Organic Process Research & Development **2005**, *9,* 555–569

Efficient Syntheses of AZD4407 via Thioether Formation by Nucleophilic Attack of Organometallic Species on Sulphur

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Abstract:

The development of two efficient strategies for the synthesis of AZD4407 is reported, both of which are considered suitable for large-scale manufacture. In the first approach, 3-bromothiophene is coupled with (2*S*)-2-methyltetrahydropyran-4-one using Grignard chemistry. Following hydroxyl protection and lithiation at thiophene C-2, reaction with a protected 5-mercapto-1-methyl-1,3-dihydro-indol-2-one derivative bearing a leaving group on sulphur provides AZD4407 after acid-catalysed deprotection and epimerisation. The second approach starts from 2,4-dibromothiophene, which undergoes a selective Grignard exchange reaction at C-2 followed by reaction with similar protected mercapto-oxindole derivatives. Reprotection of the oxindole ring, followed by a second Grignard exchange, and reaction with (2*S*)-2-methyltetrahydropyran-4-one provides AZD4407 after acid-catalysed deprotection and epimerisation.

Introduction

AZD4407 **4** is a 5-lipoxygenase inhibitor expected to have activity in a variety of inflammatory conditions such as asthma and chronic obstructive pulmonary disease (COPD). To maintain supplies for development of this drug substance, a route capable of delivering multikilogram quantities of material in a short time frame was required, alongside identification of the long-term manufacturing route. One approach to the synthesis of AZD4407 has already been disclosed,[1] in which the key bond forming reaction involves a palladium-catalysed coupling between the 2-mercaptothiophene **2** and 5-bromo-*N*-methyloxindole **3** affording AZD4407 in moderate yield, Scheme 1. The crude product mixture comprising a mixture of both the (2*S*,4*R*)- and (2*S*,4*S*)-diastereomers was then epimerised with acid to equilibrate predominantly to the thermodynamically more stable (2*S*,4*R*)-isomer **4** (ratio 92:8), which was purified by chromatography and crystallisation.

Whilst this route was successfully employed for the synthesis of several kilograms of drug substance, a number of hurdles needed to be overcome before further scale-up could be considered:

(1) The synthesis of thiol **2** from thienyl pyranol **1**, for which the final part of the process was performed at a temperature in excess of 100 °C and utilised dimethyl disulphide as reagent, thus generating a stoichiometric amount of dimethyl sulphide as byproduct.

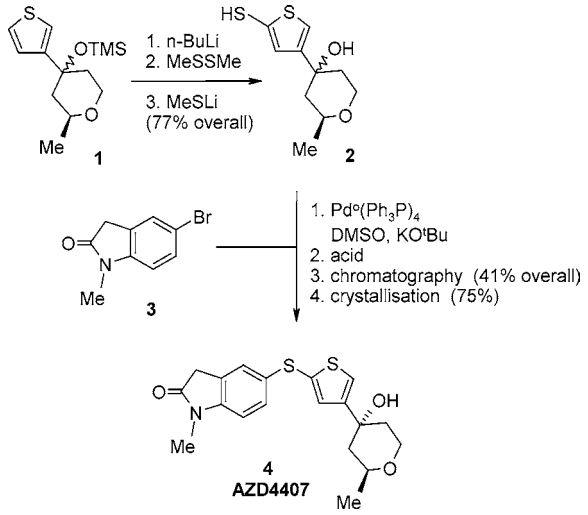
(2) The final bond forming reaction used a soluble palladium catalyst at a level of 10 mol %, having cost of goods implications and necessitating a removal regime to ensure that the palladium burden in the drug substance was reduced to an acceptable level.

(3) Lack of solid intermediates with the exception of bromo-oxindole **3**, providing little scope for purification before isolation of crude AZD4407.

(4) Requirement for purification of the crude drug substance by chromatography.

Consequently, a research program was instigated to find alternative routes to AZD4407, and the results of those studies are presented in this paper.

Scheme 1. **Previous route to AZD4407**



Thioether Formation via Pd-Catalysed Coupling. Having sulphur on the oxindole moiety rather than on the thiophene was considered preferable, since thiol **5** was expected to be a much more stable solid intermediate than **2**. Its synthesis was also expected to be relatively straightforward, avoiding the use of noxious reagents and formation

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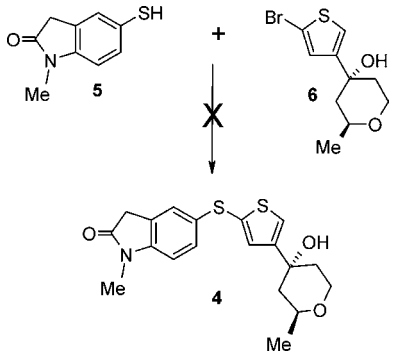
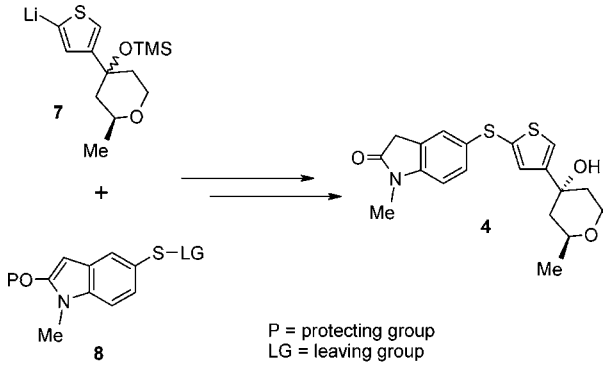
(1) Hutton, J.; Jones, A. D.; Lee, S. A.; Martin, D. M. G.; Meyrick, B. R.; Patel, I.; Peardon, R. F.; Powell, L. *Org. Process Res. Dev.* **1997**, *1*, 61.

10.1021/op0500483 CCC: $30.25
Published on Web 07/15/2005

Scheme 2. **Reverse coupling strategy**



Scheme 3. **Lithio-thiophene approach to AZD4407**



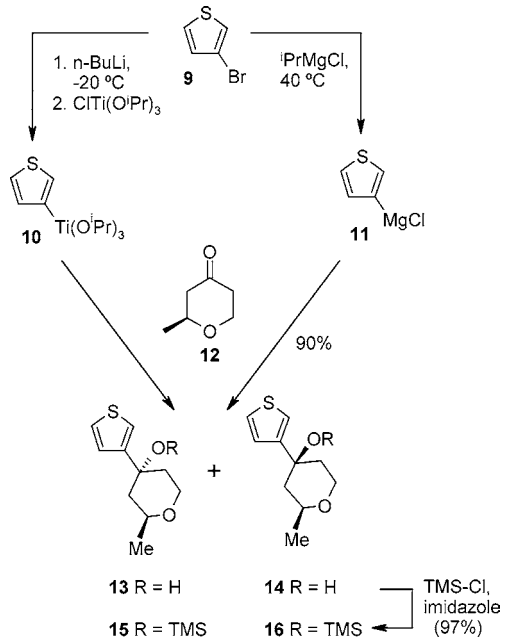
of undesirable byproducts.[2] Initial investigations centered around the use of a reverse coupling strategy, involving either a palladium-catalysed or copper-mediated reaction between oxindole thiol **5** and a bromothiophene **6**, Scheme 2. Copper-mediated couplings between 2-bromothiophene and a variety of simple aryl thiols, e.g., *p*-methoxybenzene thiol, naphthalene-2-thiol, and 4-acetamidothiophenol as model systems worked reasonably well. However, coupling between oxindole thiol **5** and bromothiophene **6** gave an unacceptably low yield of AZD4407 (**4**) under conditions in which other simple thiols such as naphthalene-2-thiol could be coupled successfully with **6**. We were unable to synthesise a suitable carbonyl-protected version of **5** to determine if the oxindole methylene unit was responsible for the lack of reactivity in these coupling reactions.

Thioether Formation using Organolithium Chemistry. By use of a suitable leaving group on sulphur, it was envisaged that the coupling reaction could be accomplished by, for example, organolithium chemistry, and the alternative strategy shown in Scheme 3 was expected to overcome most of the difficulties identified with the previous route (Scheme 1). This approach to AZD4407, using, for example, the symmetrical oxindole disulphide, was proposed in the previous paper;[1] however very little work was undertaken at that time. One of the potential problems identified with this strategy was the acidity of the oxindole benzylic protons, which would quench lithiothiophene. Hence appropriate protection of the oxindole fragment was required.

Coupling of the Thiophene and Pyran Fragments. The method used for formation of the bond between thiophene C-3 and the pyran moiety involved reaction of an organo-

(2) Bird, T. G. C.; Ple, P.; Crawley, G. C.; Large, M. S. EP 623614 B1, 1994.

Scheme 4. **Synthesis of protected thienyl pyranols 15 and 16**



metallic species derived from readily available 3-bromothiophene **9** and (2*S*)-2-methyltetrahydropyran-4-one **12**. Several syntheses of **12** and precursors have been published.[3]

In the work reported previously,[1] this step was carried out via lithium−halogen exchange followed by transmetalation with chlorotitanium triisopropoxide, which generated an intermediate titanate ester **10**, Scheme 4. The titanate has a reduced basicity, leading to cleaner carbonyl addition and therefore has a lower propensity to generate a 2-metallothiophene than the organolithium precursor. Reaction of this species with pyranone **12** provided a mixture of thienyl pyranols **13** and **14** with good regiocontrol (less than 1% of the 2-isomer **17** produced, Figure 1). As this process involved large jumps in temperature, it was further developed in order to achieve a more constant reaction temperature profile and, therefore, reduce the reaction time at larger scale from unnecessary heating and cooling cycles.

A temperature of −20 °C was found to be convenient and appropriate for the whole of this process as far as the workup. Thus, sequential lithium−halogen exchange between 3-bromothiophene and *n*-butyllithium, transmetalation using chlorotitanium triisopropoxide, and addition of pyranone **12** were all carried out at around −20 °C. After an aqueous acidic workup and extraction, a mixture of products **13** and **14** was isolated as a toluene concentrate in 80−90% yield. Whilst this procedure worked well on a laboratory scale controlling the level of the undesired 2-thienyl isomer to less than 1% GC area, scale-up to 450 L (12 kg of **12**) resulted in raised levels of the 2-isomer (at between 5 and 7% GC

(3) Atkinson, S.; Tornos, J. WO 2003051862 A1. Holt, R. A.; Rigby, S. R.; Waterson, D. WO 9719185 A1. Crawley, G. C.; Briggs, M. T. *J. Org. Chem.* **1995**, *60*, 4264. Haslegrave, J. A.; Jones, J. B. *J. Am. Chem. Soc*. **1982**, *104*, 4666. Hetero Diels−Alder approaches to a dihydropyranone have been reported: Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc*. **2005**, *127*, 1336. Mitsuda, M.; Hasegawa, J. GB 2304339 A1. A related method for the synthesis of similar pyranone precursors has also been recently reported: Reiter, M.; Ropp, S.; Gouverneur, V. *Org. Lett.* **2004**, *6*, 91.

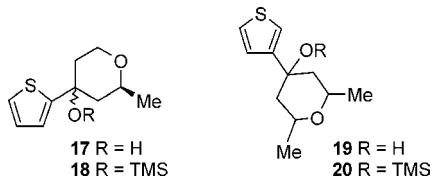


Figure 1. **Some impurities.**

area). The reasons for this were not proved conclusively; however it is thought that formation of 2-lithiothiophene is assisted by the presence of small amounts of protic material, which quench 3-lithiothiophene to provide a source of thiophene which can then undergo deprotonation at C-2. Control of the level of this impurity was thought to be crucial as it was expected to give a regioisomer of AZD4407 on progression through the synthesis. Given the difficulties of maintaining scrupulously anhydrous conditions and controlling the quality of the titanium reagent, an alternative organometallic species and more robust synthesis of intermediates **13** and **14** were sought.

Since 3-thienyl Grignard reagents are known to be difficult to prepare using standard procedures[1,4] and being keen to avoid the use of an organolithium species in a transmetalation process,[5] a Grignard exchange process[6] was evaluated and found to work well in this situation. Reaction between 3-bromothiophene and isopropylmagnesium chloride in THF required up to 18 h at ambient temperature or around 3 h at 40 °C to achieve a maximum conversion of around 80%. The reasons behind this incomplete exchange are not fully understood; however, it seems that towards the end of the exchange, there is a competing reaction which consumes isopropylmagnesium chloride, perhaps by reaction with the byproduct, isopropyl bromide. A hazard assessment study demonstrated that there were no safety concerns about the all-in nature of this reaction, the adiabatic temperature rise on mixing the reagents being only 30 °C. Reaction with pyranone **12** was accomplished after cooling slightly, and the product mixture comprising both **13** and **14** was isolated as a toluene concentrate for continuation into the next stage as these compounds exist as oils at ambient temperature. The combined yield on a 30 kg scale was 90%, and GC purity was 82 area% as the sum of **13** and **14**, with thiophene and 3-bromothiophene at 6% and 6.6% GC areas, respectively, as the major impurities. The diastereoselectivity of this addition was not a concern at this point in the synthesis, since previous work had shown that the mixture of epimers could be enriched in the desired (2*S*,4*R*)-isomer downstream by acid-catalysed epimerisation of the 3° alcohol[1]. In practice, the ratio was found to be up to 2:1 in favour of the undesired epimer **14**, although this ratio was dependent chiefly on the length of time in contact with the aqueous hydrochloric acid during workup.

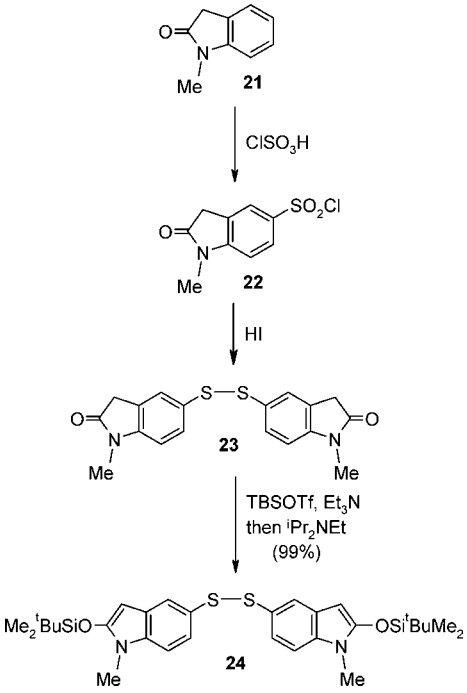
The Grignard exchange process reproducibly gave levels of 2-isomers **17** (Figure 1) of <0.5% GC area on a laboratory scale and only marginally higher on a 450 L (30 kg pyranone) scale. It is believed that the small amount of this impurity seen derives partly from the 2-bromothiophene present in the starting material (limited to <0.5%). The slightly increased level of the 2-isomer (1.09 area%) on scale-up was not a concern, since a means of removal of impurities derived from this contaminant further downstream in the process had been identified (vide infra). The other key impurity carried forward from this stage was derived from a small amount of a dimethyl analogue of pyranone **12**[7] leading to methyl homologue **19** (Figure 1). The optical purity of pyranone **12** used was typically >99.5%; thus up to 0.5% of enantiomeric compounds were also expected to carry through the synthesis. An overcharge of 3-bromothiophene was deliberately used in this process to ensure maximum consumption of the more expensive pyranone **12**, and the excess was partially removed during distillation at the end of the stage. It was demonstrated that any thiophene produced due to adventitious moisture in the reaction medium would not undergo deprotonation by isopropylmagnesium chloride, and hence the risk of formation of significant amounts of 2-metallothiophene was eliminated. A further benefit of the Grignard exchange process is that the need for cryogenic equipment is eliminated, since the exchange step takes place at ambient temperature or above and cooling only to between 0 and 15 °C is required for the exothermic pyranone addition. A range of Grignard reagents have been screened in this process, and so far, isopropylmagnesium chloride has proved the best. Cyclohexylmagnesium chloride is an alternative that merits further investigation as it avoids the issues surrounding generation of propane on quenching excess isopropylmagnesium chloride.

Protection of the Thienyl Pyranol Moiety. The protecting group chosen for pyranols **13** and **14** was trimethylsilyl (TMS), which provided a sufficiently stable intermediate and a robust enough protecting group for use with the subsequent organo-lithium chemistry[1]. This protecting group also influences the site of lithiation and favours formation of the 2-lithio-4-pyranyl thiophene. The procedure reported previously[1] was redeveloped, and imidazole was identified as a cheaper alternative to DMAP. Thus, reaction between trimethylsilyl chloride and imidazole followed by addition of the toluene solution of pyranols **13** and **14** provided a mixture of **15** and **16**, again isolated as a toluene concentrate, in 97% yield on a 50 kg scale. The level of 3-bromothiophene was further reduced to 4.4% GC area, due to codistillation with toluene. Although the residual 3-bromothiophene was expected to undergo lithiation in the next stage and react with the oxindole derivative **8**, we had shown that the levels of the resultant impurities were tolerable in the anticipated purification regime.[8] This proved to be a useful hold point in the synthesis and preferable to the previous stage, as this

(4) Rieke, R. D.; Seung-Hoi, K.; Xiaoming, W. *J. Org. Chem.* **1997**, *62*, 6921.
(5) Jayasuriya, N.; Kagan, J. *Heterocycles* **1986**, *24*, 2261.
(6) Boymond, L.; Rottlander, M.; Cahiez, G.; Knochel, P. WO 9951609 A1. Abarbri, M.; Dehmel, F.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 7449. Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G.; *Tetrahedron Lett.* **1999**, *40*, 4339. Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron* **2000**, *56*, 1349. Martin, G. J.; Mechin, B.; Leroux, Y.; Paulmier, C.; Meunier, J. C. *J. Organomet. Chem.* **1974**, *67*, 327.

(7) The synthesis of pyranone **12** by an intramolecular Prins cyclisation between 3-buten-1-ol and acetaldehyde is reversible and can go back either to the same starting materials or to formaldehyde and 4-penten-2-ol. The latter will undergo a Prins reaction with acetaldehyde to generate 2,6-dimethylpyran-4-ol.

Scheme 5. **Synthesis and protection of oxindole disulphide**



solution was stable for at least 3 months at ambient temperature.

Synthesis and Protection of Oxindole Disulphide. The synthesis of disulphide **23** via chlorosulphonylation of *N*-methyloxindole **21** followed by reduction with hydriodic acid (Scheme 5)[2] was chosen for development and scale-up. This provided an efficient preparation of **23** and was successfully used for the manufacture of over 200 kg of this intermediate.

Initial studies into the reaction of disulphide **23** with lithiothiophene **7**, Scheme 3, demonstrated that protection of the oxindole carbonyl functionality was critical for two reasons. First, the lithiothiophene would be quenched by deprotonation of the relatively acidic oxindole benzylic protons in preference to the desired reaction at the disulfide bridge. Second, the solubility of oxindole disulphide in solvents commonly used for organometallic chemistry was very low. It was found that both limitations could be overcome by formation of a bis(*tert*-butyldimethylsilyl)enol ether.[9] A screen encompassing a wide range of organic and inorganic bases failed to find conditions under which *tert*-butyldimethylsilyl (TBDMS) chloride could be utilised. However, we found that a clean reaction occurred when TBDMS triflate was used in conjunction with an organic base, preferably triethylamine. This resulted in a rapid, quantitative formation of the bis-*O*-silyl enol ether **24** and liberation of triethylammonium triflate, which separated out as a lower liquid phase. After removal of this layer, the amount of triethylammonium triflate remaining in the product solution was found to be variable and often too high, since it quenched lithiothiophene in the next stage. Therefore, further processing steps were introduced to control the level to an acceptable limit. It was found that addition of ethyldiisopropylamine achieved further removal of residual triflate by crystallisation of the salt of this base, affording residual levels reproducibly below 2 mol % after two treatments. Consequently, an aqueous workup was avoided which was important due to the instability of **24** at elevated temperatures in the presence of moisture. The product was isolated as a toluene concentrate in a yield of 99% by assay on a 35 kg scale. This intermediate could be stored for several days at 10−20 °C without any detrimental effect, although our preference was for immediate utilisation in the subsequent stage. Due to the extremely high acid sensitivity of this material, HPLC analysis could not be performed. Instead, product assays were carried out on samples treated with acid to reconvert to disulphide **23**, in conjunction with ^{1}H NMR spectroscopy to demonstrate that complete TBDMS protection had been accomplished in the reaction. Attempts to accomplish protection of **23** using ethyldiisopropylamine alone as base gave much slower conversion which was attributed to the thick heterogeneous nature of the reaction mixture.

Due to the relatively high cost of *tert*-butyldimethylsilyl protecting agents, particularly the triflate, many alternative protecting groups were considered and investigated. These included *O*-alkyl enol ethers;[10] however these were discounted due to the requirement of reagents such as trialkyloxonium tetrafluoroborates for their synthesis. Trimethylsilyl protection and formation of the bis-pivaloyl enol ether[11] were possible; however, both were found to be incompatible with the subsequent lithiothiophene chemistry.

Coupling the Thienyl Pyranol and Oxindole Fragments (Scheme 6). TMS-protected thienyl pyranol **1** is known to react with butyllithium selectively to give the 2-lithio-4-pyranylthiophene, presumably due to the bulk of the trimethylsilyl group inhibiting deprotonation at the adjacent carbon[1]. To avoid having to cope with butane evolution, the base for this stage was changed to hexyllithium in hexane, which made no difference to the chemistry.[12] The starting material was transferred from the previous stage as a toluene concentrate and required dilution with THF before deprotonation would take place. The charge of hexyllithium was regarded as critical, since an undercharge would result in an underconsumption of **1**, whereas an overcharge would result in a competing reaction of hexyllithium with **24** or a second deprotonation of the product **25** at C-5, followed by intramolecular silyl abstraction to generate a *C*-silyl analogue

(8) Wiped-film evaporation (WFE) was briefly investigated as a technique for the purification of the mixture of TMS ethers **15** and **16**. Results on a small scale demonstrated the feasibility of this technique since the purified mixture of **15** and **16** with an assay of around 100% by HPLC was produced *via* a 2-stage process. The first stage of this process distilled off residual 3-bromothiophene with the bulk of the toluene at 55 °C/1−3 mbara. In the second stage, the product itself was distilled at 110 °C/1 mbara. This process resulted in the 3-bromothiophene level being reduced from as much as 7% w/w to 0.5% w/w. However, this additional level of purification was not found to be necessary.

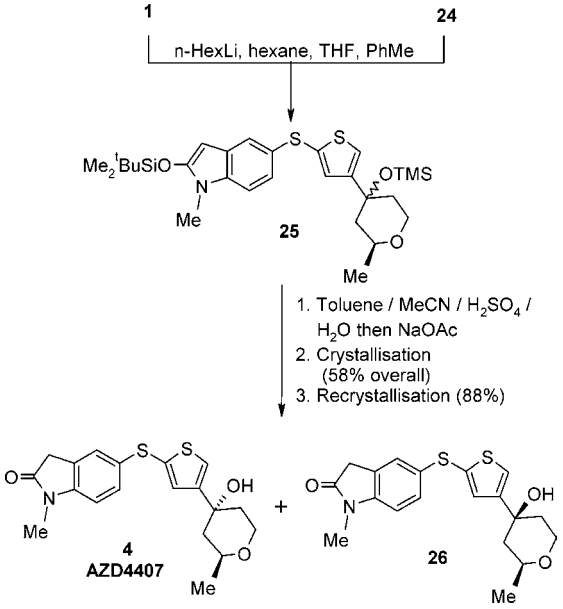
(9) Sawada, T.; Fuerst, D. E.; Wood, J. L. *Tetrahedron Lett.* **2003**, *44*, 4919. Moody, C. J.; Miah, S.; Slawin, A. M. Z.; Mansfield, D. J.; Richards, I. C. *Tetrahedron* **1998**, *54*, 9689.

(10) Esses-Reiter, K.; Reiter, J. *J. Heterocycl. Chem.* **2000**, *37*, 927. Deberly, A.; Bourdais, J. *J. Heterocycl. Chem.* **1977**, *14*, 781.

(11) Yamada, S.; Yaguchi, S.; Matsuda, K. *Tetrahedron Lett.* **2002**, *43*, 647.

(12) The cost of hexyllithium at the time this work was done was approximately the same as *n*-butyllithium on a w/w basis; therefore in terms of molar amounts, hexyllithium was only slightly more expensive.

Scheme 6. **Synthesis of AZD4407 from 1 and 24**

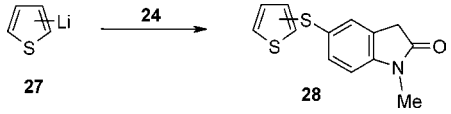


of AZD4407. The hexyllithium charge required was highly sensitive to the quality of input TMS ether. Consequently, the requirement was determined from the GC assay data for the particular batch of **1** used, taking into account the amount 3-bromothiophene present and residual unreacted thienyl pyranols **13** and **14**. The temperature at which deprotonation was carried out was found to be critical; below −20 °C, the regioselectivity of lithiation is at least 98:2, but above this limit, selectivity is lost. At −40 °C or below deprotonation still takes place at titration rate, but no advantage is gained from this additional cooling. It proved impossible to consume all the starting material **1** in this reaction, since after about 0.85 molar equiv of TBDMS-protected disulphide had been charged, no further conversion took place and excess disulphide was carried through after acid treatment. The reasons for this incomplete conversion remain unknown. Studies into the isolation of AZD4407 had indicated that the presence of excess disulphide during crystallisation led to an inefficient recovery of AZD4407. Therefore, the process was fixed with a stoichiometry of 0.85 equiv of TBDMS-protected disulphide **24** until means of improving the conversion in this stage could be found. During workup, oxindole thiolate partitioned cleanly into the aqueous layer,[13] with all the protected AZD4407 **25** remaining in the organic phase.

3-Bromothiophene brought though the synthesis to this point was shown to undergo lithium−halogen exchange and react with TBDMS-protected disulphide **24**. Rearrangement of 3-lithiothiophene to the more stable 2-lithio isomer was expected to result in a mixture of the regioisomeric oxindole thiophene sulphides **28**, Scheme 7. By tracking the fate of these impurities during crystallisation of AZD4407, it was determined that a level of residual 3-bromothiophene of up to 5% carried into this stage was tolerable.

(13) If this route had been selected for longer-term supply of AZD4407, recovery and recycling of the thiolate from the aqueous phase by oxidation to disulphide **23** would have been considered.

Scheme 7. **Impurity formation from 3-bromothiophene**



Epimerisation and Isolation. Deprotection and epimerisation of AZD4407 was carried out in a two-phase system comprising dilute aqueous sulphuric acid with an acetonitrile/toluene solvent mixture. Acetonitrile was initially chosen to ensure that sufficient water was present in the reaction medium to avoid dehydration and toluene was present due to its use as the solvent for isolation of the substrate **25**. This solvent system was favoured over ethyl acetate reported previously[1] due to hydrolysis of the latter during the course of the reaction. At ambient temperature, the acid treatment rapidly removed both protecting groups and equilibrated the epimers of AZD4407 at the 3° alcohol to a 92:8 mixture of **4** and **26**. When the epimerisation was carried out at 30 °C it was found that the ratio of diastereoisomers remained approximately the same. However, the 2,5-regioisomer of AZD4407 derived from progression of 2-thienyl pyranol **17** (Figure 1) through the synthesis selectively underwent irreversible dehydration, enabling easier removal during crystallisation. Hence, the temperature of 30 °C that was chosen as the rate of dehydration of AZD4407 was negligible, whereas the 2,5-regioisomer dehydrated readily over the course of the reaction period. At elevated temperatures in the presence of acid, AZD4407 dehydrates irreversibly; therefore, it was important to ensure complete removal of acid prior to any distillation.

Whilst early development batches of AZD4407 drug substance were purified by chromatography, isolation by crystallisation was vital for large-scale manufacture. Toluene proved a suitable solvent for crystallisation of AZD4407, since it not only gave a good recovery of product with acceptable quality and good physical form but also was used as solvent in preceding stages and facilitated removal of acetonitrile by distillation. It was found, however, that seeding was essential, otherwise the product failed to crystallise, and this was done at an appropriate point in the cooling ramp. On scale-up of this process to a 20 kg scale, the solid filtered in less than 30 min on a 0.3 m^2 14 μm filter-dryer and the isolated yield from disulphide **24** was 58%.

Toluene was also selected as the solvent for recrystallisation since longer-term this would have facilitated progression of the damp crude product.[14] It also provided a solid with the desired polymorphic form, suitable filtration characteristics, and very good quality. Seeding was used during recrystallisation to ensure that the correct polymorphic form was produced, and meta-stable zone width experiments defined the optimal temperature window at which to seed.

(14) One issue concerning the use of toluene in the final stage of the process is the level of benzene in the final product, and until we had more information on the amount in the dried product, a grade of low-benzene toluene was chosen for this stage. A change in the risk phrases for toluene published recently may have necessitated a change of solvent for this recrystallisation. This change was made as a result of the 29th ATP to EU Directive 67/548/EEC.

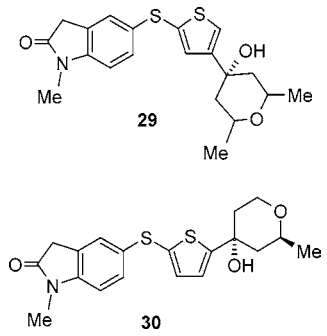


Figure 2. **Some impurities in AZD4407.**

This afforded AZD4407 pure in 88% recovery on a 22 kg scale with a residual toluene level of below 0.1% w/w after drying.

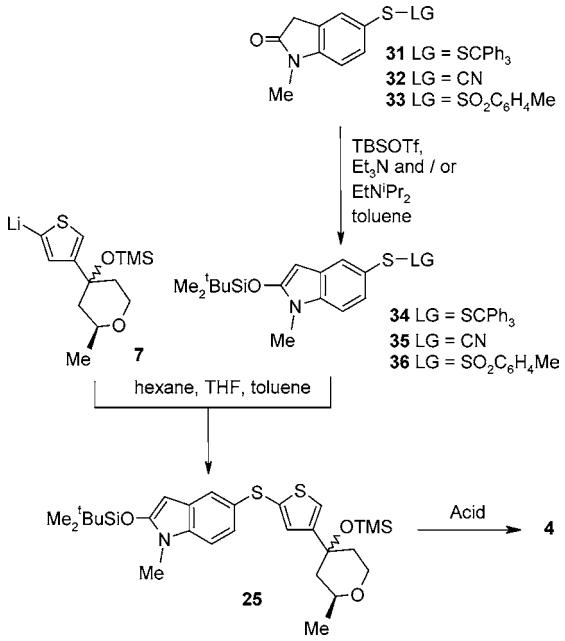
Impurities. A consequence of telescoping the whole route from 3-bromothiophene and pyranone **12** through to crude AZD4407 meant that particular attention had to be paid to the carry through of impurities. The key impurities found to cocrystallize with AZD4407 and therefore not reduce in level were the dimethyl analogue **29**, the enantiomer [(2*R*,4*S*)-isomer], and 2,5-regioisomer **30**, for which a method of removal had been discovered (see above)(Figure 2). No enhancement in optical purity was achieved during crystallisation of AZD4407 so the optical purity mirrored the optical purity of the input pyranone **12**. Likewise, the dimethyl impurity **29** was present at a level of 0.5%, unchanged from the level in the input pyranone. The (2*S*,4*S*)-diastereoisomer **26** was reduced to below 1 area%, and disulphide **23**, to below 0.1 area% when the level in the input crude product solution was below 1 area% relative to AZD4407.

Further Improvement Using Sacrificial Leaving Groups. Whilst the chemistry described above utilising oxindole disulphide was highly successful and was expected to be suitable for further scale-up, the drive for a more efficient process led us to consider alternative, sacrificial leaving groups on sulphur. A number of substrates were identified as potential replacements including a mixed disulphide from mercaptobenzothiazole, a mixed oxindole trityl disulphide, *p*-toluenethiosulphonate, thiocyanate, and a thiosulphate salt. Several of these were selected for further evaluation, Scheme 8, and the results are presented herein.

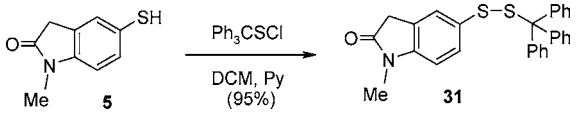
Mixed Trityl Oxindole Disulphide. A mixed disulphide of the form **31** was anticipated to undergo nucleophilic attack at the least sterically crowded sulphur atom, thus forming protected AZD4407 and liberating trityl thiolate on reaction with lithiothiophene **7**. This intermediate was synthesised in high yield on a small laboratory scale by the reaction between triphenylmethylsulphenyl chloride and oxindole thiol **5**, Scheme 9. Formation of the silyl enol ether and further conversion through to AZD4407 proceeded in an unoptimised solution yield of 34% after acid treatment.

Oxindole Thiocyanate. Use of thiocyanates in the formation of thioethers by reaction with either Grignard reagents or organo-lithium species is known,[15] and this strategy was investigated for the synthesis of AZD4407. Direct electrophilic thiocyanation of *N*-methyloxindole using well-established conditions such as *N*-bromosuccinimide with sodium thiocyanate in acetic acid[16] proved very difficult; therefore the synthesis given in Scheme 10 was used for the preparation of thiocyanate **32**.[17] Transformation of thiols to thiosulphate (Bunte) salts using pyridine−sulphur trioxide complex is precedented,[18] as is conversion of an organic

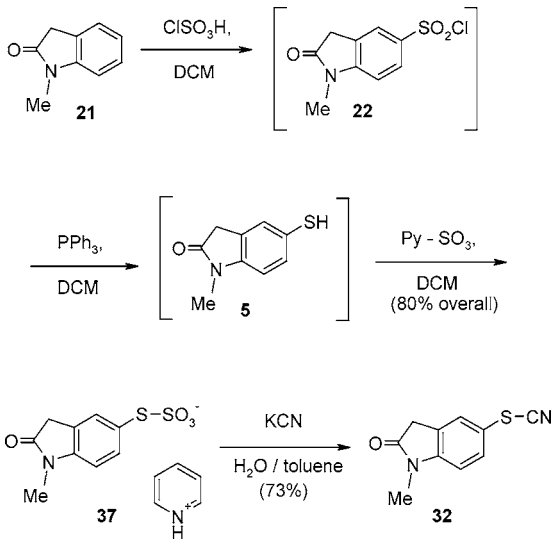
Scheme 8. **Synthesis of AZD4407 from oxindoles having sacrificial leaving groups on sulphur**



Scheme 9. **Synthesis of a mixed oxindole trityl disulphide**



Scheme 10. **Synthesis of oxindole thiocyanate 32**



(16) Toste, F. D.; De Stefano, V.; Still, I. W. J. *Synth. Commum.* **1995**, *25*, 1277.

(17) A recently reported procedure describes direct electrophilic thiocyanation of a range of aromatic and heteroaromatic compounds including oxindoles using ammonium thiocyanate and iodine: Yadav, J. S.; Reddy, B. V. S.; Shubashree, S.; Sadashiv, K. *Tetrahedron Lett.* **2004**, *45*, 2951.

(18) Kice, J. L.; Anderson, J. M.; Pawlowski, N. E. *J. Am. Chem. Soc.* **1966**, *88*, 5245.

(15) Pakulski, Z.; Pierożyński, D.; Zamojski, A. *Tetrahedron* **1994**, *50*, 2975.

thiosulphate to a thiocyanate, although this is uncommon.[19] Once its viability had been demonstrated, this synthesis was developed using dichloromethane as solvent, since the synthesis of oxindole sulphonyl chloride **22** in this solvent was already established and its use allowed a telescope of some of the later stages.

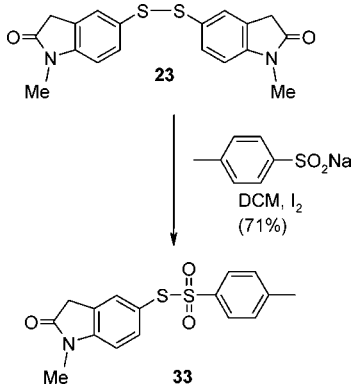
It has been reported that sulphonyl chlorides can be reduced to thiols directly using triphenylphosphine in aqueous dioxane.[20] This procedure was successfully applied to oxindole sulphonyl chloride **22** in dichloromethane in the presence of water, providing thiol **5** in 80−90% yield. Conversion to Bunte salt **37** was achieved using pyridine−sulphur trioxide complex in up to 80% yield from *N*-methyloxindole **21**. Reaction of pyridinium thiosulphate **37** with excess potassium cyanide in a biphasic aqueous toluene mixture gave thiocyanate **32** in 73% yield.

TBDMS-protection was carried out using TBDMS triflate in conjunction with Hünig's base as described below for oxindole thiosulphonate **36**. Reaction with excess lithiothiophene **7** at around −50 °C proved best giving AZD4407 with a yield in solution of 52%, Scheme 8. When the reaction was carried out at slightly higher temperatures (−30 to −45 °C) the yield decreased to 44% and dropped further still to 34% at −20 °C.[21] Although proven as a viable approach for the synthesis of AZD4407, the use of oxindole thiocyanate **32** was discontinued for the following reasons: the requirement for a lower reaction temperature, suboptimal stoichiometry, potential competing attack at carbon of the −SCN unit, and the formation of tarlike byproducts during the course of the reaction.

Oxindole Thiosulphonate. The synthesis of thiosulphonates by reaction of thiols with a sulphonyl halide has precedence[22] and was investigated for the synthesis of oxindole thiosulphonate **33**. The results from a small number of experiments with *p*-toluenesulphonyl chloride suggested that this reagent was unsuitable, since oxindole disulphide **23** was formed as the sole product, presumably via nucleophilic attack of unreacted thiol on the thiosulphonate as soon as it forms. Use of tosyl bromide[22] did afford the desired thiosulphonate; however, at present this reagent is not commercially available and had to be synthesised. The best yields were obtained by a slow addition of thiol **5** to a solution of *p*-toluenesulphonyl bromide and pyridine in dichloromethane at −10 °C, which minimised disulphide formation.

A convenient method for the conversion of disulphides to thiosulphonates has recently been published.[23] Moreover, a well-established synthesis of oxindole disulphide **23** was already in place. Therefore, after proving its viability, this approach was selected for development and scale-up, Scheme 11. For a multikilogram scale synthesis, a modified process was developed and implemented in which a solution of iodine in dichloromethane was added slowly to a hot solution of disulphide and *p*-toluene sulphinic acid in dichloromethane, whilst allowing solvent to distill out so as to maintain a roughly constant reaction volume. Thiosulphonate **33** was prepared in a yield of 71% using this method with a purity by HPLC of 97 area% on a 2 kg scale.

Scheme 11. **Synthesis of oxindole thiosulphonate 33**



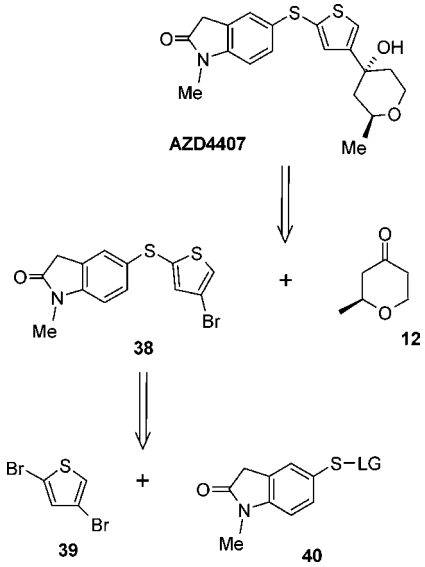
Silylation of oxindole thiosulphonate **33** was achieved using a modification of the procedure developed for the symmetrical disulphide **23**, including a reduced TBDMS triflate charge, Scheme 8.[24] In contrast to disulphide **23**, thiosulphonate **33** was found to undergo successful protection using ethyldiisopropylamine alone, which provided the triflate byproduct as a solid and would have facilitated recovery and recycling of the expensive triflic acid. It also had the benefits of a simpler and more effective removal of the byproduct and provided a more stable product solution. Concentration of the solution by distillation was not necessary and in fact was not possible with this material due to thermal instability.

Reaction between lithiothiophene **7** and protected thiosulphonate **36** was carried out at −30 °C, Scheme 8. A rapid reaction followed, and on completion, the byproduct, a salt of *p*-toluenesulphinic acid, was removed in the aqueous layer during workup, leaving a solution of protected AZD4407 **25** in toluene/THF/hexanes which was progressed as described above for the route using oxindole disulphide **23**.

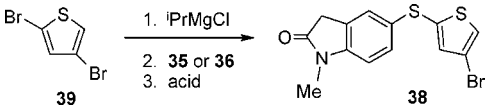
After acid treatment, AZD4407 crude was isolated by crystallisation from toluene in 32% overall yield from TMS-protected thienyl pyranol **1** on a 1.6 kg scale. This proved the viability of this approach for the large-scale manufacture of AZD4407, and this route was preferred over that using the symmetrical disulphide **23** due to lower cost from more efficient utilisation of oxindole disulphide. The discovery of an alternative strategy for the synthesis of AZD4407 offering the additional benefits of a solid isolable intermediate and later incorporation of the enantiopure pyranone **12** (see below) meant that no further development and optimisation of this approach was carried out.

(19) Tyrrell, A. W. R. *Tetrahedron Lett*. **1985**, *26*, 1753.
(20) Oae, S.; Togo, H. *Bull. Chem. Soc. Jpn*. **1983**, *56*, 3802.
(21) The reasons for this reduction in yield with increasing temperature were not fully elucidated; however competing attack of the nucleophile at the carbon in the thiocyanate unit was thought possible leading to a 2-cyanothiophene and liberation of oxindole thiolate. This in turn could react as a nucleophile with oxindole thiocyanate forming the symmetrical disulphide **23**, significant quantities of which were seen in many of the coupling reactions tried.
(22) Ranasinghe, M. G.; Fuchs, P. L. *Synth Commun*. **1988**, *18*, 227. Prasad, J. V. N. V. *Org. Lett*. **2000**, *2*, 1069.
(23) Fujiki, K.; Tanifuji, N.; Sasaki, Y.; Yokoyama, T. *Synthesis* **2002**, 343.
(24) Protection of **33** was attempted using TBDMS chloride in the presence of an alkoxide base but without success. Previous attempts at the coupling of **33** without protection using an excess of lithiothiophene **7** had demonstrated that the enolate of **33** was unstable, and this was thought to be the reason protection of the enolate under anionic conditions could not be accomplished.

Scheme 12. **Alternative approach to AZD4407 starting from 2,4-dibromothiophene**



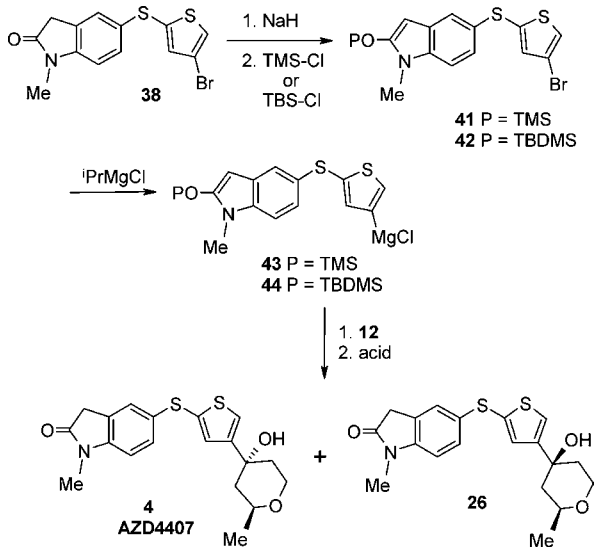
Scheme 13. **Thioether formation from 2,4-dibromothiophene**



Thioether Formation on 2,4-Dibromothiophene. While the strategy described above worked well and was successfully scaled up in our pilot plant to deliver a total of 25 kg of AZD4407, an alternative approach was devised and developed, Scheme 12, in which the pyranone was incorporated late in the synthesis. This strategy was appealing on the grounds that intermediate **38** was predicted to be crystalline, and thus represent a potential control point. It was envisaged that **38** would derive from a selective metalation of 2,4-dibromothiophene **39** at C-2 followed by reaction with a suitable electrophilic sulphur derivative **40**.

Although the selective lithiation of **39** with butyllithium has been described,[25] in our hands this reaction was not selective, even at −78 °C; therefore we turned again to the Grignard exchange reaction pioneered by Knochel.[6] This procedure has been described for this substrate, although temperatures below 0 °C were stated to be a requirement. In contrast, we found that, at +5 °C, magnesium−bromine exchange occurred exclusively at C-2,[26] Scheme 13. Three possibilities were considered for the coupling partner: the symmetrical disulphide **23**, thiocyanate **32**, and *p*-tolyl thiosulphonate **33**. In each case the oxindole carbonyl group was protected as the *tert*-butyldimethylsilyl enol ether, as described previously. In view of the lack of reactivity of the TBDMS-protected disulphide with Grignard reagents, this candidate was dismissed. TBDMS-protected thiocyanate **35**

Scheme 14. **Synthesis of AZD4407 from 38 with oxindole protection**



was more successful, giving an 80% solution yield of **38**. The problem here was that workup under basic conditions gave an inseparable emulsion. This was resolved by adopting an acidic workup, but the evolution of stoichiometric HCN under these conditions precluded scale-up of this chemistry.

In contrast, TBDMS-protected thiosulphonate **36** proved to be an ideal substrate, and reaction occurred on mixing with the thienyl Grignard reagent at −20 °C followed by warming to ambient temperature.[27] After an acidic quench, the sulphinate byproduct was washed out during the workup using aqueous sodium acetate and thioether **38** isolated by crystallisation from toluene[28] 65% yield.

Initial efforts into progression of intermediate **38** focused upon a deprotonation−Grignard exchange tactic, using excess isopropylmagnesium chloride, obviating the need for a second oxindole protection step. However, this led to formation of addition products between the oxindole enolate and pyranone carbonyl group. A variety of other reagents were therefore tried for deprotonation prior to Grignard exchange. Using hexyllithium as base, lithium−bromine exchange was found to occur faster than deprotonation. Other bases (NaH, LiHMDS, KHMDS, KOMe, KOMe/ TMEDA) all gave product mixtures containing the oxindole−pyranone adducts.

Protection of the oxindole was therefore required, Scheme 14. Formation of the magnesium enolate with isopropylmagnesium chloride followed by quenching with chlorotrimethylsilane (TMSCl) failed to give the TMS protected oxindole **41**. Changing the base to sodium hydride however resulted in successful protection with TMSCl. After the derived Grignard reagent **43** was reacted with pyranone **12**,

(25) Crawley, G. C.; Briggs, M. T. *J. Med. Chem*. **1995**, *38*, 3951.

(26) This reaction was also applied to 2,3- and 2,5-dibromothiophene, to determine the fate of impurities in **39**. The former was totally unreactive towards Grignard exchange, and the latter gave only the product arising from a single Grignard exchange. An iterated process did give the 2,5-dithioether, but this was found to be extremely sensitive towards acid-catalysed decomposition.

(27) The excess *i*PrMgCl was much less reactive towards **36** than the aryl Grignard reagent. A reaction between stoichiometric *i*PrMgCl and **36** was only 80% complete after 24 h. The isopropyl sulphide derived from this side reaction was not detectable in crude solutions.

(28) Several other solvents were examined for the isolation: IMS (industrial methylated spirit), IPA, THF, acetonitrile, ethyl acetate. IMS gave an excellent recovery, but in one experiment a different, less soluble polymorph was produced. In view of the success and practicality of the toluene procedure, this was not pursued further.

diastereoisomers **4** and **26** were obtained at a combined solution yield of 48%, still accompanied by significant amounts of the oxindole−pyranone adducts. Substitution of TMSCl by *tert*-butyldimethylsilyl chloride (TBDMS−Cl) reduced formation of these byproducts to undetectable levels; therefore this strategy was adopted for further development.

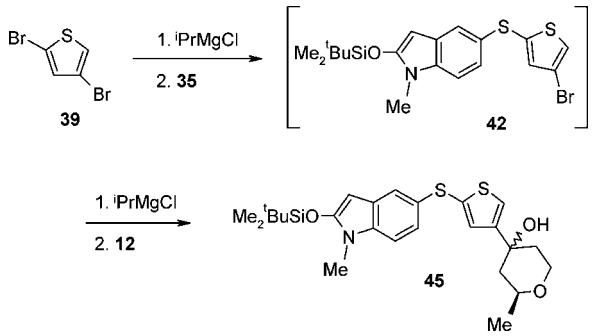
The most practical way of carrying out the deprotonation was to charge a solution of **38** in THF to the sodium hydride. The addition was performed in this manner to allow control of the hydrogen evolution and dispersion in the large-scale laboratory setup used. A solution of TBDMS chloride was then charged, and the extent of formation of silyl enol ether **42** was monitored by ^{1}H NMR spectroscopy. This process worked well on a small scale; however, on the sole occasion it was scaled up to 374 g, multiple sodium hydride and TBDMS chloride charges were needed to achieve complete conversion, and the reasons behind this difference were not determined.

The second Grignard exchange using isopropylmagnesium chloride was carried out 40 °C, and the extent of exchange was followed by GC−MS analysis of a sample quenched with CD_3OD. From this, it was shown that maximum conversion to **44** occurred after heating for between 2 and 20 h and required 2.0 molar equiv of isopropylmagnesium chloride, giving a ratio of **44:42** of around 92:8 on a laboratory scale. Increased reaction times and reagent stoichiometry did not lead to higher conversion. Conducting the reaction at reflux while distilling off solvent in an attempt to remove the byproduct, isopropyl bromide, did not improve conversion, while the higher temperature led to the formation of new byproducts. The use of a substoichiometric quantity of isopropylmagnesium chloride as an initiator with stoichiometric magnesium metal again offered no improvement in conversion, but this did provide evidence that the reaction could be run with catalytic isopropylmagnesium chloride. Again, on the occasion this was run at a 374 g scale, this step required additional reagent charges to achieve the target conversion.

The reaction mixture containing Grignard reagent **44** was reacted with pyranone **12** at 0 °C and then quenched with aqueous sulphuric acid to remove the protecting group, which provided a 60:40 mixture of diastereomers **4** and **26**. Removal of THF from the solvent mixture was found to be important, as epimerisation of the diastereomeric mixture to give predominantly AZD4407 **4** was found to be impracticably slow in the presence of this solvent. Epimerisation was carried out under conditions described previously affording crude AZD4407 in a 58% solution yield from **38**. Crystallisation from a relatively dilute toluene solution gave only a 23% recovery of AZD4407 **4** in 94.6% purity[29] which was upgraded upon recrystallisation to 97% purity, comprising an almost identical impurity profile to material prepared via the alternative strategy described above. Preliminary experiments suggested that more concentrated solutions afforded up to 75% recovery of AZD4407 **4** without seriously compromising product quality.

(29) By HPLC peak area. The largest impurity was (2*S*,4*S*)-AZD4407 at 3.7%, with **38** and the desbromo analogue reduced to 0.3% and 0.5%, respectively.

Scheme 15. **One-pot synthesis of an AZD4407 precursor from 2,4-dibromothiophene**



Telescoped Synthesis. Although there was a keen desire to incorporate the crystalline intermediate **38** in the synthesis as a point of control and hold point, it was considered feasible that the second protection stage could be omitted by carrying out the second Grignard exchange reaction on intermediate **42** without isolation and deprotection, Scheme 15. This would therefore represent a one-pot synthesis of AZD4407 from 2,4-dibromothiophene, a TBDMS-protected oxindole thiol derivative and pyranone **12**. In practice, this chemistry only worked successfully with oxindole thiocyanate **35**. Thus, an excess of 2,4-dibromothiophene **39** was treated with isopropylmagnesium chloride at below 5 °C to form the Grignard reagent at C-2 which was then reacted with TBDMS-protected thiocyanate **35** to give intermediate **42** in solution. The second Grignard exchange was carried out at 40 °C over 18 h and was followed by reaction with pyranone **12**. An aqueous work up gave **45** with a solution yield calculated as AZD4407 of 21% based on the amount of input pyranone **12**. Although this telescoped sequence was only done on a small laboratory scale and remains unoptimised, it proved the concept of coupling the three fragments together in a one-pot process.

Conclusions

Two new strategies for the synthesis of AZD4407 have been developed, which involve reaction of a lithio-thiophene or thienyl Grignard reagent with electrophilic sulphur derivatives to form the key thioether linkage. During the course of this work, the utility of the Grignard exchange process[6] has been demonstrated for the formation of stable 3-metallothiophenes, allowing clean addition to a ketone under noncryogenic conditions. In addition, a simple method for synthesis and isolation of moisture and acid sensitive TBS-protected oxindoles in solution has been developed enabling their use on a large scale.

The first strategy, starting from 3-bromothiophene, was successfully scaled up to pilot plant affording AZD4407 with good chemical purity and excellent control over the formation of regioisomeric impurities. This approach avoided the majority of the challenges presented by the previously published route,[1] specifically no requirement for chromatography at any stage of the process and no volatile thiol- or thioether-containing waste streams to treat, and avoided the use of palladium and other heavy metals. The number of stages was similar, and the overall yield was significantly

improved at 45%, providing AZD4407 in good physical form and with high purity after a single recrystallisation.

In addition, more efficient utilisation of oxindole disulphide was implemented by conversion to a thiosulphonate. Although requiring an additional chemical step, the amounts of materials required for protection of the oxindole were consequently halved and the need for longer-term recycling of oxindole thiol was avoided.

A second approach, starting from 2,4-dibromothiophene, has been identified, which has the important additional advantage of proceeding via a solid isolable intermediate. This provided a convenient hold point in the synthesis together with a point of control for removal of impurities and incorporated the enantiopure pyranone **12** later in the synthesis. Although not developed or scaled up to the same extent, it was intended that this route would have been subjected to further in-depth study to develop it to a point where it would have been used for further supply of AZD4407 had the project continued.

Experimental Details

General. All reactions were performed under a nitrogen atmosphere unless otherwise stated. NMR spectra were recorded using a Varian Unity-Inova 300 spectrometer (operating at 300 MHz for proton and 75 MHz for 13-carbon detection) or a Varian Unity-Inova 400 spectrometer (operating at 400 MHz for proton and 100 MHz for 13-carbon detection) at a probe temperature of 25 °C. Chemical shifts are reported in ppm downfield relative to TMS as an internal standard in $CDCl_3$ or DMSO-d_6. GC−MS data were obtained on an HP6890 Series GC and HP5973 Mass Selective Detector (MSD) using electron impact ionisation at 70 eV. Assays by HPLC were performed against purified and fully characterised reference materials. Samples of TBDMS-protected oxindoles for analysis were collected in plastic containers, since decomposition was catalysed by certain types of glass vials. Full analytical methods are provided in the Supporting Information.

(2*S*,4*R*)- and (2*S*,4*S*)-2-Methyl-4-thiophen-3-yltetrahydropyran-4-ols (13 and 14). THF (106.0 kg) was added to a solution of isopropylmagnesium chloride in THF (20% w/w, 187.0 kg, 1.4 mol equiv) and the temperature was adjusted to 20 °C. 3-Bromothiophene (51.5 kg, 1.2 mol equiv) was added to the Grignard reagent, maintaining the temperature below 25 °C during the addition. THF (5.5 kg) was used to wash in any remaining 3-bromothiophene. The reaction mixture was stirred at 40 °C for 3 h, and then a quenched sample was analysed by GC to check the extent of Grignard exchange, showing a ratio of thiophene/3-bromothiophene of 4.6:1. The reaction mixture was cooled to 3 °C, and **12**[3] (30.0 kg, 1 mol equiv) was added, maintaining the temperature between 0 and 15 °C (note that the vessel jacket was cooled to −15 °C during this addition to control the exotherm). This was followed by THF (4.9 kg) as a line rinse, and the reaction mixture was held at 10 °C for 40 min. The reaction was quenched by addition to a mixture of *tert*-butylmethyl ether (222.3 kg) and 2 M hydrochloric acid (307.5 kg). The temperature was maintained below 20 °C by controlling the rate of addition. The reaction vessel was rinsed with THF (53.1 kg), and this was added to the quenched reaction mixture. The phases were allowed to separate, and the upper organic layer was washed with 6−8% sodium bicarbonate solution (303.2 kg) and the basic lower layer (pH 9) was discarded. The organic layer was distilled at atmospheric pressure to remove TBME (213.4 kg, maximum temperature 61.6 °C), and then toluene (259.0 kg) was added. A further distillation under reduced pressure was carried out to provide a mixture of **13** and **14** as a solution in toluene. Assay by HPLC was 32% w/w, giving a contained weight of **13** and **14** of 47.1 kg (90.4% yield). The isomer ratio was 2:3 by GC analysis. Spectral data are quoted for isolated, purified samples of each diastereoisomer.

(2*S*,4*R*)-isomer **13**. GC retention time = 9.1 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, J = 5.0, 2.9 Hz, 1H), 7.20 (dd, J = 3.1, 1.3 Hz, 1H), 7.13 (dd, J = 5.0, 1.4 Hz, 1H), 4.00−3.87 (m, 3H), 2.07 (ddd, J = 13.8, 12.3, 5.6 Hz, 1H), 1.84 (dt, J = 13.8, 2.4 Hz, 1H), 1.77−1.69 (m, 2H), 1.21 (d, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.64 (s), 126.25 (d), 125.11 (d), 119.26 (d), 70.17 (s), 68.92 (d), 63.48 (t), 46.23 (t), 38.34 (t), 21.69 (q). GC−MS: m/z 198 (M^+).

(2*S*,4*S*)-isomer **14**. GC retention time = 9.0 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, J = 5.1, 2.8 Hz, 1H), 7.23 (dd, J = 2.8, 1.5 Hz, 1H), 7.17 (dd, J = 5.0, 1.4 Hz, 1H), 3.95 (ddd, J = 11.8, 4.9, 2.1 Hz, 1H), 3.47−3.36 (m, 2H), 2.31 (dt, J = 13.2, 2.3 Hz, 1H), 2.25 (dq, J = 13.3, 2.3 Hz, 1H), 1.98 (td, J = 12.9, 4.9 Hz, 1H), 1.68 (dd, J = 13.1, 11.3 Hz, 1H), 1.21 (d, J = 6.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.90 (s), 126.52 (d), 126.24 (d), 121.97 (d), 71.12 (d), 69.89 (s), 65.08 (t), 46.74 (t), 39.07 (t), 21.76 (q). GC−MS m/z 198 (M^+)

(2*S*,4*R*)- and (2*S*,4*S*)-2-Methyl-4-(trimethylsilyloxy)-4-thiophen-3-yltetrahydropyrans (15 and 16). Imidazole (21.2 kg, 1.3 mol equiv) was dissolved in THF (150.0 kg), and the solution heated to 23 °C. A solution of trimethylsilyl chloride (31.5 kg, 1.2 mol equiv) in toluene (123.3 kg) was added to the imidazole solution below 25 °C and washed in with toluene (4.5 kg). The solution of **13** and **14** in toluene prepared above (147.3 kg, 32% w/w, 1 mol equiv) was added at such a rate to maintain the temperature between 20 and 30 °C and was washed in with toluene (5.3 kg). The reaction mixture was stirred at 35 °C for 4 h when less than 1% starting material remained by GC analysis. After cooling to 23 °C, the reaction mixture was washed with water (2 × 90 kg), and the organic layer distilled under reduced pressure to provide a mixture of **15** and **16** as a solution in toluene. Assay by HPLC was 52.9% *w/w*, giving a contained weight of **15** and **16** of 62.3 kg (97% yield). Purity by GC (area%): sum of isomers **15** and **16** 89.0, 3-bromothiophene 4.37, 2-isomers 0.72.

Bis[2-*tert*-butyldimethylsilyloxy)-1-methyl-1*H*-indol-5-yl]disulphide (24). Triethylamine (23.3 kg, 2.3 mol equiv) was added to a slurry of **23**[2] (34.8 kg) in toluene (241.5 kg) and washed in with toluene (16.0 kg). The suspension was cooled to 0 °C, and TBDMS-triflate (57.8 kg, 2.2 mol equiv) was added at such a rate to maintain the temperature below

10 °C. This was followed by a toluene rinse (15.5 kg), and then the reaction mixture stirred at 0−10 °C for 15 min. The reaction mixture was warmed to 19 °C and analysed by ^{1}H NMR to ensure complete reaction. The biphasic mixture was allowed to separate, and the lower triethylammonium triflate/toluene layer separated off. Diisopropylethylamine (12.9 kg) and toluene (15.3 kg) were added to the upper layer, and the reaction mixture concentrated under reduced pressure (maximum temperature 32.3 °C) and then cooled to 20 °C. The mixture was filtered to remove diisopropylethylammonium triflate. Then a second diisopropylethylamine charge (6.3 kg) in toluene (142.2 kg) was added, and the distillation/filtration process was repeated to provide **24** as a solution in toluene, 140.3 kg. Assay by HPLC[30] was 40.2% w/w, giving a contained weight of **24** of 56.4 kg (99% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, J = 1.7 Hz, 2H), 6.74 (d, J = 8.3 Hz, 2H), 5.19 (s, 2H), 3.20 (s, 6H), 0.73 (s, 18H), 0.00 (s, 12H). The remaining resonances were coincident with the toluene signals at 7.1−7.3 ppm.

AZD4407 Crude. THF (106.3 kg) and toluene (31.2 kg) were added to a mixture of **15** and **16** in toluene (57.9 kg solution weight, 30.7 kg contained weight, 1.0 mol equiv). The resulting solution was cooled to −23.5 °C, and *n*-hexyllithium in hexanes (33% w/w, 40.1 kg, 1.28 mol equiv)[31] was added, maintaining the temperature below −20 °C, followed by a THF rinse (5.4 kg). A solution of **24** in toluene (40.2% w/w, 56.4 kg contained weight, 0.85 mol equiv) was added, keeping the temperature below −20 °C. The reaction mixture was warmed to −5 °C and quenched with aqueous sodium chloride (11.1 kg in 211 kg of water). After warming to ambient temperature, the aqueous layer was removed and the organic phase distilled under reduced pressure to remove THF and hexane to leave intermediate **25** as a toluene solution. Acetonitrile (156.0 kg) and aqueous sulphuric acid (2 M, 67.8 kg) were added to the toluene concentrate, and the reaction mixture stirred at 30 °C for 21 h and then at 20 °C for 44 h. The lower acidic layer was removed, and the organic layer was washed with sodium acetate solution (2.5 M, 68.6 kg) followed by *iso*hexane (89.8 kg). Water (141.0 kg) and toluene (160.8 kg) were added, and the aqueous layer was removed. The organic layer was concentrated by distillation under reduced pressure until 197.4 kg of distillate had been removed. Further toluene (152.7 kg) was added, and distillation continued until 156.5 kg of distillate had been removed. The solution was cooled to 50 °C, seeded with AZD4407 (27 g) and cooled further to 10 °C. During laboratory development work, particle size analysis using focused beam reflectance measurements confirmed steady growth in the 93−250 μm range during this time alongside attrition of the larger particles. The mean particle size (chord length) was consistently around 35 μm. After holding at this temperature overnight, the product was filtered, washed with toluene (30.9 kg), and dried under vacuum (jacket temp 50 °C) to provide AZD4407 crude, 22.15 kg. Yield based on HPLC assay of 95.5% w/w was 58% from **24**. Purity by HPLC (area%): 95.8, largest impurity (2*S*,4*S*)-isomer **26** at 2.54.

AZD4407 Pure (4). Toluene (159.3 kg) was added to AZD4407 crude (22.05 kg), and the mixture was heated to 85 °C to dissolve the solid. The solution was filtered, cooled to 59 °C, and then seeded with AZD4407 of the desired polymorphic form (33.1 g). The crystallisation was further cooled to 10 °C and then stirred at this temperature for 15 h. The solid was filtered off, washed with toluene (38.0 kg), and dried under vacuum (maximum jacket temperature 50 °C) to afford AZD4407 pure, 19.5 kg (88% yield, including the heel). HPLC purity (area%): 98.4, largest impurity (2*S*,4*S*)-isomer **26** at 0.83.

1-Methyl-5-trityldisulfanyl-1,3-dihydro-indol-2-one (31). A solution of **5** (3.0 g, 16.8 mmol) in dichloromethane (10 mL) was cooled to 0 °C and then was slowly added to a suspension of triphenylmethanesulfenyl chloride (5.2 g, 16.7 mmol) and pyridine (1.32 g, 16.7 mmol) in dichloromethane at 0 °C. The mixture was allowed to warm to ambient temperature, stirred for ca. 20 h, and then washed with water (2 × 30 mL). The organic phase was dried over magnesium sulphate, and the dichloromethane was removed to leave **31** as a solvent-damp, pale yellow solid, 8.40 g. By ^{1}H NMR analysis this contained 14% w/w dichloromethane; therefore contained product weight was 7.22 g (95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.14 (m, 15H), 6.98 (dd, J = 8.1, 1.2 Hz, 1H), 6.78 (d, J = 1.2 Hz, 1H), 6.53 (d, J = 8.2 Hz, 1H), 3.36 (s, 2H), 3.17 (s, 3H).

2-(*tert*-Butyldimethylsilyloxy)-1-methyl-5-trityldisulfanyl-1*H*-indole (34). TBDMS-protection of **31** was carried out on a 2 g scale using a similar process to that given above for the symmetrical disulphide **24**. Product **34** was isolated as a toluene solution and was progressed without further treatment. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (d, J = 1.3 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H), 6.83 (dd, J = 8.2, 1.8 Hz, 1H), 5.39 (s, 1H), 3.54 (s, 3H), 1.04 (s, 9H), 0.32 (s, 6H). The remaining protons were coincident with toluene resonances at 7.1−7.3 ppm.

Synthesis of AZD4407 (4) Using 34. The solution of **34** prepared above (assumed 90% yield, 3.96 mmol) was reacted with the lithiothiophene **7** (1.07 g, 3.96 mmol) at −40 °C as described above for the symmetrical disulphide **24**. After workup and acid-catalysed epimerisation/deprotection, the yield of AZD4407 in solution by HPLC assay was 0.50 g (34% from **34**).

Pyridinium *S*-(1-Methyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl) Thiosulphate (37). Chlorosulfonic acid (272 mL, 4.09 mol) was heated to 70 °C. A solution of **21** (80 g, 0.54 mol) in dichloromethane (240 mL, 3 vol) was added to the chlorosulfonic acid over 45 min, whilst allowing the dichloromethane to distil out. Dichloromethane (40 mL, 0.5 vol)

(30) Assays were performed on samples of material treated with acid to hydrolyze back to disulphide **23**, since TBDMS-protected disulphide **24** was unstable to HPLC. ^{1}H NMR was carried out before acid treatment to demonstrate that the TBDMS-protection had gone to completion.

(31) A multiplication factor for the hexyllithium charge to account for reagent consumed by reaction with impurities was determined as follows. Area percentages of impurities undergoing lithiation (thiophene, 3-bromothiophene, pyranone **12**, and residual thienyl pyranols **13** and **14**) were converted to mole percentages by multiplying each by molecular weight ratios relative to TMS thienyl pyranols **1** (3.07, 1.61, 2.35, 1.36, respectively) and their relative response factors (1.0, 1.7, 1.0, 1.0, respectively). The multiplication factor for the hexyllithium charge was then calculated as 1 + (Σ mol % impurities/total area% **15** and **16**).

was used as a line wash. The reaction was allowed to stir at 70 °C for a further 25 min. The mixture was cooled to 20 °C and then added dropwise to a rapidly stirred mixture of dichloromethane (1400 mL, 17.5 vol) and ice/water (1400 mL, 17.5 vol) over a period of 20 min, maintaining the temperature below 10 °C (exothermic). The mixture was stirred for 10 min, and then the layers were allowed to separate and the aqueous phase was discarded. The dichloromethane phase was washed twice with water (320 mL, 4 vol each) and then concentrated by distillation removing 400 mL (5 vol) of solvent to yield **22** as a solution in dichloromethane. Typical ^{1}H NMR data for an isolated sample ($CDCl_3$, 300 MHz): δ 8.03 (m, 1H), 7.90 (s, 1H), 6.97 (d, J = 8.3 Hz, 1H), 3.65 (s, 2H), 3.29 (s, 3H).

A solution of triphenylphosphine (427 g, 1.63 mol) in dichloromethane (200 mL, 2.5 vol), prepared by warming the mixture to 30 °C, was added to the solution of **22** prepared above over a period of 25 min (exothermic addition), followed by a dichloromethane line wash (40 mL, 0.5 vol). Water (80 mL, 1 vol) was then added to the reaction mixture, and after heating under reflux for 30 min no starting material remained, so the mixture was allowed to cool to ambient temperature and held overnight. Water (600 mL, 7.5 vol) was added followed by dropwise addition of aqueous sodium hydroxide until pH 12 was achieved (10 M, 90 mL used, 1.13 vol). The layers (both orange in colour) were allowed to separate, the dichloromethane phase was discarded, and the aqueous phase was washed with one portion of dichloromethane (400 mL, 5 vol). Dichloromethane (1200 mL, 15 vol) was then added to the aqueous phase followed by HCl until pH 2 was achieved (11.65 M, 50 mL used, 0.63 vol). The mixture was stirred for 5 min before allowing the layers to separate. The organic phase was concentrated by distillation removing 400 mL (5 vol) of solvent to yield **5** as a solution in dichloromethane. Typical ^{1}H NMR data for an isolated sample ($CDCl_3$, 300 MHz): δ 7.20−7.29 (m, 2H), 6.70 (d, J = 8.1 Hz, 1H), 3.49 (s, 2H), 3.42 (s, 1H), 3.19 (s, 3H).

Pyridine−sulfur trioxide complex (86.5 g, 0.54 mol) was slurried in dichloromethane (400 mL, 5 vol), and the solution of **5** in dichloromethane prepared above was added. The mixture was heated under reflux for 2 h and then cooled to 5 °C and stirred at this temperature for 100 min. The solid product was filtered off, and the filter cake was washed with dichloromethane (2 × 200 mL). The resulting solid was dried in a vacuum oven at 40 °C to yield **37** as a white solid, 155 g, assay by ^{1}H NMR 95% w/w, giving an overall yield from *N*-methyloxindole (**21**) of 80%. ^{1}H NMR (d_6-DMSO, 400 MHz): δ 8.92 (dd, J = 6.5, 1.4 Hz, 2H), 8.58 (m, 1H), 8.02−8.09 (m, 2H), 7.39−7.45 (m, 2H), 6.93 (d, J = 7.7 Hz, 1H), 3.55 (s, 2H), 3.11 (s, 3H). HPLC purity: 98.5 area%.

1-Methyl-5-thiocyanato-1,3-dihydro-indol-2-one (32). Bunte salt **37** (50.3 g, 59.6% w/w, 30 g contained weight, 0.089 mol) was slurried in water (150 mL). Aqueous sodium carbonate was added slowly until pH 10 was achieved (20% w/w, 150 mL used), causing effervescence and producing a yellow solution. Toluene (450 mL) was then added to the vessel,[33] and the mixture vigorously stirred. A solution of potassium cyanide (46.1 g, 0.71 mol) in water (100 mL) was then added to the reaction vessel. After stirring for 60 min, the biphasic mixture was filtered. The two layers were separated, the organic phase was washed with water (120 mL) and then two portions of 80% aqueous ethanol (120 mL each). The volume was reduced to 90 mL by distillation at 35 °C/40−70 mbar (360 mL of toluene was removed). The resulting slurry was heated to 95 °C to give a solution and then allowed to cool to 80 °C. Acetonitrile (4.5 mL, 5% v/v with respect to toluene) was then added, and the solution was allowed to cool to ambient temperature overnight. The resulting slurry was cooled to 0 °C, held for 3 h, and then filtered. The filter cake was washed with isohexane (90 mL) and then dried in a vacuum oven at 40 °C to provide **37** as a white solid 13.25 g (73%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46−7.55 (m, 2H), 6.86 (d, J = 8.2 Hz, 1H), 3.57 (s, 2H), 3.23 (s, 3H). HPLC purity (area%): 98.8, disulphide **23**, 1.2.

2-(*tert*-Butyldimethylsilanyloxy)-1-methyl-5-thiocyanato-1*H*-indole (35). This was prepared using the method described below for thiosulphonate **33**. **35** was isolated as a solution in toluene in an assumed 100% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58−7.43 (d, J = 1.8 Hz, 1H), 5.54 (s, 1H), 3.51 (s, 3H), 1.02 (s, 9H), 0.31 (s, 6H). The remaining resonances were coincident with toluene at 7.1−7.3 ppm.

Synthesis of AZD4407 Using 35. This was carried out on a 12 g scale of **15** and **16** using a similar process to that described above for disulphide **24**, with a relative stoichiometry of 1:0.83 **15** and **16**/**35**, except that the reaction was performed at between −50 and −54 °C. After epimerisation, the yield of AZD4407 in solution by HPLC assay was 52% from **35**. Crystallisation from toluene afforded 4.0 g (64% recovery) of crude AZD4407. Recrystallisation from toluene gave 3.0 g (75%) of purified AZD4407 (22% overall yield from **35**). Purity by HPLC (area%): 97.3, largest impurity was the (2*S*,4*S*)-diastereoisomer **26** at 1.22.

Toluene-4-thiosulfonic Acid, *S*-(1-Methyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl) Ester (33). Disulphide **23** (2.2 kg, 6.17 mol), anhydrous sodium *p*-toluenesulfinate (2.9 kg, 16.3 mol), and dichloromethane (33 L) were charged to a reaction vessel. Separately, iodine (1.74 kg, 6.86 mol) was dissolved in dichloromethane (55 L). The suspension in the reaction vessel was heated to reflux, and the solution of iodine in

(32) It was found that the product was unstable in the presence of excess aqueous sodium thiosulphate, particularly during a prolonged workup. To generate a more robust process by minimising risk of degradation in the workup, the amount of sodium thiosulphate solution charged was reduced by calculating a slight excess over the amount of excess iodine input over the 1 molar equiv required for reaction. Although this process was not proven on any scale larger than 10 g, the stability of the reaction mixture in the presence of the wash solution over a period of 2 h indicated that no problems with workup were expected on scale-up. This wash regime was preferred over the use of mildly basic aqueous systems which led to emulsion formation.

(33) The rationale behind use of this two-phase aqueous organic solvent system was to minimise contact between the product **32** and cyanide, by extraction into the organic phase. Degradation occurred when water alone was used as solvent leading to formation of large amounts of oxindole disulphide by nucleophilic displacement of thiolate from thiocyanate by cyanide, which would then react with thiocyanate to form disulphide and liberate cyanide. It is important to add the toluene before the potassium cyanide, since the reaction is rapid.

dichloromethane was added to this in portions (6 L every 30 min). As the iodine solution was added, a similar volume of dichloromethane was removed from the batch by distillation so as to keep the reaction volume constant. At the end of the addition, the mixture was stirred for 1 h at reflux. The amount of starting material remaining was 4%, so further iodine (157 g, 0.62 mol) was added in one portion and the mixture was heated overnight at 38 °C. This led to completion of reaction, so the mixture was cooled to room temperature and washed with sodium thiosulfate solution (1 M, 22 L) by stirring for 23 min.[32] The phases were separated, and the dichloromethane solution was washed again with sodium thiosulfate solution (1 M, 24 L) and then with water (22 L). The resulting dichloromethane solution was distilled to leave a volume of approximately 12 L, and then toluene (17 L) was added. The remaining dichloromethane was removed by distillation under vacuum, and the resulting toluene solution cooled from 50 °C to 0 °C over 6 h and then stirred at 0 °C overnight. The product was filtered, washed with toluene (4.4 L), and dried to constant weight at 40 °C under vacuum to provide **33** as an off-white solid (2.92 kg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J = 8 Hz, 2H), 7.23−7.28 (m, 4H), 6.77 (d, J = 8 Hz, 1H), 3.49 (s, 2H), 3.22 (s, 3H), 2.43 (s, 3H). HPLC purity: 96.8 area%.

Toluene-4-thiosulfonic Acid *S*-(2-*tert*-Butyldimethylsilyloxy)-1-methyl-1*H*-indol-5-yl) Ester (36). Diisopropylethylamine (0.95 kg, 7.35 mol) was added over 13 min to a stirred suspension of **33** (2.16 kg, 6.48 mol) in toluene (13.7 L) at between −2 °C and +2 °C followed by a toluene line wash (0.5 L). TBDMS triflate (1.85 kg, 7.00 mol) was then added to the reaction mixture over 1 h at −5 °C to −3 °C followed by a toluene line wash (0.5 L). The mixture was stirred at between −3 °C and −1 °C for 30 min, warmed to 20−25 °C over 30 min, and then sampled. Analysis by ^{1}H NMR showed complete reaction, so the suspension was filtered. The collected solid was washed with toluene (2.1 L), and the filtrates were combined to provide **36** as a pale brown solution in toluene, which was stored at 0 °C until used in the subsequent step. The yield was assumed to be 100%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.43 (m, 3H), 6.97−7.05 (m, 2H), 5.49 (s, 1H), 3.53 (s, 3H), 2.38 (s, 3H), 1.02 (s, 9H), 0.31 (s, 6H). The remaining resonances were coincident with toluene at 7.1−7.3 ppm.

Synthesis of AZD4407 (4) from 36. *n*-Hexyllithium in hexanes (2.02 kg, 32.9% w/w, 7.22 mol)[31] was added over 50 min to a stirred solution of **15** and **16** (3.2 kg, 52.3% w/w in toluene, 6.19 mol) diluted with THF (4.25 L) and toluene (4.25 L) at −28 °C to −25 °C. The solution was stirred at −25 °C to −28 °C for 5 min. TMS-chloride quench of a sample and analysis by ^{1}H NMR showed incomplete lithiation, so additional *n*-hexyllithium in hexanes (0.1 kg, 32.9% *w/w*, 0.36 mol) was added. The solution was stirred for 5 min and then resampled. Analysis as above demonstrated complete lithiation, so the reaction solution was cooled to −33 °C. The solution of **36** (assumed 6.48 mol) in toluene prepared above was then added over 70 min at −33 °C to −25 °C. The mixture was stirred at −25 °C for 30 min and then warmed to −5 °C over 15 min. A line wash of toluene (3 L) was added, followed by 5% aqueous sodium chloride solution (9.2 L), and then the mixture was warmed to 20−25 °C over 30 min and stirred at this temperature for 30 min. The phases were separated, and the upper layer was washed again with 5% aqueous sodium chloride solution by stirring for 30 min at 20−25 °C. The upper layer was then concentrated to 8.5 L by distillation under vacuum at below 50 °C, and then the contents of the reaction vessel were cooled to 20−25 °C. Acetonitrile (14 L) and 2 M sulphuric acid (4.5 L) were added, and the mixture stirred at 30 °C for 24 h. Stirring was stopped, the lower aqueous layer was removed, the upper layer was cooled to 20−25 °C and then washed with 20% aqueous sodium acetate solution (4.7 L), followed by isohexane (9.3 L). The lower product-containing layer was washed with water (4.7 L). The toluene/acetonitrile solution was concentrated to 8 L by distillation under vacuum at below 50 °C, additional toluene (20.5 L) was added, and the distillation was repeated to reduce the volume to 8 L. The mixture was heated to 80 °C and then cooled to 56 °C over 40 min and seeded with AZD4407 (5 g). The mixture was held at 56 °C for 10 min, cooled to 10 °C over 5.5 h, and then stirred at 10 °C overnight. The product was filtered off, washed with toluene (3.1 L), and dried to constant weight at 40 °C under vacuum to give AZD4407 (**4**) as an off-white solid (0.76 kg, 32%). HPLC purity (area%): 94.3, (2*S*,4*S*)-isomer **26** was 2.13.

A portion of this material was recrystallised from toluene on a 20 g scale as described above to afford AZD4407 pure, 16.6 g (83%). HPLC purity (area%): 97.6, (2*S*,4*S*)-isomer **26**, 0.94, dimethyl analogue **29**, 0.54.

5-(4-Bromothiophen-2-ylsulfanyl)-1-methyl-1,3-dihydroindol-2-one (38). 2,4-Dibromothiophene (30.89 g, 94% w/w, 29 g contained weight, 120 mmol) was dissolved in THF (154 mL) and cooled to 0 °C. A solution of isopropylmagnesium chloride in THF (2 M, 66 mL, 132 mmol)[34] was added whilst maintaining the reaction temperature between 0 and 5 °C. The reaction was left stirring for 1 h on completion of the addition, at which point a sample was removed and analysed by HPLC to check conversion and confirmed that the Grignard reagent had formed. The reaction was cooled to −20 °C, and a solution of **36** in toluene (320 g, 16.8% w/w, 120 mmol) was added whilst maintaining the reaction temperature between −10 and −20 °C. Once the addition was complete the reaction was warmed to 20 °C over 2 h. The reaction was then quenched by the addition of aqueous sulphuric acid (2 M, 230 mL, 460 mmol). The layers were separated, the organic layer was washed with aqueous sodium acetate solution (20% w/v, 2 × 220 mL) followed by water (220 mL), and then toluene (290 mL) was added. The organic phase was concentrated by distillation under vacuum until the concentration of **38** was around 20% w/w. The mixture was heated to 80 °C and then cooled to ambient temperature. The solid product was collected by filtration, washed with toluene (29 mL), and then dried in a vacuum

(34) The excess ^{i}PrMgCl was much less reactive towards **36** than the aryl Grignard reagent. A reaction between stoichiometric ^{i}PrMgCl and **36** was only 80% complete after 24 h. The isopropyl sulphide derived from this side reaction was not detectable in crude solutions.

oven at 40°C to afford a beige crystalline solid, 26.6 g (65% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34−7.37 (m, 1H), 7.26−7.28 (m, 2H), 7.10 (d, J = 1.5 Hz, 1H), 6.76 (d, J = 8 Hz, 1H), 3.52 (s, 2H), 3.19 (s, 3H). Purity by HPLC: 98.52 area%.

Synthesis of AZD4407 (4) from 38. Compound **38** (0.374 kg, 1.10 mol) was dissolved in THF (2.91 kg) by heating to 50 °C with stirring. The solution was cooled to 25 °C and then added to a suspension of sodium hydride (0.048 kg of a 60% dispersion in mineral oil, 1.20 mol) in THF (0.355 kg) followed by a THF line wash (0.172 kg). A solution of TBDMS chloride (0.185 kg, 1.23 mol) in THF (0.353 kg) was added followed by a THF line wash (0.170 kg). The mixture was stirred at 20 °C for 2 h and then analysed by ^{1}H NMR which showed only 50% conversion had taken place. The mixture was then added to sodium hydride (0.026 kg of a 60% dispersion in mineral oil, 0.65 mol). The mixture was stirred at 20 °C for 2 h and then analysed by ^{1}H NMR which showed only 60% conversion had taken place. A solution of TBDMS chloride (0.101 kg, 0.67 mol) in THF (0.179 kg) was added. The mixture was stirred for 16.5 h at 20 °C and then analysed by ^{1}H NMR which showed only 75% conversion had taken place. The mixture was then added to sodium hydride (0.023 kg of a 60% dispersion in mineral oil, 0.58 mol). A solution of TBDMS chloride (0.085 kg, 0.56 mol) in THF (0.168 kg) was added. The mixture was stirred for 1 h at 20 °C and then analysed by ^{1}H NMR which showed that complete conversion to **42** had taken place.

A solution of isopropylmagnesium chloride in THF (2 M, 1.142 kg, 2.34 mol) was added to the reaction mixture, followed by a THF line wash (0.189 kg), resulting in a 5.4 °C exotherm. The mixture was heated to 40 °C and stirred at this temperature. After 5 h, analysis by ^{1}H NMR indicated that 50% conversion to the arylmagnesium halide **44** had taken place. The mixture was cooled to 35 °C, and a further charge of isopropylmagnesium chloride in THF (2 M, 0.564 kg, 1.16 mol) was added. The mixture was heated to 40 °C and stirred at this temperature for 1.5 h. Analysis by ^{1}H NMR indicated that 92% conversion to the arylmagnesium halide **44** had taken place.

The mixture was cooled to 0 °C, and a solution of **12** (0.127 kg, 1.11 mol)) in THF (0.334 kg) was added, followed by a THF line rinse (0.165 kg). The mixture was warmed to 20 °C and stirred at this temperature for 14 h and then added to aqueous sulphuric acid (0.24 M, 7.00 kg) held at 5 °C (exotherm of 9 °C observed) followed by a toluene line wash (1.414 kg). The mixture was warmed to 20 °C over 30 min with stirring. The layers were allowed to separate, and the lower layer was discarded. The organic layer was washed with sodium acetate solution (20% w/v, 0.78 L), followed by water (1.523 kg), then distilled under vacuum (150 mbarg) to remove THF. A further charge of toluene (1.426 kg) was added once the volume had been reduced by approximately 50%, and distillation continued until 1.936 kg remained. Analysis of this mixture by ^{1}H NMR showed the solvent composition to be toluene/THF 97:3 w/w.

The mixture was cooled to 20 °C, and acetonitrile (1.943 kg) was added, followed by aqueous sulphuric acid (2 M, 0.784 kg). The mixture was heated to 30 °C with stirring, and stirring continued at this temperature for 18 h. The layers were allowed to separate, and the lower aqueous layer was discarded. The organic (toluene/acetonitrile) phase was washed with sodium acetate solution (20% w/v, 0.75 L), isohexane (1.088 kg), and then water (1.7 kg). The product-containing solution was diluted with toluene (2.196 kg) and distilled under reduced pressure (200−80 mbarg) to give 1.871 kg of a solution of AZD4407 in toluene (12.7% w/w, contained weight of AZD4407 therefore 237.4 g, 58% yield). This was heated to 60 °C, and a cooling ramp of 10 °C/h was set. When the temperature had fallen to 45 °C, the mixture was seeded with AZD4407 (2.37 g, 1 mol %). Stirring was continued at 10 °C for 72 h. The product was collected by filtration, and the filter cake was washed with toluene (0.375 L) and dried under vacuum at 40 °C for 4 h, to give AZD4407 crude (54.9 g, 23%) in 95% purity by HPLC peak area. This was slurried in toluene (0.46 L) and heated to 85 °C and filtered at this temperature, and a cooling ramp of 10 °C/h was set. When the temperature had fallen to 45 °C, the mixture was seeded with AZD4407 (2.37 g, 1 mol %). Stirring was continued at 10 °C for 18 h. The product was collected by suction filtration, and the filter cake was washed with toluene (0.11 L) and dried under vacuum at 50 °C for 4 h, to give AZD4407 (43.9 g, 80%) in 97.2% purity by HPLC peak area.

Synthesis of AZD4407 (4) from 2,4-Dibromothiphene via a One-Pot Process. A solution of isopropylmagnesium chloride in THF (16.7 mL, 20.5% w/w, 33.5 mmol) was added over 10 min to a solution of 2,4-dibromothiophene (7.37 g, 30.5 mmol) in THF (26.5 mL) at 3 °C causing an exotherm to +12 °C. The resulting reaction mixture was stirred at this temperature for 30 min during which time a thick light-coloured precipitate formed. A solution of **35** in toluene (21.9 g, 31% w/w, 21.3 mmol) was added over a period of 5 min. The reaction mixture was allowed to warm to ambient temperature and stirred overnight. A solution of isopropylmagnesium chloride in THF (12.1 mL, 20.5% w/w, 24.4 mmol) was added, and the reaction mixture was heated to 40 °C. After 18 h the exchange reaction had proceeded to >80% conversion, so the reaction mixture was cooled to 12 °C and pyranone **12** (2.78 g, 24.4 mmol) was added over 5 min. The reaction was stirred for 1 h at 10 °C and then warmed to 20 °C. Aqueous sodium chloride (5% w/v, 100 mL) was added, and stirring continued for 20 min. Toluene (100 mL) was added, and the mixture was allowed to stand for 1 h, after which the layers had separated. The lower aqueous layer was re-extracted with toluene (100 mL), and the combined organic layers were washed with water (100 mL) to leave a dark brown solution of **45**, weight 33.4 g. Assay by HPLC of an acidified sample gave a result of 5.7% w/w for the combined isomers **4** and **26**, corresponding to a 21% yield of AZD4407 and the (2*S*,4*S*)-epimer (**26**) from **12**.

Acknowledgment

We thank the following who were also involved in this project: Members of the Process Analysis Section at AstraZeneca Charnwood, in particular Annabelle Germon,

Lee Mallard, and Kevin Sutcliffe for their input to analytical aspects. The staff of the Avlon and Macclesfield Large Scale Laboratories for scale-up studies of some of the processes published in this paper. Members of the AstraZeneca Process R&D Laboratories in Bangalore for additional investigations into the synthesis of **23**. Neil Barnwell, Steve Eyley, Melvyn Giles, Paul Hurved, and Anil Mistry of AstraZeneca Charnwood for their contribution to the project. We also acknowledge the contribution to this project made by Laporte plc, subsequently part of Degussa AG, for development and scale-up of the synthesis of **23** and Orgamol S.A. for scale-up of the synthesis of **32**.

Supporting Information Available

HPLC and GC analytical methods for AZD4407 and various intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review March 24, 2005.

OP0500483