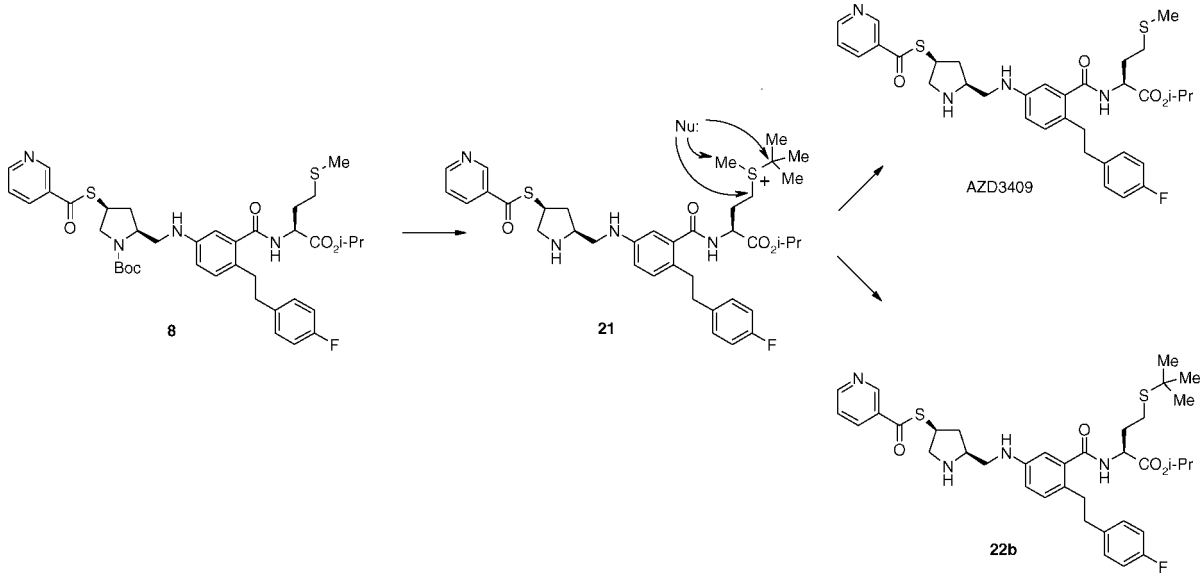
Material recovered from AZD3409 mother liquors was subjected to repeated crystallization followed by careful chromatography. This gave a sufficiently enriched sample of the impurity to allow its tentative identification by NMR as the *S*-*tert*-butyl derivative **22b**. Evidently a proportion of the *tert*-

(5) (a) Izutsu, K. *Acid-Base Dissociation Constants in Dipolar Aprotic Solvents*; IUPAC Chemical Data Series, No 35; Blackwell: Cambridge, MA, 1990; p 23. (b) Izutsu, K. *Acid-Base Dissociation Constants in Dipolar Aprotic Solvents*; IUPAC Chemical Data Series No 35; Blackwell: Cambridge, MA, 1990; p 17.

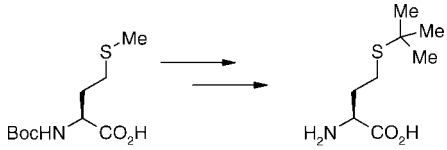
(6) Overberger, C. G.; Weise, J. K. *J. Am. Chem. Soc.* **1968**, *90*, 3533.

(7) Li, B.; Bemish, R.; Buzon, R. A.; Chiu, C. K.-F.; Colgan, S. T.; Kissel, W.; Le, T.; Leeman, K. R.; Newell, L.; Roth, J. *Tetrahedron Lett.* **2003**, *44*, 8113.

Scheme 8



Scheme 9



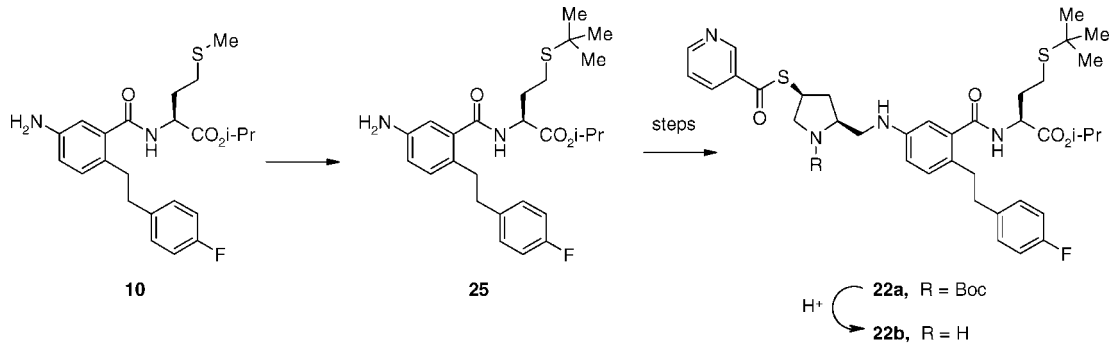
butyl carbocation generated in the deprotection is trapped by the sulfur atom of the methionine moiety to give sulfonium ion **21** (Scheme 8). In the presence of a suitable nucleophile this could undergo cleavage of any of the bonds to sulfur: attack at the methyl group would give the *S-tert*-butyl impurity, attack at the *tert*-butyl group (disfavoured on steric grounds) would regenerate AZD3409, and attack at the methylene group would generate methyl *tert*-butyl sulfide (possibly with formation of a five-membered lactone by intramolecular involvement of the ester group). There was no evidence for an impurity derived from the last pathway.

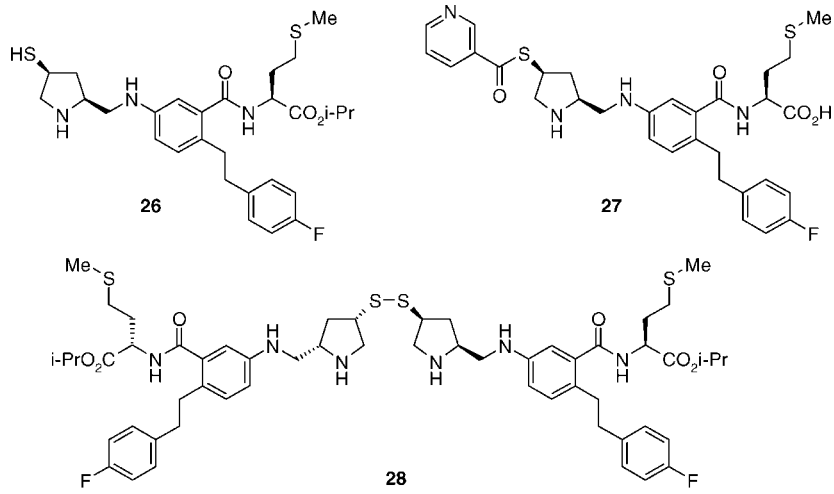
Preparation of *S-tert*-Butyl Impurity 22b. To confirm the identity of impurity **22b** and provide an analytical reference sample, an independent preparation was required. The conversion of Boc-methionine into the *tert*-butyl sulfonium ion with hydrogen fluoride followed by ion-exchange chromatography and then treatment with sodium 2-hydroxyethylsulfide to give *S-tert*-butylhomocysteine has been reported (Scheme 9).[8]

Since the use of hydrogen fluoride was unattractive, a modified process was devised involving sulfuric acid and *tert*-butanol followed by neutralization with calcium carbonate. Application of this method to AZD3409 did not produce the desired *S-tert* butyl impurity **22b** due to the unstable nature of the thioester group. Success was achieved starting with the aniline precursor **10** (Scheme 10). The desired sulfonium ion was formed (together with a small amount of the corresponding acid resulting from hydrolysis of the isopropyl ester). Treatment with sodium 2-hydroxyethylsulfide followed by chromatography on silica afforded the *S-tert*-butyl derivative **25** in 30% yield. Subjecting this to standard coupling conditions gave **22a** which was deprotected to give the required **22b**.

Form and Quality of the Drug Substance. Initial small batches of AZD3409 were prepared as an amorphous free base. It quickly became apparent that the stability of the free base was inadequate for development as a solid dosage form. In particular, the nicotinoyl group has a propensity to migrate onto the proline nitrogen when the latter is unprotonated. Various salts were screened for crystallinity, but initially only the monohydrochloride gave a positive result. This form showed moderate stability and was selected for use in early clinical studies where it was administered in capsules. Work aimed at developing a tablet formulation showed the hydrochloride to be unsuitable because it became amorphous on compression and this led to unacceptable degradation. This threatened the

Scheme 10





long-term viability of the drug, so further screening of potential salts was initiated, leading to the discovery of a crystalline salt with L-malic acid. This salt (which could be obtained in high purity) proved to have superior stability and formulation characteristics to the hydrochloride and formed the basis of a viable tablet formulation for use in phase II clinical studies.

The thioester and isopropyl ester groups in AZD3409 are chemically labile and, not surprisingly, thiol **26** (together with disulfide **28**) and acid **27** were detected in all samples of drug substance. These compounds are recognised metabolites of AZD3409 and were qualified at relatively high levels in toxicological studies. Accordingly, control levels in the drug substance specification reflected this: **26** (1% maximum), **27** (1%), and **28** (2%). In addition, the sulfoxide (of the methionine fragment) was controlled at 0.5%. In plant manufacture of the malate salt, all these impurities were well within the required limits (total organic impurities 2.4% w/w). The enantiomeric purity of individual stereocentres was controlled by appropriate analysis of key intermediates as described in earlier sections of this paper.

Conclusion

A new, convergent route has been developed for large-scale manufacture of the candidate drug AZD3409. Undesirable features of the Medicinal Chemistry route (e.g., use of trityl mercaptan and formation of a Weinreb amide) were conveniently avoided by employing a bicyclic thiolactol (itself derived from a thiolactone) as a substrate in the key reductive amination step. Problems of reproducibility in the preparation of the thiolactone were solved, allowing >1000 kg of this intermediate to be manufactured. From *N*-Boc-4-hydroxyproline was manufactured 170 kg of AZD3409 malate in 31% overall yield. Selective removal of the *N*-Boc protecting group in the presence of other labile esters was achieved with hydrogen chloride in isopropanol. An impurity produced at low levels during the Boc deprotection step was identified as the *S-tert*-butyl analogue resulting from modification of the methionine fragment.

Experimental Section

General. Starting materials, reagents, and solvents were obtained from commercial suppliers and used without further purification. IR spectra were recorded using a Thermo Electron Avatar FT-IR instrument. Melting points were obtained with a Mettler Toledo DSC822e instrument. NMR spectra were obtained using Bruker DPX 400, DRX 500, and Avance 600 instruments; ^{1}H spectra were measured with reference to an internal standard of tetramethylsilane at 0 ppm, and ^{13}C spectra were measured with reference to the DMSO signal at 39.5 ppm. LC−MS and HRMS data were obtained using Waters Micromass ZMD4000 and Waters Micromass LCT Classic instruments, respectively. HPLC analyses were performed with an Agilent 1100 instrument using the following conditions: synthetic stages to acid **6b**, HiChrom HI-5C18 column (4.6 mm × 150 mm, 5 μm) at 40 °C and 220 or 230 nm with a flow rate of 1.5 mL/min and a mobile phase gradient consisting of 5–90% CH_3CN in water (with a constant level of 0.1% TFA in the mixture); synthesis of thiolactone **11**, Alltima HP C18EPS column (3.0 mm × 150 mm, 3 μm) at 20 °C and 205 nm with a flow rate of 0.43 mL/min and a mobile phase gradient consisting of 5–85% CH_3CN in water (with a constant level of 0.05% TFA in the mixture); conversion of thiolactone **11** to thiolactol **12**, Waters Spherisorb ODS2 column (4.6 mm × 100 mm, 3 μm) at 30 °C and 205 nm with a flow rate of 0.7 mL/min and a mobile phase consisting of CH_3CN and water (1:1 mixture containing 0.1% methanesulfonic acid); synthetic stages from acid **6b** to AZD3409, Jones Genesis C18 column (4.6 mm × 150 mm, 4 μm) at 50 °C and 265 nm with a flow rate of 1.5 mL/min and a mobile phase gradient consisting of 40–90% CH_3CN in water (with a constant level of 0.1% TFA in the mixture) (approximate RRTs are **10**, 0.40; **8**, 1.00; **7**, 1.04; **14**, 1.08). The enantiomeric purity of thiolactone **11** was determined by HPLC using the following conditions: Chiralpak AD-H column (4.6 mm × 150 mm, 5 μm) at 15 °C and 210 nm with a flow rate of 1.0 mL/min and a mobile phase of MeOH (approximate retention times *R*,*R*-isomer 2.61 min, *S*,*S*-isomer 3.46 min). The chemical purity of thiolactone **11** was measured with an HP6890 gas chromatograph equipped for cool-on-column injection and fitted with a flame ionisation detector using the following conditions: DB17MS capillary column (15 m × 0.25 mm, 0.15 μm film), 40 °C for 1 min, 40 °C/min to 160 °C (no hold), 5 °C/min to 250 °C (no hold), 50 °C/min to 300 °C (5 min hold), carrier gas He at 1.2 mL/min.

(8) Chassaing, G.; Lavielle, S.; Marquet, A. *J. Org. Chem.* **1983**, *48*, 1757.

The enantiomeric purity of amine **10** was determined by CE with a Beckman Coulter P/ACE MDQ instrument using the following conditions: polyimide-coated fused silica capillary (50 μm i.d., 365 μm, 50 cm total length, 10 cm effective length), capillary temperature 20 °C, 100 mM lithium phosphate buffer (pH 2.5) containing 10 mM HS-β-CD, voltage +20 kV (increased from 0 to 20 kV over 0.3 min), current draw 90 μA (approx), injection of 15 s at 0.5 psi (hydrodynamic, capillary inlet at cathode) ,and detection at 200 nm (approximate migration times L-isomer 4.8 min, D-isomer 5.4 min).

Preparation of (1*S*,4*S*)-3-Oxo-2-thia-5-azabicyclo-[2.2.1]heptane-5-carboxylic Acid *tert*-Butyl Ester (11). A solution of *trans*-*N*-Boc-(2*S*,4*R*)-4-hydroxyproline **1** (49.45 kg, 213 mol) in tetrahydrofuran (THF) (725 L) was stirred and cooled to −22 °C. A temperature of about −20 °C was maintained throughout the following additions required to produce mesylate ester **18**. Diisopropylethylamine (62.0 kg, 479 mol) was added over 35 min followed by a line wash of THF (11.9 L). Isobutyl chloroformate (32.0 kg, 234 mol) was added over 30 min (slightly exothermic) followed by a line wash of THF (11.9 L), and the mixture was stirred for 32 min. Triethylamine (23.8 kg, 234 mol) was added over 22 min followed by a line wash of THF (11.9 L). After 15 min, methanesulfonyl chloride (27.0 kg, 236 mol) was added over 2.25 h (exothermic) followed by a line wash of THF (11.9 L), and the mixture was stirred for a further 3 h. In a second reactor, hydrated sodium sulfide (29.2 kg at 60% w/w content, 224 mol) was dissolved in water (128 kg) and cooled to −5 °C (below this temperature the sodium sulfide crystallizes out). The sodium sulfide solution was added as quickly as possible to the reaction mixture containing the mesylate ester **18**; the addition was completed in 100 s, and the temperature rose from −22 to −8 °C. A rinse wash of water (108 kg) was applied to the vessel that contained the sodium sulfide solution and thence to the main reactor. The reaction mixture was warmed to +20 °C over about 40 min then agitated at this temperature for 6 h. A solution of citric acid monohydrate (69.9 kg, 332 mol) in water was added to the reaction mixture over about 30 min followed by a rinse wash of water (21.4 kg). The mixture was agitated at 20 °C for about 30 min, and then the layers were separated. The organic phase was concentrated by distillation under reduced pressure (238 to 60 mbar) at 26–28 °C until 670 L of distillate was collected. The aqueous phase was extracted with *tert*-butyl methyl ether (TBME) (375 L), and the extract was combined with the residue obtained by concentrating the organic phase; the residue dissolved to give a solution at 25 °C. The organic solution was washed with water (161 L), then with 10% w/w aqueous brine (161 kg), and finally with more water (161 kg). The organic solution was then concentrated by distillation under reduced pressure (293 to 94 mbar) at 25–30 °C until 390 L of distillate was collected. The residue was dissolved in more TBME (215 L), and the solution was again concentrated by distillation under reduced pressure (275 to 160 mbar) at about 25 °C until 205 L of distillate was collected. The residue was dissolved in more TBME (72 L), and the solution was cooled to −8 °C over 1 h 20 min and agitated at this temperature for 2 h. The suspension was diluted with hexane (99 L) and agitated at −5 °C for another 2.5 h. The crystalline solid was collected in a precooled filter-drier, washed with a mixture of hexane (49.5 L) and TBME (21.6 L), cooled to −8 °C, and dried *in vacuo* at 30 °C. The yield of thiolactone **11** was 39.5 kg (80% based on *trans*-Boc-(2*S*,4*R*)-4-hydroxyproline). Chiral HPLC assay: 99.6% ee.

^{1}H NMR (400 MHz, 343 K, DMSO-d_6) δ 4.44 (1H, br s), 4.34 (1H, br m), 3.75 (1H, dd, J = 10.2, 2.7 Hz), 3.41 (1H, dd, J = 10.2, 1.6 Hz), 2.17 (1H, dt, J = 11.5, 2.5 Hz), 2.11 (1H, dq, J = 11.5, 1.6, 1.2 Hz), 1.41 (9H, s).

Preparation of (1*S*,4*S*)-3-Hydroxy-2-thia-5-azabicyclo-[2.2.1]heptane-5-carboxylic Acid *tert*-Butyl Ester (12). A mixture of thiolactone **11** (66.5 kg, 290 mol) and toluene (268 L) was stirred and cooled to −5 °C. A 1.0 M solution of diisobutylaluminium hydride (DIBAL) in toluene (363 L, 363 mol) was added over about 1 h, keeping the temperature below 5 °C. When the reaction was complete, acetone (133 L) was added. The reaction mixture was then added to a solution of sodium potassium tartrate tetrahydrate (145 kg, 507 mol) in water (145 L) at 60 °C at such a rate as to control the gas evolution. The mixture was cooled to 20 °C, and the lower aqueous phase was separated and discarded. The organic solution was concentrated by distillation under reduced pressure to 335 L. The temperature of the concentrated solution was adjusted to 65 °C and diluted with *n*-heptane (335 L). The solution was cooled to 20 °C over 1.5 h and held at that temperature for 1 h. The crystalline product was collected by filtration, washed with *n*-heptane (168 L), and dried *in vacuo* at 40 °C. The yield of thiolactol **12** (mean of three batches) was 47.9 kg (73%).

^{1}H NMR (400 MHz, 343 K, DMSO-d_6) δ 6.07 (1H, br d, J = 6.6 Hz), 5.29 (1H, br d, J = 5.3 Hz), 4.20 (1H, br s), 3.75 (1H, br t), 3.37 (1H, br d, J = 9.7 Hz), 2.11 (1H, br d, J = 10.4 Hz), 1.97 (1H, br d, J = 10.1 Hz), 1.41 (9H, s). IR ν_{max} (KBr disk) 3380br, 2972, 1666 cm^{-1}.

Preparation of Methyl 2[(*E*)-2-(4-fluorophenyl)vinyl]-5-nitrobenzoate (9). A mixture of methyl 2-chloro-5-nitrobenzoate (31.0 kg, 144 mol), sodium carbonate (16.0 kg, 151 mol), tetra-*n*-butylammonium bromide (4.67 kg, 14.5 mol), 4-fluorostyrene (22.5 kg, 184 mol) and *N*,*N*-dimethylacetamide (110 kg) was stirred at ambient temperature under a nitrogen atmosphere. Palladium chloride (1.06 kg, 5.98 mol) and triethyl phosphite (1.01 kg, 6.11 mol) were added, and the mixture was heated at 90 °C for 4 h. The hot mixture was diluted with toluene (82.5 kg) and filtered to remove catalyst and other insoluble material; the filter cake was washed with hot toluene (34.5 kg). The total filtrate was concentrated by distillation under reduced pressure until all the toluene had been removed. The residue was diluted with methanol (159 kg) and cooled and stirred at −5 °C for 30 min. The crystalline product was collected by filtration and washed with cold methanol (49 kg). The methanol-wet solid (60 kg) was used directly in the next stage without further drying. The yield of stilbene **9** was about 90%.

^{1}H NMR (400 MHz, 300 K, DMSO-d_6) δ 8.56 (1H, d, J = 2.1 Hz), 8.39 (1H, dd, J = 8.8, 2.6 Hz), 8.14 (1H, d, J = 8.8 Hz), 7.84 (1H, d, J = 16.4 Hz), 7.72–7.66 (2H, m), 7.47 (1H, d, J = 16.8 Hz), 7.31–7.24 (2H, m), 3.94 (3H, s); ^{13}C NMR (100 MHz, 300 K, DMSO-d_6) δ 165.5, 162.4 (d, J_{CF} = 241.1

Hz), 145.7, 144.0, 134.0, 132.9 (d, J_{CF} = 3.0 Hz), 129.3 (d, J_{CF} = 8.3 Hz), 129.2, 128.0, 126.4, 125.3, 124.4 (d, J_{CF} = 2.2 Hz), 115.9 (d, J_{CF} = 21.8 Hz), 52.8; IR ν_{max} (KBr disk) 1728, 1585, 1505, 1331, 1227 cm^{-1}.

Preparation of Methyl 5-Amino-2-[2-(4-fluorophenyl)-ethyl Benzoate] (6a). Methanol (216 kg) was added to a mixture of a stilbene **9** (60 kg of methanol-wet solid containing an estimated 39 kg at 100% strength, 129 mol) and 10% palladium on carbon wet paste (water content 57.0% w/w, Pd content on dry weight 9.84% w/w) (0.78 kg, 0.31 mol). The mixture was stirred and heated at 35 °C under a hydrogen atmosphere (3.0 bar gauge) for 2 h. When the reaction was complete, the mixture was heated to 50 °C and passed through a filter aid to remove the catalyst; the filter cake was washed with methanol (26 kg). The total filtrate was diluted with water (56.7 kg), cooled to −5 °C with stirring and maintained at −5 °C for 30 min. The crystalline product was collected by filtration, washed with a mixture of methanol (23 kg) and water (28.7 kg) and dried at ambient temperature and pressure. The yield of aminoester **6a** (mean of four batches) was 31.8 kg (88%).

^{1}H NMR (400 MHz, 300 K, DMSO-d_6) δ 7.24–7.16 (2H, m), 7.11–7.04 (3H, m), 6.95 (1H, d, J = 8.4 Hz), 6.69 (1H, dd, J = 8.3, 2.6 Hz), 5.16 (2H, br s), 3.80 (3H, s), 2.99–2.92 (2H, m), 2.76–2.68 (2H, m); MS (ES) m/z 274.1 $(M+H)^+$.

Preparation of 5-Amino-2-[2-(4-fluorophenyl)ethyl Benzoic Acid (6b). A mixture of aminoester **6a** (73.3 kg, 268 mol), methanol (220 L), and 47% w/w sodium hydroxide solution (34.5 kg, 402 mol) was stirred and heated at 60 °C for 6.5 h. The solution was cooled to room temperature and adjusted to pH 5 with 1 M aqueous hydrochloric acid (402 L, about 402 mol). The precipitated solid was collected by filtration, washed with water (2 × 147 L), and dried *in vacuo* at 40 °C. The yield of acid **6b** (mean of three batches) was 65.0 kg (93%).

^{1}H NMR (400 MHz, 300 K, DMSO-d_6) δ 7.25–7.17 (2H, m), 7.11–7.02 (3H, m), 6.90 (1H, d, J = 8.2 Hz), 6.64 (1H, dd, J = 8.1, 2.6 Hz), 3.33 (1H, br s), 3.01–2.93 (2H, m), 2.77–2.69 (2H, m); ^{13}C NMR (100 MHz, 300 K, DMSO-d_6) δ 169.2, 160.5 (d, J_{CF} = 241.1 Hz), 146.6, 138.2 (d, J_{CF} = 3.0 Hz), 131.4, 130.4, 129.9 (d, J_{CF} = 7.9 Hz), 129.3, 117.2, 115.5, 114.8 (d, J_{CF} = 21.1 Hz), 37.0, 35.5; MS (ES) m/z 260.1 $(M + H)^+$, 301 $(MH + CH_3CN)^+$.

Preparation of Isopropyl *N*-{5-Amino[2-(4-fluorophenyl)-ethyl]benzoyl}-L-methioninate (10). A mixture of L-methionine isopropyl ester hydrochloride (135.3 kg, 594 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (113.9 kg, 594 mol) and *N*-methylpyrrolidin-2-one (NMP) (420 L) was stirred at about 20 °C. *N*-Methylmorpholine (27.3 kg, 270 mol) was added to the mixture followed by a solution of 1-hydroxybenzotriazole (29.2 kg, 217 mol) in *N*-methylmorpholine (87.6 kg, 866 mol) and water (29.1 kg) and a wash of NMP (35 L). A solution of the amino acid **6b** (140.0 kg, 540 mol) in NMP (350 L) was added over 2 h, keeping the temperature at about 20 °C, and this was followed by a wash of NMP (35 L). The mixture was maintained at 20 °C for a further 8 h to complete the reaction. Water (420 L) was added, and after stirring for 1 h at 20 °C the product began to crystallize. The mixture was warmed to 40 °C, and more water (980 L) was added over 2 h. After stirring the mixture at 40 °C for 1 h, the solid was collected by filtration, washed with water (2 × 420 L), and dried *in vacuo* at 40 °C. The yield of amine **10** (mean of four batches) was 208.7 kg (89%).

^{1}H NMR (500 MHz, 300 K, DMSO-d_6) δ 8.56 (1H, d, J = 7.7 Hz), 7.23–7.16 (2H, m), 7.08–7.01 (2H, m), 6.86 (1H, d, J = 7.9 Hz), 6.60 (1H, d, J = 2.1 Hz), 6.52 (1H, dd, J = 8.1, 2.4 Hz), 5.06 (2H, br s), 4.97 (1H, septet, J = 6.3 Hz), 4.48 (1H, q, J = 7.1 Hz), 2.84–2.66 (4H, m), 2.64–2.51 (2H, m), 2.04 (3H, s), 1.99 (2H, q, J = 6.4 Hz), 1.20 (3H, d, J = 6.3 Hz), 1.17 (3H, d, J = 6.2 Hz); ^{13}C NMR (125 MHz, 300 K, DMSO-d_6) δ 171.4, 170.2, 160.5 (d, J_{CF} = 240.7 Hz), 146.4, 138.2 (d, J_{CF} = 2.8 Hz), 136.7, 130.2, 130.0 (d, J_{CF} = 8.9 Hz), 125.9, 114.8, 114.7 (d, J_{CF} = 20.7 Hz), 112.9, 67.9, 51.4, 36.8, 34.4, 30.0, 29.8, 21.5, 21.4, 14.5; MS (ES) m/z 433.2 $(M + H)^+$.

Preparation of Isopropyl *N*-{5-({[(2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(pyridin-3-ylcarbonyl)thiopyrrolidin-2-yl]methyl}amino)-2-[2-(4-fluorophenyl)ethyl]benzoyl}-L-methioninate (8). A mixture of amine **10** (73.0 kg, 169 mol), thiolactol **12** (39.4 kg, 170 mol), 5 M hydrogen chloride in isopropanol (14.6 L, 73 mol), and toluene (507 L) was stirred at about 20 °C for about 30 min. Then 8 M borane·pyridine complex (16.8 L, 134 mol) was added over about 30 min, followed by a wash of toluene (24.8 L). A further portion of 5 M hydrogen chloride in isopropanol (22.6 L, 113 mol) was added over about 20 min followed by a wash of toluene (12.4 L). The mixture was stirred for 4.5 h at 20 °C to complete the formation of thiol **7**. 1,1′-Carbonyldiimidazole (CDI) (34.3, 212 mol) was dissolved in acetonitrile (219 L) at 40 °C, and the solution was added to a stirred suspension of nicotinic acid (24.8 kg, 201 mol) in acetonitrile (146 L), keeping the temperature below 20 °C, followed by a wash of acetonitrile (53 L). The mixture was stirred at about 15 °C for 50 min and then added to the solution of thiol **7** over about 25 min, followed by a wash of acetonitrile (53 L). The mixture was stirred at about 20 °C for 4 h and then diluted with water (358 L). The mixture was heated to 40 °C, and the lower aqueous phase was separated and discarded. The organic solution was washed with an additional portion of water (358 L) at 40 °C and then concentrated by distillation under reduced pressure to about 330 L. The temperature of the residual solution was adjusted to 43 °C, and *n*-heptane (110 L) was added. The solution was cooled to about 20 °C, seeded, and held at 20 °C for 5 h until crystallization was well established. A second portion of *n*-heptane (110 L) was added, and the mixture was stirred at 20 °C for 3 h. The crystalline solid was collected by filtration, washed with a mixture of toluene and *n*-heptane (1:1 v/v, 146 L) and dried *in vacuo* at 40 °C. The yield of thioester **8** (mean of three batches) was 96.1 kg (76%).

^{1}H NMR (500 MHz, 343 K, DMSO-d_6) δ 9.03 (1H, d, J = 2 Hz), 8.83 (1H, dd, J = 5, 2 Hz), 8.27 (1H, d, J = 8 Hz), 8.22 (1H, ddd, J = 8, 2, 2 Hz), 7.58 (1H, dd, J = 8, 5 Hz), 7.21–7.18 (2H, m), 7.03–6.99 (2H, m), 6.92 (1H, d, J = 8 Hz), 6.66 (1H, s), 6.65 (1H dd, J = 9, 2 Hz), 5.61 (1H, br t, J = 6 Hz), 4.93 (1H, septet, J = 6 Hz), 4.51 (1H, q, J = 7 Hz), 4.11 (1H, qn, J = 7 Hz), 4.10–4.04 (1H, m), 4.06 (1H, dd, J = 11, 7 Hz), 3.49 (1H, ddd, J = 13, 5, 5 Hz), 3.25 (1H, dd, J = 11, 6 Hz), 3.15 (1H, ddd, J = 14, 8, 6 Hz), 2.85–2.79 (2H, m), 2.79–2.74

(2H, m), 2.65–2.53 (3H, m), 2.04 (3H, s), 2.05–1.98 (3H, m), 1.46 (9H, s), 1.20 (3H, d, $J = 6$ Hz), 1.18 (3H, d, J 6 Hz); ^{13}C NMR (125 MHz, 343 K, DMSO-d_6) δ 189.4, 170.8, 169.6, 160.2 (d, $J_{CF} = 242$ Hz), 153.8, 153.4, 147.1, 146.3, 137.8 (d, $J_{CF} = 3$ Hz), 136.7, 134.1, 131.7, 129.9, 129.5 (d, $J_{CF} = 8$ Hz), 125.9, 123.7, 114.2 (d, $J_{CF} = 21$ Hz), 112.2, 111.3, 79.0, 67.6, 55.5, 52.1, 51.3, 46.2, 38.7, 36.3, 34.4, 33.7, 30.2, 29.7, 27.8, 21.1, 14.3. MS (ES) m/z 753.3 $(M+H)^+$.

Preparation of Isopropyl *N*-{5-({[(2*S*,4*S*)-4-(Pyridin-3-ylcarbonyl)thiopyrrolidin-2-yl]methyl}amino)-2-[2-(4-fluorophenyl)ethyl]benzoyl}-L-methioninate L-Malate (AZD3409 Malate). *(a). Removal of Boc-Protecting Group.* A mixture of thioester **8** (Boc-protected AZD3409) (85.0 kg, 113 mol) and toluene (255 L) was stirred and heated to 50 °C. 5 N Hydrogen chloride in isopropanol (90.1 L, 451 mol) was added over 20 min followed by a wash of toluene (8.5 L). The mixture was stirred at 50 °C for 4 h then cooled to 20 °C. A solution of potassium hydrogen carbonate (45.2 kg, 451 mol) in water (340 L) was added followed by a wash of water (17 L), giving a pH of 7–8. The lower aqueous phase was separated and discarded. The organic phase was diluted with toluene (425 L) and concentrated to about 595 L at 40–50 °C under reduced pressure. The temperature of the residual solution was adjusted to 45 °C, and seed crystals were added. *n*-Heptane (85 L) was added over 20 min, and the mixture was cooled to 20 °C over 3 h. After 1 h at 20 °C, the solid was collected by filtration, washed with a mixture of toluene and *n*-heptane (1:1 v/v, 170 L), and dried *in vacuo* at 40 °C. The yield of AZD3409 free base (mean of three batches) was 58.5 kg (79%) (total impurities 2.5–7.0 area % by HPLC).

(b). Salt Formation. AZD3409 free base (40.0 kg, 61.3 mol) was dissolved in a mixture of ethyl acetate (360 L) and water (4 L) at 35 °C. The warm solution was screened to remove any extraneous material, and the filter was washed with ethyl acetate (40 L). The filtrate was warmed to 40 °C. A solution of L-malic acid (8.54 kg, 63.7 mol) in water (12 L) was prepared, and approximately half of this solution was added to the AZD3409 solution, keeping the temperature at 40 °C. Seed crystals of AZD3409 malate (400 g, 0.5 mol) were added, and the mixture was stirred at 40 °C for 1 h until crystallization was established. The remainder of the malic acid solution was added over 2 h followed by a wash of water (4 L). The mixture was kept at 40 °C for another 2 h, cooled to 20 °C over 4 h, and stirred at that temperature for 1 h. The white crystalline solid was collected by filtration, washed with ethyl acetate (2 × 40 L), and dried *in vacuo* at 45 °C. The yield of AZD3409 malate (mean of four batches) was 42.6 kg (89%) (total organic impurities 2.4% w/w by HPLC). Mp 148 °C (DSC analysis).

^{1}H NMR (500 MHz, 300 K, DMSO-d_6) δ 9.05 (1H, dd, $J = 2.4$, 0.8 Hz), 8.86 (1H, dd, $J = 4.8$, 1.6 Hz), 8.60 (1H, d, $J = 7.5$ Hz), 8.26 (1H, ddd, $J = 8.0$, 2.4, 1.8 Hz), 7.61 (1H, ddd, $J = 8.0$, 4.8, 0.9 Hz), 7.21 (2H, dd, $J = 8.7$, 5.6 Hz), 7.06 (2H, t, $J = 8.9$ Hz), 6.97 (1H, d, $J = 8.1$ Hz), 6.62 (2H, m), 5.79 (1H, br s), 4.92 (1H, m), 4.50 (1H, m), 4.15 (1H, m), 4.05 (1H, dd, $J = 7.7$, 5.6 Hz), 3.64 (3H, m), 3.25 (2H, m), 3.09 (1H, dd, $J = 11.8$, 6.7 Hz), 2.78 (4H, m), 2.59 (4H, m), 2.37 (1H, dd, $J = 15.6$, 5.8 Hz), 2.04 (3H, s), 2.00 (2H, m), 1.19 (6H, m); ^{13}C NMR (125 MHz, DMSO-d_6) δ 190.1, 175.8, 172.0, 171.4, 170.1, 160.5 (d, $J_{CF} = 240.6$ Hz), 154.4, 147.5, 146.2, 138.2 (d, $J_{CF} = 3.3$ Hz), 136.8, 134.6, 131.7, 130.4, 130.0 (d, $J_{CF} = 7.5$ Hz), 126.6, 124.3, 114.7 (d, $J_{CF} = 20.7$ Hz), 113.0, 111.7, 68.0, 66.5, 57.6, 51.5, 51.1, 45.8, 40.7, 39.5, 36.7, 34.8, 34.3, 30.1, 29.9, 21.5, 21.4, 14.5; HRMS (accurate mass) calcd for $C_{34}H_{41}N_4O_4S_2F$ (free base) 653.2632, found 653.2661. Anal. calcd for $C_{34}H_{41}N_4O_4S_2F \cdot C_4H_6O_5$: C, 58.0; H, 6.0; F, 2.4; N, 7.1; S, 8.1. Found: C, 57.7; H, 5.9; F, 2.6; N, 6.8; S, 8.4.

Preparation of Isopropyl (2*S*)-2-({2-(4-Fluorophenyl)-ethyl-5-[({(2*S*,4*S*)-4-[(pyridin-3-ylcarbonyl)thio]pyrrolidin-2-yl}methyl)amino]benzoyl}amino)-4-(*tert*-butylthio)butanoate (22b). *(a). Introduction of S-tert-Butyl Group.* Sulfuric acid (10 mL, 187 mmol) was added to a stirred solution of amine **10** (25.0 g, 57.8 mmol) and *tert*-butanol (50 mL, 526 mmol) in toluene (200 mL) at ambient temperature; the temperature of the mixture rose to 36 °C. The solution was stirred at 30 °C for 2 h and then at 45 °C for 2 h, whereupon HPLC analysis showed the sulfonium species to be the predominant component. The mixture was cooled to 9 °C and diluted with water (100 mL) and adjusted to pH 7.3 by addition of precipitated calcium carbonate (26.0 g, 260 mmol). The mixture was filtered and the filter cake washed with water (50 mL). The layers were separated, and the organic phase was discarded. 2-Mercaptoethanol (8.90 g, 114 mmol) and 47% w/w sodium hydroxide solution (5.5 mL, 104 mmol) were added to the aqueous phase containing the sulfonium species. The mixture was stirred overnight at ambient temperature and for 30 min at 40 °C, then it was cooled to ambient temperature and extracted with ethyl acetate (150 mL). The organic phase was washed with water (100 mL), dried over magnesium sulfate, and evaporated under reduced pressure to give a yellow oil (14 g) containing mainly the required product **25** (59% by area on HPLC analysis). The crude oil was purified in two portions by chromatography on silica gel 60 (500 g) using ethyl acetate/isohexane (1:1 v/v) as eluent to give **25** (7.2 g, 26%) (95% by area on HPLC analysis).

*(b). Coupling between tert-Butyl Analogue **25** and Thiolactol **12**.* *S-tert*-Butyl sulfide **25** (6.56 g, 13.8 mmol) was dissolved in toluene (50 mL). The solution was concentrated to about 35 mL under reduced pressure to remove any water or residual ethyl acetate and then diluted with toluene (20 mL). Whilst the temperature was maintained at about 20 °C, thiolactol **12** (3.28 g, 14.0 mmol) was added, followed by 5 M hydrogen chloride in isopropanol (1.22 mL, 6.1 mmol), 8 M borane·pyridine complex (1.38 mL, 11.1 mmol), and a further portion of 5 M hydrogen chloride in isopropanol (1.82 mL, 9.1 mmol). The solution was stirred at 20–23 °C for 24 h to complete the reductive amination step. Meanwhile, 1,1′-carbonyldiimidazole (2.80 g, 17.3 mmol) was added portionwise to a solution of nicotinic acid (2.04 g, 16.6 mmol) in acetonitrile (35 mL) at 10 °C. The solution was warmed to 20 °C to form the activated nicotinic acid and then was added to the pyrrolidinethiol solution. After 3.5 h, HPLC anlysis indicated substantial conversion to the required Boc-protected thioester **22a**. The mixture was diluted with water (32 mL) and warmed to 43 °C whereupon the suspended solid dissolved and enabled the layers to be separated. The organic phase was washed with water (2 × 32 mL) at 40 °C, dried over magnesium sulfate, and

concentrated under reduced pressure to about 22 mL. The residual solution was diluted with isohexane (28 mL). Attempts to crystallize the product failed, and thus the mixture was evaporated under reduced pressure to give **22a** (9 g, 82%) as an amorphous solid.

(c). Removal of Boc-Protecting Group. Phosphoric acid (36.0 g, 310 mmol) was added over 30 min to a solution of Boc-protected thioester **22a** (9 g, 10.2 mmol) in 2-methyltetrahydrofuran (18 mL) whilst keeping the temperature below 36 °C. The mixture was stirred at 36 °C for 1 h 20 min (HPLC analysis showed complete conversion) and then cooled to 10 °C and diluted with water (30 mL). The mixture was neutralized by addition of potassium bicarbonate (31.5 g, 315 mmol) dissolved in water (250 mL), and the gum that deposited was extracted into ethyl acetate (300 mL). The organic solution was dried over magnesium sulfate and evaporated under reduced pressure to give **22b** (6.6 g, 81%) as a solid that was dried *in vacuo* at 40 °C.

^{1}H NMR (600 MHz, 300 K, DMSO-d_6) δ 9.03 (1H, s), 8.84 (1H, d, J = 4.20 Hz), 8.65 (1H, d, J = 7.27 Hz), 8.23 (1H, d, J = 7.76 Hz), 7.59 (1H, dd, J = 7.60, 5.01 Hz), 7.17–7.25 (2H, m), 7.05 (2H, t, J = 8.65 Hz), 6.96 (1H, d, J = 8.08 Hz), 6.61–6.70 (2H, m), 6.00–8.00 (2H, br s), 4.89–4.96 (1H, m), 4.49–4.56 (1H, m), 4.10–4.19 (1H, m), 3.59–3.73 (2H, m), 3.27–3.35 (2H, m), 3.07–3.15 (1H, m), 2.69–2.86 (4H, m), 2.57–2.65 (3H, m), 1.93–2.01 (2H, m), 1.65–1.76 (1H, m), 1.23 (9H, s), 1.20 (3H, d, J = 6.30 Hz), 1.17 (3H, d, J = 6.14 Hz).

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