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A Convergent Synthesis of AR-C123196 Utilising Reaction Between a Cyclic Carbonate and a Phenol for Aryl Alkyl Ether Formation

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Abstract:

The development of a convergent synthesis of AR-C123196 is reported in which the alkyl aryl ether linkage was formed by nucleophilic attack of a phenolic hydroxyl group onto a cyclic carbonate. This approach was successfully operated on a multikilogram scale.

Introduction

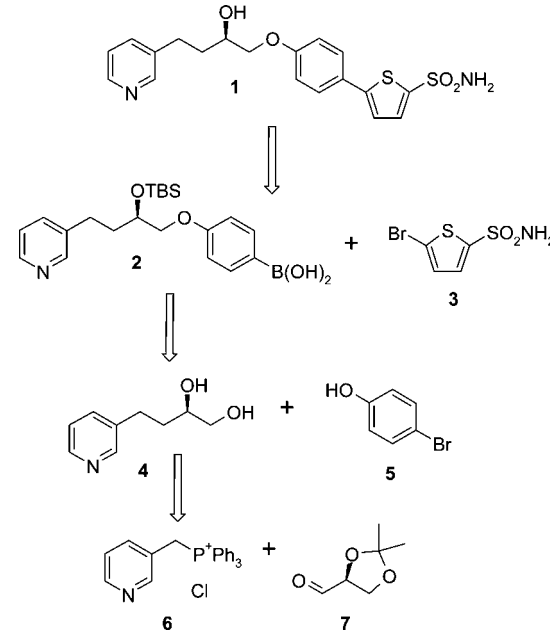
AR-C123196 (**1**) was selected for development within AstraZeneca as a potential treatment for a range of inflammatory and allergic conditions such as asthma and rhinitis.[1] The structure conceptually breaks down into a pyridyl butane-1,2-diol fragment and a functionalised biaryl unit composed of phenyl and thiophene rings. AR-C123196 is a chiral molecule and as such was required in enantiomerically pure form. While the synthesis of diol **4** was a considerable challenge, both in terms of manufacture using the established route from (*S*)-2,3-*O*-isopropylideneglyceraldehyde (**7**)[1] and with the prospect of needing an efficient route for large-scale future supply, this paper focuses on the chemistry downstream of this to AR-C123196. The free base of AR-C123196 had acceptable physical properties and was thus selected as the form for progression through development.

The initial strategy adopted for synthesis of this class of compounds was the linear route given in Scheme 1, in which the biaryl unit is built up stepwise onto the optically pure diol **4**. This route was used for delivery of tens of gram quantities of AR-C123196; however, it clearly gave rise to many concerns when considering its use for larger-scale manufacture:

- The synthesis is long, nine steps overall from (*S*)-2,3-*O*-isopropylideneglyceraldehyde (**7**).
- The most expensive building block was the L-gulonic-γ-lactone, precursor to (*S*)-2,3-*O*-isopropylideneglyceraldehyde (**7**), a key element used in the synthesis of diol **4**.
- A Pd-catalysed biaryl formation was used as the final bond-forming step of the synthesis, and thus reduction of residual Pd levels to an acceptable level for clinical use would be a key consideration.
- *tert*-Butyl lithium was used for the boronic acid formation.
- The hydroxyl group needed protection prior to boronic acid formation.
- Chromatography was used at many stages.

Consequently, there was a strong desire to establish a much more efficient synthesis of AR-C123196 early in development.

Scheme 1. **Discovery approach to AR-C123196 (1)**



This paper reports the identification, development and scale up of a convergent synthesis of AR-C123196 to allow delivery of the first multikilogram (multikg) batches of drug substance.

Results and Discussion

A Convergent Strategy. There were clear benefits in implementation of a more convergent approach to AR-C123196 by coupling a preformed biaryl unit **8** with a derivative of diol **4** in forming the ether bond, Scheme 2. The convergent nature of this approach meant much more efficient usage of the expensive diol whilst having the biaryl formation earlier in the synthesis provided much more scope for removal of residual Pd or other metals carried forward from the coupling reaction.

For the left-hand side coupling partner, an adequate route to diol **4** for manufacture of multikg quantities was already in place from 2,3-*O*-(*S*)-isopropylidene glyceraldehyde (**7**) and phosphonium salt **6**, derived from 3-chloromethylpyridine, Scheme 1. In the longer term, we envisaged a much more efficient synthesis[2] through enantioselective reduction of the

* To whom correspondence should be addressed. Fax: +44 (0)1509 645588. E-mail: eric.merifield@astrazeneca.com.

(1) Cheshire, D.; Cladingboel, D.; Cooper, M.; Hardern, D.; Hirst, S.; Manners, C.; Stocks, M. Preparation of novel (hydroxyalkyl)pyridine derivatives and pharmaceutical compositions containing them. WO 9843971 A1, 1998.

(2) Butters, M.; Catterick, D.; Craig, A.; Curzons, A.; Dale, D.; Gillmore, A.; Green, S. P.; Marziano, I.; Sherlock, J.-P.; White, W. *Chem. Rev.* **2006**, *106*, 3002.

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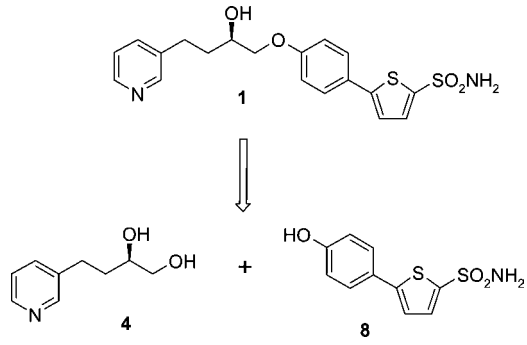
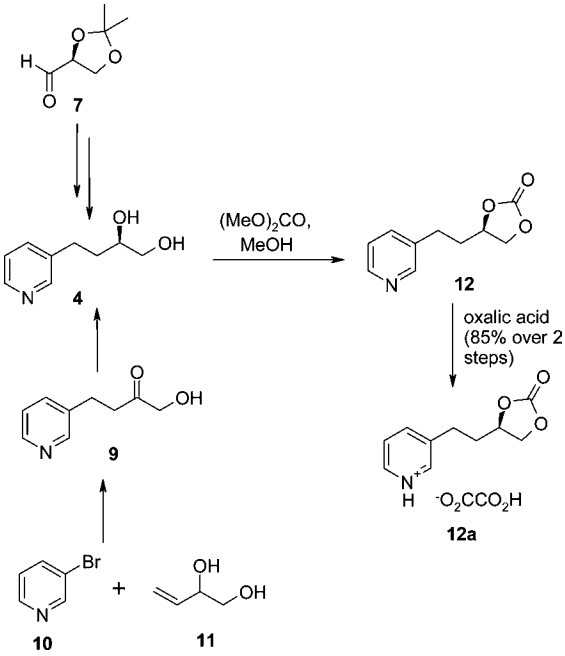
Scheme 2. **Convergent approach to AR-C123196 (1)**



Scheme 3. **Some strategies for the synthesis of carbonate 12**



α-hydroxyketone **9**, either by hydrogenation in the presence of a chiral catalyst or by enzymatic means,[3] Scheme 3. The highly enantioselective reduction of hydroxyketone **9** was indeed demonstrated in high yield on a small lab scale using a ruthenium catalyst containing a chiral phosphine ligand.[4] A short route to the reduction substrate was developed *via* Heck coupling between 3-bromopyridine (**10**) and 3-buten-1,2-diol (**11**) with concomitant isomerisation to the ketonic product.[5]

Precedence exists for reaction of a number of cyclic electrophilic derivatives of diols in coupling reactions with aryl alcohols to form aryl ethers such as epoxide,[6] cyclic sulphate,[7] cyclic sulphite[8] and cyclic carbonate.[9] For the coupling partner derived from diol **4**, we remained with the cyclic carbonate **12**[1] due to its ease of synthesis and stability. While carbonyl diimidazole (CDI) in dichloromethane was an acceptable method for its synthesis on a small scale, use of dimethylcarbonate in the presence of a catalytic amount of base[10] was preferable for scale up. Free base **12** was not a solid; however, the oxalate salt **12a** had suitable physical properties. Synthesis was carried out by heating a methanolic solution of diol **4** with dimethyl carbonate under reflux in the presence of a catalytic amount of tetra-*n*-butylammonium hydroxide. Removal of some methanol by distillation towards the end of reaction was found to be necessary to drive the reaction to completion. Tetra-*n*-butylammonium hydroxide was preferred over sodium methoxide as base since the latter tended to precipitate from the reaction mixture during concentration. The solid oxalate salt **12a** was isolated in good yield and purity after addition of just over one molar equivalent of oxalic acid.

The reaction between phenols and ethylene carbonate is well precedented.[9] A few examples of reactions in which propylene carbonate is used as substrate have also been published[11] and, as expected, the least substituted carbon is susceptible to attack during ring-opening under base-mediated conditions. A key consideration regarding use of this approach for formation of the ether bond using a reactant such as **8** was whether or not the primary sulphonamide group would compete with the hydroxyl group for addition into the electrophile **12**. Nitrogen-containing nucleophiles are known to react with carbonates and can afford either carbamates or *N*-alkylated products, depending on nature of the substrates and conditions. A few examples of sulphonamides reacting with ethylene carbonate through an sp^3-carbon affording the *N*-(2-hydroxyethyl)sulphonamides have been published.[12]

To check which reaction pathway biaryl **8** would take, its reaction with carbonate **12** was investigated. A mixture of products was obtained comprising AR-C123196 (**1**), the sulphonamide-coupled product **13** and product **14** arising from reaction through both the phenolic hydroxyl group and the sulphonamide moiety, Figure 1. It was anticipated that the *tert*-butyl sulphonamide group would have sufficient steric hindrance to prevent it acting as a nucleophile in the coupling with carbonate **12**. Once the carbon framework of AR-C123196 was

(3) For an example of enzymatic reduction of a similar substrate see: Tsujigami, T.; Sugai, T.; Ohta, H. *Tetrahedron: Asymmetry* **2001**, *12*, 2543.

(4) Reduction of hydroxyketone **9** as the hydrochloride salt was demonstrated on a small lab scale using 1 mol % (*R*)-MeOBiphepRuBr$_2$ at 50 °C in a mixture of acetone and methanol under 4 bar hydrogen pressure providing diol **4** with an optical purity of 98.5% and chemical purity of 94 area %. This work was carried out by Zach System S.A. (formerly PPG-Sipsy).

(5) Ainge, D.; Vaz, L.-M. *Org. Process Res. Dev.* **2002**, *6*, 811.

(6) For examples of reactions of aryl alcohols with epoxides see: Nelson, T. D.; Rosen, J. D.; Smitrovich, J. H.; Payack, J.; Craig, B.; Matty, L.; Huffman, M. A.; McNamara, J. *Org. Lett.* **2005**, *7*, 55. Kuwabe, S.-i.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202. Chen, J.; Shum, W. *Tetrahedron Lett.* **1995**, *36*, 2379.

(7) For examples of reactions of aryl alcohols with cyclic sulphates see: Sugimura, H.; Hosogai, N. *Chem. Lett.* **2007**, *36*, 36. Kato, N.; Tomita, D.; Maki, K.; Kanai, M.; Shibasaki, M. *J. Org. Chem.* **2004**, *69*, 6128.

(8) For examples of reactions of aryl alcohols with cyclic sulphites see: Carlson, W. W.; Cretcher, L. H. *J. Am. Chem. Soc.* **1947**, *69*, 1952. Carlsen, P. H. J.; Aase, K. *Acta Chem. Scand.* **1993**, *47*, 617. Carlsen, P. H. J.; Aase, K. *Acta Chem. Scand.* **1993**, *47*, 737.

(9) For examples of reactions of aryl alcohols with cyclic carbonates see: Ruzie, C.; Krayer, M.; Balasubramanian, T.; Lindsey, J. S. *J. Org. Chem.* **2008**, *73*, 5806. Marsault, E. et al. *J. Med. Chem.* **2006**, *49*, 7190. Pallavicini, M.; Fumagalli, L.; Gobbi, M.; Bolchi, C.; Colleoni, S.; Moroni, B.; Pedretti, A.; Rusconi, C.; Vistoli, G.; Valoti, E. *Eur. J. Med. Chem.* **2006**, *41*, 1025. Papageorgiou, G.; Corrie, J. E. T. *Tetrahedron* **2005**, *61*, 609. Atkins, R. J.; Breen, G. F.; Crawford, L. P.; Grinter, T. J.; Harris, M. A.; Hayes, J. F.; Moores, C. J.; Saunders, R. N.; Share, A. C.; Walsgrove, T. C.; Wicks, C. *Org. Process Res. Dev.* **1997**, *1*, 185. Yoshino, T.; Inaba, S.; Ishido, Y. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 553.

(10) Fleet, G. W. J.; Smith, P. W. *Tetrahedron* **1987**, *43*, 971.

(11) See for example Wurm, G.; Rehn, D. *Arch. Pharm.* **1985**, *318*, 747.

(12) See for example: Niederpruem, H.; Voss, P.; Wechsberg, M. *Liebig's Ann. Chem.* **1973**, 11. Wagler, T. R.; Burrows, C. J. *Chem. Commun.* **1987**, 277. Pulacchini, S.; Watkinson, M. *Eur. J. Org. Chem.* **2001**, 4233.

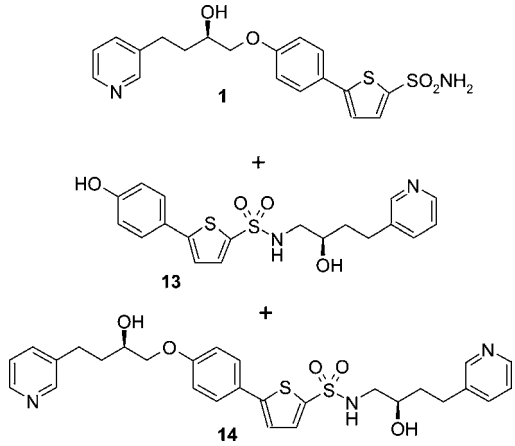
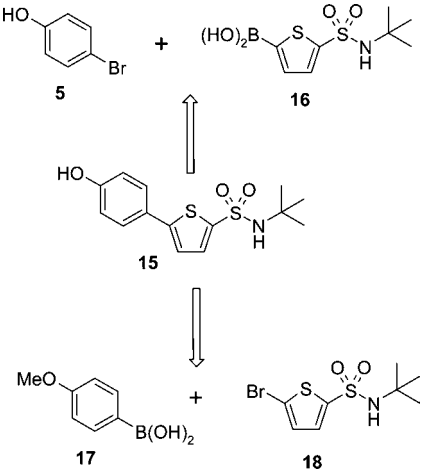


Figure 1. **Product mixture arising from reaction between carbonate 12 and biaryl 8.**

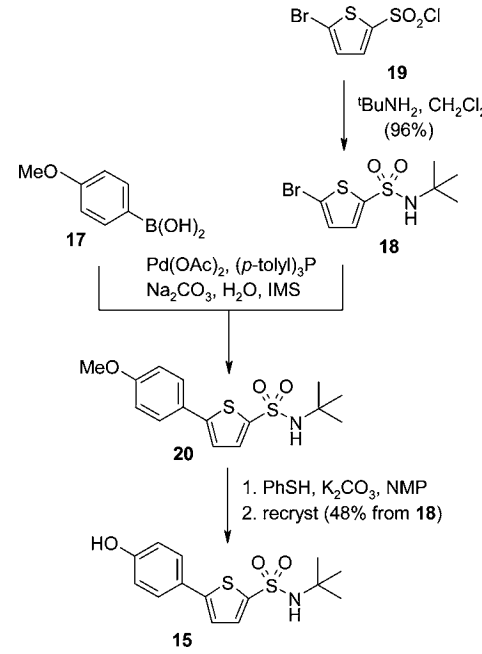
Scheme 4. **Strategies for the synthesis of biaryl 15**



in place, a simple acid-catalysed deprotection was envisaged to generate the primary sulphonamide.

Biaryl Formation. For synthesis of *tert*-butyl-protected biaryl **15**, the obvious choice was the Suzuki coupling, and two options were available which are shown in Scheme 4. Synthesis of a thiophene-2-boronic acid **16** would allow coupling with 4-bromophenol (**5**) giving the desired biaryl directly. Alternatively, a commercially available boronic acid **17** could be used with bromothiophene **18**, which would necessitate a demethylation step following Suzuki coupling. Although 4-hydroxybenzeneboronic acid is now commercially available and its use in Suzuki coupling reactions has been well established over recent years,[13] at the time this work was carried out, this material was much less widely available, and its cost would have been prohibitive. While it was possible to synthesise thiophene boronic acid **16** *via* double deprotonation of thiophene-2-*N*-*tert*-butyl sulphonamide[14] in the presence of triisopropyl borate followed by hydrolysis of the resulting boronate ester, the crude product was found to undergo facile protodeboronation in solution. Therefore, we chose to develop and scale up the coupling between 4-methoxybenzeneboronic acid (**17**) and

Scheme 5. **First route for the synthesis of biaryl 15**



bromothiophene **18** for the first multikg manufacture. The only restriction with this approach was the requirement for neutral or basic demethylation conditions in order to preserve the *tert*-butyl sulphonamide moiety.[15]

The chemistry used for the synthesis of biaryl **15** is given in Scheme 5. Sulphonamide **18** was prepared in a straightforward manner from the readily available sulphonyl chloride **19** by reaction with *tert*-butylamine in dichloromethane. After washing with water to remove *tert*-butylamine hydrochloride, the product was isolated in 95% yield following solvent swap into IMS (industrial methylated spirits)[16] and crystallisation.

The starting point for development of the Suzuki coupling was the conditions used in the initial discovery route[1] to AR-C123196, namely tetrakis(triphenylphosphine)palladium (0) as catalyst with sodium carbonate in aqueous ethanol. With the intention of preparing the catalyst from a Pd (II) source and ligand just before use, a quick screen of a few readily available ligands (triphenylphosphine, trifurylphosphine, 1,2-bis(diphenylphosphino)ethane (DPPE), 1,2-bis(diphenylphosphino)propane (DPPP) and tri(*p*-tolyl)phosphine) in conjunction with palladium acetate, identified *p*-tolylphosphine as the best of those evaluated. Alcoholic solvents such as ethanol, IMS or isopropanol were all found suitable, and IMS was selected with aqueous sodium carbonate as base. During development, it became apparent that homocoupling of the boronic acid was occurring as a significant side reaction under certain conditions, forming 4,4′-bismethoxybiphenyl, a well-known phenomenon which is catalysed either by palladium (II) or palladium (0).[17] Studies aimed at identifying the factors promoting its formation demonstrated that this was particularly prevalent when the boronic acid was stirred in the presence of catalyst at ambient

(13) See for example: Ishikawa, S.; Manabe, K. *Chem. Lett.* **2007**, *36*, 1302. Sipos, A.; Kiss, B.; Schmidt, E.; Greiner, I.; Berenyi, S. *Bioorg. Med. Chem.* **2008**, *16*, 3773. Pizzirani, D.; Roberti, M.; Recanatini, M. *Tetrahedron Lett.* **2007**, *48*, 7120.

(14) Graham, S. L.; Scholz, T. H. *J. Org. Chem.* **1991**, *56*, 4260.

(15) We subsequently demonstrated that use of BBr_3 caused loss of the *tert*-butyl group in biaryl **20**.

(16) Industrial methylated spirits, approximate composition: water 1%, methanol 5%, remainder ethanol.

(17) Moreno-Manas, M.; Perez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346.

temperature and more so when the solvent used for the reaction had been deliberately saturated with air, thus invoking a more facile Pd(II)-mediated process, in accord with recent literature.[18] Several aspects of the process were fixed in order to control the formation of 4,4′-bismethoxybiphenyl. It was found beneficial to use 5 mol equiv of phosphine over palladium and to ensure complete catalyst formation by stirring the mixture of palladium acetate and tri(*p*-tolyl)phosphine in IMS for 3−5 h at ambient temperature. Only a very slight excess of boronic acid was used, and the order of addition was established so that the aqueous base was added to the mixed substrates in IMS followed by the preformed catalyst solution last before heating the reaction mixture to reflux. Under these conditions, with 1 mol % catalyst, the biphenyl impurity was controlled to below 1 area % on a lab scale, whereas under the rigorously inerted conditions in the pilot plant, levels were much lower or not detectable. At the end of reaction, water was added to the cooled reaction mixture and the crude product isolated simply by filtration. As expected, the residual palladium level was high, between 2000 and 3000 ppm, and although it was possible to lower the Pd level at this stage, Pd removal was more effective following demethylation (see below). Since biaryl **20** was progressed downstream in a crude damp state, the overall yield to biaryl **15** following demthylation is a more reliable figure and is quoted below.

For the demethylation step, acidic reaction conditions were avoided due to the sensitivity of the *tert*-butyl protecting group. Several known basic or neutral reagent systems were investigated for this transformation, and thiophenol with a catalytic amount of potassium carbonate in *N*-methylpyrrolidone (NMP) was selected, despite the reported requirement for high reaction temperatures.[19] To avoid an unnecessary drying operation, biaryl **20** was progressed damp into the demethylation step. Thus, the mixture of crude damp biaryl **20** and potassium carbonate in NMP was dried by allowing water to distill out at atmospheric pressure whilst it was heated up to the temperature at which the demethylation would be performed. This was done prior to charging thiophenol due to its boiling point being close to the internal temperature achieved at the end of distillation. Treatment with thiophenol and maintaining the mixture at 160−170 °C accomplished demethylation within 6 h. Work up took advantage of the solubility of the potassium salt of biaryl **15** in water. Consequently, after addition of aqueous potassium hydroxide, the aqueous solution of the product was washed with dichloromethane, which removed neutral impurities (including thioanisole) and NMP. Acidification to pH 8−8.5 then caused crystallisation of the crude product, whilst leaving unreacted thiophenol in solution as the potassium salt. Following isolation, a toluene wash of the filter cake was introduced to remove a small amount of diphenyl disulphide formed. Recrystallisation from methanol−water gave biaryl **15** in 81% overall yield from bromothiophene **18** on a 300-g lab scale. On a 25-kg scale the overall yield was 48% from bromothiophene **18**, which reflects a 64% yield for crude biaryl **15** and a 77% recovery for recrystallisation. Due to termination of the project, no further investigation or development was carried out. In total, 60 kg of biaryl **15** were successfully produced using this chemistry.

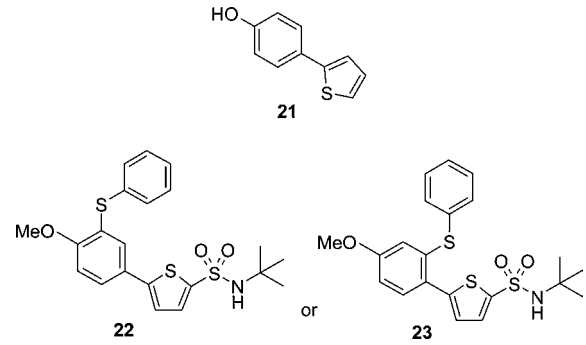


Figure 2. **Impurities in biaryl 15.**

Interestingly, it was discovered on small lab-scale runs that the use of thiophenol for demethylation fortuitously converted much of the residual palladium into an orange-coloured compound. Although the structure of this Pd-containing species remains unknown, analysis by inductively coupled plasma (ICP) revealed a palladium content of 26% *w/w*. This material was soluble in dichloromethane, partly explaining the choice of wash solvent, and insoluble in methanol. Thus, part was removed in the dichloromethane wash of the aqueous solution and any remaining was isolated during recrystallisation by filtration from a methanolic solution of biaryl **15**. The recrystallised biaryl isolated under these conditions was found to have a palladium level of up to 60 ppm on a lab scale, although usually this was below 10 ppm. On scale up, the palladium level in crude biaryl **15** was 165 ppm and was reduced to 57 ppm on recrystallisation. Progression of this material downstream without any special treatment confirmed that the residual palladium was reduced to below 10 ppm in AR-C123196.

Unfortunately, such harsh reaction conditions for the demethylation led to base-induced desulphonamidation, giving rise to approximately 9 area% of impurity **21** (Figure 2) on the pilot-scale run, which was reduced to a level of 0.2 area % after recrystallisation of the crude product. The extent of desulphonamidation was a consequence of both the time the substrate was heated in NMP in the presence of potassium carbonate during distillation and the time and temperature for the subsequent demethylation. The main impurity carried forward was a compound having either structure **22** or **23**, identified following analysis of an enriched sample by HPLC/MS and HPLC/NMR, although assignment of the position of the phenylthio- substituent unequivocally was not possible. The characteristic doublets from C(3)-H and C(4)-H in the thiophene ring were present in the ^{1}H NMR spectrum, indicating substitution on the phenyl ring. Two modes of reaction would appear feasible for conversion of methoxy biaryl **20** to these impurities, either nucleophilic addition of thiophenol into the aromatic system followed by oxidation or electrophilic substitution with diphenyldisulphide, itself either present in the reagent or formed by oxidation of thiophenol during the course of the reaction. The former should lead to a meta-substitution relative to the methoxy substituent in biaryl **20**, whereas electrophilic substitution is expected to occur ortho to the methoxy substituent. Electronic plus steric factors may explain why the resulting

(18) Adamo, C.; Amatore, C.; Ciofini, I.; Jutand, A.; Lakmini, H. *J. Am. Chem. Soc.* **2006**, *128*, 6829.
(19) Nayak, M. K.; Chakraborti, A. K. *Tetrahedron Lett.* **1997**, *38*, 8749. Chakraborti, A. K.; Sharma, L.; Nayak, M. K. *J. Org. Chem.* **2002**, *67*, 6406.

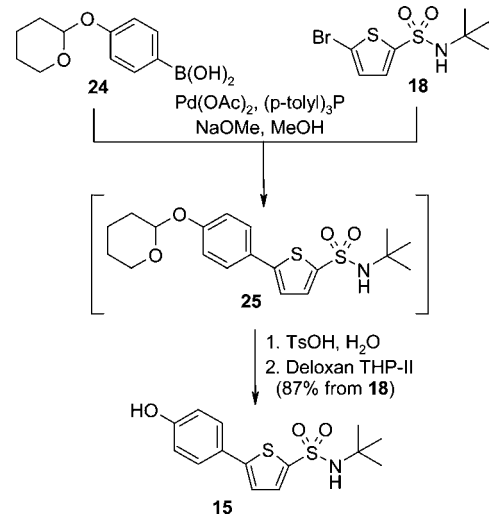
material was resilient to demethylation and therefore favor an ortho-substituted product **22** as the more likely structure. Indeed, a small amount of diphenyldisulphide was observed as an impurity during the reaction, although interestingly, biaryl **20** showed no reaction upon treatment with diphenyldisulphide in NMP at 160 °C, which contradicts a simple electrophilic substitution mechanism. The level of impurity **22** or **23** in large-scale batches was up to 4 area %; however, this was not a concern since it lacked the necessary functional group to participate in the coupling reaction with carbonate **12** and was removed unreacted in a downstream filtrate.

It was anticipated that synthesis of biaryl **15** could be performed without isolation of sulphonamide **18** by progression as a solution into the Suzuki coupling reaction. To demonstrate this, sulphonamide **18** was prepared under the established conditions and isolated as a solution in IMS after solvent swap from the reaction solvent (dichloromethane). This was progressed into the Suzuki coupling reaction under the conditions described above and the crude product **20** isolated as a damp solid. A small-scale trial demonstrated that the Suzuki coupling reaction was unaffected by the presence of up to 5% v/v dichloromethane. The damp crude biaryl **20** was then subjected to the thiophenol/potassium carbonate demethylation conditions and the product purified by recrystallisation. Biaryl **15** was prepared in an overall yield of 75% from sulphonyl chloride **19**, in high purity and with an acceptable residual Pd level.

Replacement of 4-methoxybenzeneboronic acid. As described earlier, the downside of demethylation under such harsh conditions was degradation of the substrate, particularly under prolonged heating on a larger scale. A study demonstrated that biaryl **20** when heated with potassium carbonate in NMP at 165−170 °C underwent significant degradation over 7 h, including formation of 5 area % of impurities having lost the sulphonamide group within a total of 14 area % decomposition products. Obviously, there was a desire to implement less volatile thiols[20] as deprotection reagents as well as reducing the temperature required for reaction. However, our preference was use of a boronic acid with a protected phenolic hydroxyl group that would allow deprotection under much milder conditions.[21] The THP group was deemed a preferable alternative since deprotection would be achievable under mild acid-catalysed conditions, Scheme 6. The downside of using an acid-labile protecting group was loss of the beneficial effect of thiophenol on palladium removal.

For the Suzuki coupling using boronic acid **24**,[22] we opted for homogeneous reaction conditions rather than the heterogeneous reaction conditions used previously, which facilitated palladium removal afterwards. Sodium methoxide was selected as base in methanol with a catalyst again preformed from palladium acetate and tri(*p*-tolyl)phosphine (5 mol equiv relative to Pd). Under such conditions the catalyst loading could be

Scheme 6. **Second route for the synthesis of biaryl 15**



reduced to 0.1 mol % while maintaining a 3 h reaction time. Deprotection of the THP protecting group was accomplished following the Suzuki coupling by treatment with excess *p*-toluenesulphonic acid in water. A consequence of the lower catalyst loading was a reduction in the residual palladium level in biaryl **15** from over 2000 ppm to around 240 ppm (with no deliberate attempt at reduction). Treatment with a variety of charcoals resulted in palladium levels of 75−190 ppm, whereas use of Deloxan THP-II resin, carried out on the aqueous methanolic solution following deprotection, achieved the best reduction in palladium level. Biaryl **15** of high purity was isolated by crystallisation in 87% yield (from bromothiophene **18**) following addition of water and had a palladium content of less than 2 ppm. While this approach was not scaled up beyond the laboratory, it had clear benefits over the original process and would have been used for manufacture of future large-scale batches had the project continued.

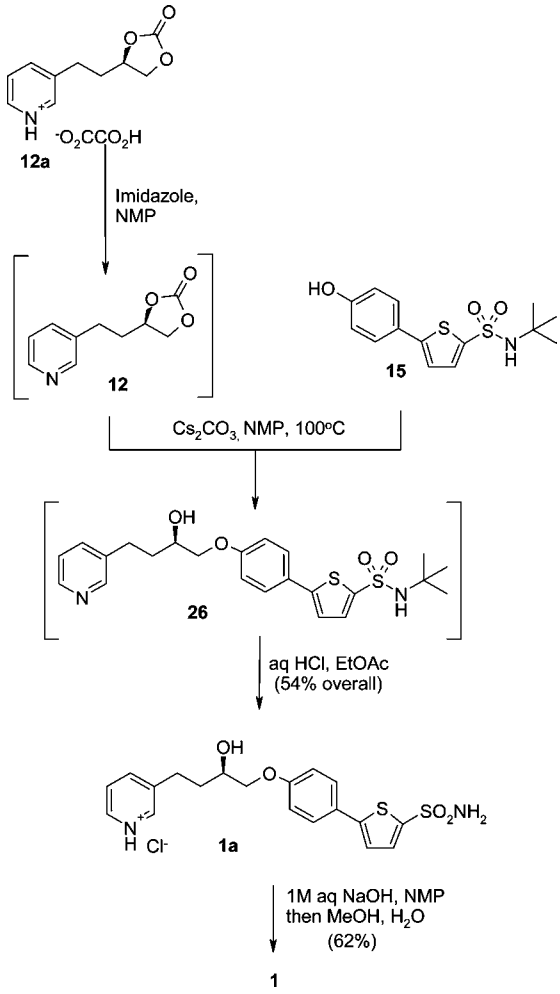
Coupling. Scheme 7 shows the key coupling reaction to form the AR-C123196 skeleton and downstream processing to remove the *tert*-butyl protecting group followed by generation of the free base. Various conditions were screened for the coupling between biaryl **15** and carbonate **12**, initially as the oxalate salt, using sufficient base (3 equiv) to ensure complete formation of the pyridine free base prior to reaction. Organic bases and inorganic bases, both with and without phase-transfer catalysts, were all investigated in solvents such as DMF, NMP, toluene and acetonitrile. With organic bases alone (such as triethylamine or 2,6-lutidine), product **26** only began to form at high temperatures (180 °C), at which point degradation of carbonate **12** became significant. Use of 2 equivalents of the organic base to form the pyridine free base and up to one equivalent of an inorganic base for reaction did give the coupled product **26** but still required high reaction temperatures for any product to form. Moving towards use of inorganic bases alone, a screen of alkali metal carbonates identified cesium carbonate in NMP as best for this transformation, and under these conditions, an acceptable conversion to **26** could be achieved at 100 °C with a reaction time of up to 24 h. Prior generation of the free base of salt **12a** was desirable to reduce the amount of cesium carbonate needed for reaction and to speed up the coupling. While it was possible to do this by washing a

(20) Interestingly, *p*-chlorothiophenol was found to accomplish demethylation in NMP at 160 °C within 1.5 h but required a stoichiometric amount of potassium carbonate. This reagent system would also achieve demethylation, albeit more slowly, at 130 °C.

(21) Whilst the chemistry in which the boronic acid was used was not expected to require protection of the phenolic hydroxyl group, the chemistry used for the manufacture of boronic acids, *via* trialkylborate quench of the aryl Grignard reagent would require hydroxyl protection.

(22) Cladingboel, D. E. *Org. Process Res. Dev.* **2000**, *4*, 153.

Scheme 7. **Ether formation and deprotection**



dichloromethane solution of the oxalate salt with aqueous sodium bicarbonate, a much more convenient salt exchange method was devised. Treatment of a suspension of oxalate salt **12a** in NMP with two equivalents of imidazole at ambient temperature resulted in formation of the insoluble di-imidazole salt of oxalic acid and left the carbonate free base as a solution in NMP after filtration. It was necessary to ensure complete removal of the salt byproduct since its presence in the subsequent coupling reaction was detrimental due to consumption of the added base. By using the free base, the amount of cesium carbonate needed was reduced to one equivalent, and the conversion to ether **26** under these conditions, although not fully optimised, was satisfactory at around 70−80 area% after heating for 8−24 h. Competing hydrolysis of the carbonate to regenerate diol **4** was observed to a variable extent of between 1 and 14 area % at the end of reaction, despite running the reactions under an inert atmosphere. The higher levels were attributed to the presence of water, possibly arising from reaction between cesium carbonate and residual imidazole oxalate. Attack at the more substituted carbon of the carbonate ring was found to compete and generated between 1 and 2 area % of the isomeric product **28** after deprotection, Figure 3 (assumed stereochemistry shown). In theory, only a catalytic amount of base is needed for the coupling between carbonate free base **12** and biaryl **15**; however, the conversion was lower when substoichiometric amounts of the inorganic base were employed.

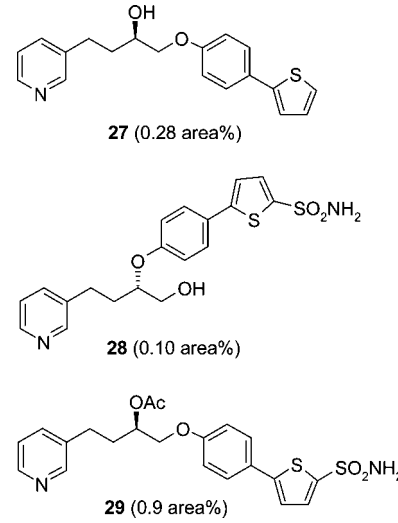


Figure 3. **Some impurities formed during the synthesis of AR-C123196.**

Use of 0.2 equiv of cesium carbonate gave only 58 area % product after heating at 100 °C for 20 h, compared with 79% for a comparable reaction using one equivalent of the base. Use of tetra-*n*-butylammonium bromide as a phase transfer catalyst with a stoichiometric amount of cesium carbonate showed only a marginal improvement and so was not adopted. On a 14 kg (**12a**) scale, the conversion was 70 area % with a reaction time of 7 h.

Attempts to isolate the coupled product in a solid form as either the free base **26** or a salt were unsuccessful. Instead, after quenching the reaction with water, the product was extracted into an organic solvent for progression directly into the acid-catalysed deprotection reaction. Both methyl isobutyl ketone (MIBK) and ethyl acetate were identified as suitable extraction solvents, and despite much effort into using MIBK as solvent for the next stage, a difficult separation and an additional unit operation in the workup counted against its implementation. Therefore, ethyl acetate was selected for development and scale up, despite the anticipated hydrolysis under the highly acidic reaction conditions in the next step. In fact, its *in situ* hydrolysis resulted in a homogeneous reaction mixture, which facilitated deprotection of the *tert*-butyl group. The amount of NMP carried forward in the ethyl acetate extracts was generally up to 8% w/w, and if higher, the ethyl acetate solution was given an additional water wash at the start of the deprotection step to reduce the amount present.

Acid-catalysed deprotection of the *tert*-butylsulphonamide was accomplished simply by heating in the presence of aqueous hydrochloric acid. Development studies undertaken on MIBK solutions of **26** demonstrated that an elevated temperature was required and also that the rate of reaction was dependent on the concentration of the acid used. Using 2 M aqueous hydrochloric acid gave an extremely slow deprotection at 60 °C, whereas 9 M acid gave complete reaction in 4 h. Once ethyl acetate was selected as the extraction solvent for the previous stage, the chosen conditions were transferred without any further development. Thus, the ethyl acetate solution of ether **26** was treated with concentrated aqueous hydrochloric acid with heating. The hydrochloride salt of AR-C123196 (**1a**) was then isolated as a solid following addition of methanol to

the cooled reaction mixture in 57% yield on a 50 g scale and in 54% yield on a multikg scale (calculated over two stages). A chiral purity check demonstrated no loss in optical purity.

To generate the free base of AR-C123196, a process was desirable which would allow a controlled crystallisation of the product. Due to the very limited solubility of AR-C123196 in most organic solvents, NMP was chosen as it was expected that AR-C123196 free base could be crystallised from a solution in this solvent in a controlled manner. A suspension of the hydrochloride salt in NMP was treated with one equivalent of aqueous sodium hydroxide with heating. Addition of both methanol and water as cosolvents was found necessary to provide a filterable solid in an acceptable yield, and the amount of water added was a balance between maximising yield and limiting the amount of residual NMP in the isolated product. Thus, it was concluded that addition of methanol (3 volumes) then water (5 volumes) gave the best compromise between yield (93%) and residual NMP content (0.22% w/w) on a 38 g scale. On scale up to pilot plant, the yield was lower at 62% and is believed to have resulted from losses during filtration due to the crystal shape (plates of thickness around 1 μm). It was demonstrated that excess sodium hydroxide would not form a salt of the sulphonamide under the chosen conditions.

Impurities found in AR-C123196 hydrochloride salt and free base are given in Figure 3. The largest impurity in the hydrochloride salt was unreacted biaryl **8**, left over from the coupling reaction, which subsequently underwent deprotection of the *tert*-butyl group. Due to solubility in aqueous NMP, the amount of this was reduced significantly on isolation of AR-C123196 free base to 1.4 area %. The desulphonamidation product **27** was also present together with a small amount of the regioisomer **28** (presumed stereochemistry shown). One unforeseen consequence of using ethyl acetate as cosolvent for the deprotection step was a transesterification reaction forming the acetate impurity **29**. This was present at a level of 0.9 area % in the isolated AR-C123196 free base in the 3.4 kg batch.[23] On scale up, the level of residual NMP in the batch was higher than expected at 1.3% w/w, and this may reflect a much more rapid crystallisation than anticipated. Unfortunately, this appeared to be occluded since prolonged drying did not reduce the level further.

Conclusions

An efficient, convergent route for the synthesis of AR-C123196 has been demonstrated which is suitable for manufacture of multikg batches. Although yields for some of the later stages were lower than expected on scale up, in principle, with further development, this strategy could provide larger quantities of AR-C123196. Efficient routes to the biaryl precursor were developed with good control over residual palladium, and the use of a more labile protecting group on the phenolic hydroxyl group greatly improved the synthesis of the biaryl and would have been the method of choice for future manufacture.

(23) It was not determined whether a prolonged stir with the aqueous sodium hydroxide in NMP treatment would have had any effect on the level of this impurity.

Experimental Details

General. All reactions were performed under a nitrogen atmosphere. ^{1}H NMR spectra were recorded using a Varian Unity-Inova 300 spectrometer operating at 300 MHz at a probe temperature of 25 °C in D_6-DMSO solution. Chemical shifts are reported in ppm downfield relative to TMS as an internal standard. Assays by HPLC were performed against purified and fully characterised reference materials. Palladium levels were determined by inductively coupled plasma (ICP) analysis on samples made up into DMSO solution. All commercially available starting materials, reagents and solvents were used as received.

(2*R*)-4-(Pyridin-3-ylethyl)-1,3-dioxolan-2-one, Oxalic Acid Salt (12a). (2*R*)-4-(3-Pyridyl)-1,2-butanediol (300 g, 1.79 mol) was dissolved in methanol (900 mL) at rt with stirring, giving a deep amber solution. Dimethylcarbonate (3000 mL) was added with stirring followed by tetra-*n*-butylammonium hydroxide in methanol (1 M, 180 mL, 0.18 mol). The mixture was then heated under reflux (68 °C) and maintained at this temperature for 1.25 h, before being partially concentrated by distillation at atmospheric pressure through a 6-in. Vigreux column. A total of 2.7 L of methanol and dimethylcarbonate were removed over 1.25 h with a final batch temperature of 92 °C. Analysis of the reaction mixture at this time by HPLC showed 0.6 area % of diol **4** remaining. The mixture was allowed to cool to 60 °C, and then a solution of oxalic acid (178 g, 1.98 mol) in methanol (600 mL) was added over a period of 20 min, keeping the temperature between 57 and 62 °C. After stirring the mixture for 10 min, ethyl acetate (1000 mL) was added over 10 min with rapid stirring. The product then began to crystallise from solution, and so additional ethyl acetate (2600 mL) was added to facilitate stirring during crystallisation. The mixture was then allowed to cool to rt and held overnight. The mixture was further cooled to 0 °C and stirred at this temperature for 1.5 h. The product was collected by filtration, washed with ethyl acetate (2 × 900 mL) followed by isohexane (900 mL), and then dried in a vacuum oven at 40 °C to provide **12a** as an off-white solid, 431.4 g (85%). Purity by HPLC (YMC-Pack ODS-AQ C18, 3.0 mm × 250 mm at 40 °C, eluting with 10 mM aqueous NH_4OAc at pH4.5/MeCN at 1.5 mL/min, 254 nm detection): 99.6 area %. $[\alpha]^{20}_D$ +40.2° (c = 1, water). Mp 123.9 °C. ^{1}H NMR δ 8.50 (d, J = 1.7 Hz, 1H), 8.44 (dd, J = 4.8, 1.7 Hz, 1H), 7.72 (dt, J = 8.1, 1.9 Hz, 1H), 7.36 (dd, J = 7.8, 4.8 Hz, 1H), 4.80 (m, 1H), 4.58 (t, J = 8.1 Hz, 1H), 4.20 (dd, J = 8.3, 7.1 Hz, 1H), 2.81−2.61 (m, 2H), 2.09−1.98 (m, 2H). 2.04 (m, 2H), Anal. Calcd for $C_{12}H_{13}NO_7$: C, 50.89; H, 4.63; N, 4.75%. Found: C, 50.83; H, 4.75; N, 5.19.

5-Bromothiophene-2-sulphonic Acid, *tert*-Butylamide (18). 5-Bromothiophene-2-sulphonyl chloride (500 g, 1.91 mol) was dissolved in dichloromethane (2000 mL) at rt with stirring under nitrogen and then cooled to 4 °C. *tert*-Butylamine (442 mL, 4.21 mol) diluted with dichloromethane (500 mL) was added over a period of 20 min (exothermic), and stirring continued. During the addition the internal temperature rose steadily and reached a maximum of 18 °C. The mixture was stirred for 25 min (during which time the internal temperature had dropped

to 11 °C) and then the cooling bath was removed. After allowing to warm to rt and stirring for 24 h the mixture was washed with water (2 × 1200 mL). The dichloromethane solution was distilled at atmospheric pressure until 2060 mL of dichloromethane had been removed. IMS[16] (74 O.P., 2000 mL) was then added, and distillation continued until an additional 1500 mL of distillate had been collected (distillation head temperature reached 78 °C). The resulting mixture was allowed to cool to 60 °C, and water (290 mL) was added over 10 min with stirring to give a turbid solution. The mixture was seeded, and stirring continued for 30 min whilst cooling further during which crystallisation began at 29 °C. Further water (110 mL) was added to the mixture over a 15 min period, and stirring continued for 10 min. A final portion of water (100 mL) was added over 10 min, and stirring was continued for 16 h. The stirred suspension was cooled to between 5 and 10 °C, stirred for 2 h, and then the solid product was collected by filtration and washed with a mixture of water (300 mL) and IMS (100 mL) then dried in a vacuum oven at 45−50 °C for 24 h to give **18** as a white solid, 545 g (96%). Mp 62 °C. ^{1}H NMR δ 7.87 (s, 1H), 7.40 (d, J = 4.0 Hz, 1H), 7.29 (d, J = 4.0 Hz, 1H), 1.17 (s, 9H).

5-(4-Methoxyphenyl)thiophene-2-sulphonic Acid, *tert*-Butylamide (20). A mixture of tri(*p*-tolyl)phosphine (0.716 kg, 2.35 mol), palladium acetate (0.105 kg, 0.47 mol) and IMS[16] (74 O.P., 38.75 kg) was stirred at rt for 4 h to give a yellow solution with some suspended solid. Meanwhile, sulphonamide **18** (14.0 kg, 46.9 mol), 4-methoxybenzeneboronic acid (7.50 kg, 49.4 mol), aqueous sodium carbonate (2 M, 58.07 kg) and IMS (74 O.P., 63.75 kg) were mixed by stirring at rt (slightly exothermic). The prepared catalyst solution was added to mixed substrates and base in IMS, and the reaction mixture was then heated under reflux (77−83 °C) for 1.25 h, when 1.25 area % sulphonamide **18** remained. After cooling to 70 °C, water (135 kg) was added, and the thick heterogeneous reaction mixture was cooled slowly to 20 °C with stirring. After holding overnight at this temperature, the crude solid product was isolated on a centrifuge in 3−4 kg portions, washing each with 50% w/w aqueous IMS (3.0 kg) followed by water (3.0 kg). The portions were then combined to give the title compound as a damp orange solid, weight 18.8 kg. Assay by HPLC 83.2% w/w, therefore contained weight 15.6 kg (>100%). HPLC purity (Waters Symmetry C8, 4.6 mm × 150 mm at 80 °C, eluting with 10 mM aqueous NH_4OAc/MeCN at 1.5 mL/min, 254 nm detection): 98.0 area % (largest single impurity 1.43 area %).

Spectral data for a purified sample (recrystallised from aqueous methanol): Mp 120 °C. LC−MS (AP^-): *m*/*z* 325 (M^-). ^{1}H NMR δ 7.76 (1H, s), 7.65 (2H, m), 7.52 (1H, d), 7.40, (1H, d), 7.02 (2H, m), 3.81 (3H, s), 1.18 (9H, s). Anal. Calcd for $C_{15}H_{19}NO_3S_2$: C, 55.36; H, 5.88; N, 4.30%; S, 19.70%. Found: C, 55.43; H, 5.88; N, 4.42; S, 19.35%.

5-(4-Hydroxyphenyl)thiophene-2-sulphonic Acid, *tert*-Butylamide (15). Method 1. A mixture of damp methoxy biaryl **20** (30.3 kg, weight corrected for assay 25.1 kg, 77.1 mol) and potassium carbonate (0.80 kg, 5.79 mol) in *N*-methylpyrrolidone (108 kg) was heated with stirring until the mixture started boiling (130 °C). Water was allowed to distill out, and heating continued until the reaction mixture reached a temperature of 165−170 °C. A solution of thiophenol (12.75 kg, 116 mol) in *N*-methylpyrrolidone (23.0 kg) was then added and the mixture held at 162−168 °C for 4 h when 0.48 area % starting material remained. After being cooled to 15 °C and held overnight, to the reaction mixture was added a solution of potassium hydroxide (10.2 kg, 181.8 mol) in water (117.9 kg) (exothermic). The resulting solution was washed three times with dichloromethane (233.9 kg, 137.9 kg, 134.7 kg), and then the aqueous layer was acidified to pH 8−8.5 with dilute hydrochloric acid (prepared from 123 kg of water and 20.3 kg of concentrated hydrochloric acid) with cooling to maintain the temperature at around 15 °C. After stirring at 20 °C for 2 h, the solid was collected on a centrifuge and washed with water (25 kg) to leave the crude product as a damp grey solid, weight 24.2 kg. Loss on drying of a sample 36.9%, therefore 15.3 kg dry weight equivalent. Purity by HPLC (Waters Symmetry C8, 4.6 mm × 150 mm at 40 °C, eluting with 10 mM aqueous NH_4OAc/MeCN at 1.5 mL/min, 254 nm detection): 84.5 area % (8.90 area % **21**). Pd level 165 ppm.

Damp crude biaryl **15** prepared above (24.0 kg actual weight, 15.1 kg dry weight equivalent) was dissolved in methanol (113.7 kg), by warming to 60 °C and then was passed through a cartridge filter to remove insoluble material. The filter was washed with further hot (60 °C) methanol (39.7 kg), and the filtrates were combined and then cooled to 50 °C. Water (139.7 kg) was added, the mixture was cooled to 20 °C and held at this temperature with stirring overnight. The resulting solid was collected on a centrifuge, washed with toluene (30.0 kg) followed by water (24.0 kg), and then dried at 45 °C/−950 mbar to afford biaryl **15** as pale-yellow crystals 11.60 kg (48% yield from sulphonamide **18**). HPLC purity (conditions as above): 95.6% area % (3.22 area % impurity **22** or **23**). Palladium content: 57 ppm. Mp 186 °C. LC−MS (AP^-): *m*/*z* 310 (M − 1). ^{1}H NMR δ 9.86 (s, 1H), 7.71 (s, 1H), 7.56−7.47 (m, 3H), 7.31, (d, J = 4.0 Hz, 1H), 6.84 (dd, J = 11.6, 3.0 Hz, 2H), 1.18 (s, 9H).

5-(4-Hydroxyphenyl)-thiophene-2-sulphonic Acid, *tert*-Butylamide (15). Method 2 (Telescoped Process). Sulphonamide **18** was prepared from 175 g (0.67 mol) of 5-bromothiophene-2-sulphonyl chloride in a similar manner to the process given above, with appropriate scaling of quantities. For the work up, after the reaction mixture had been washed twice with water, it was concentrated by distillation at atmospheric pressure until 700 mL of solvent had been collected. After cooling to 30 °C, IMS (680 mL) was added and a further 600 mL of solvent removed by distillation at atmospheric pressure leaving a solution of **18** in IMS (volume ∼300 mL, assumed quantitative yield, 199.5 g). This was converted to methoxybiaryl **20** using the procedure described above, with appropriate scaling of quantities, to afford the damp crude product, weight 386.5 g (assumed quantitative yield for the purposes of calculating the reagent charges for the next step). Purity by HPLC 97.3 area %. This was converted to hydroxy biaryl **15** using the procedure given above, with appropriate scaling of quantities, except that the reaction was carried out at 168 °C for 7 h. After work up, the crude solid product was dried on the filter for 30 min to afford crude damp biaryl **15**, weight 258.3 g. This material was recrystallised as described above,

with appropriate scaling of quantities, and then dried under vacuum at 50 °C to leave biaryl **15** as a yellow solid, 156.3 g (75% from 5-bromothiophene-2-sulphonyl chloride **19**). HPLC purity (conditions as above): 97.4 area %. Palladium level 40 ppm. Anal. Calcd for $C_{14}H_{17}NO_3S_2$: C, 53.99; H, 5.50; N, 4.50%; S, 20.59%. Found: C, 53.97; H, 5.50; N, 4.66; S, 20.59.

5-(4-Hydroxyphenyl)-thiophene-2-sulphonic Acid, *tert*-Butylamide (15). Method 3. A mixture of palladium acetate (0.0753 g, 0.34 mmol) and tri-(*p*-tolyl)phosphine (0.511 g, 1.68 mmol) in methanol (170 mL) was stirred at rt for 3.25 h to afford a pale-yellow solution. This solution was added to a mixture of boronic acid **24** (82 g, 369 mmol), sulphonamide **18** (100 g, 335 mmol) and sodium methoxide (25% w/w, 159 mL, 695 mmol) in methanol (1130 mL) and the mixture was heated under reflux for 3 h. Product started crystallising out of solution at 2.25 h. The reaction mixture was then cooled to 50 °C, and a solution of *p*-toluenesulphonic acid monohydrate (128 g, 0.67 mol) in water (110 mL) was added. The reaction mixture was then allowed to cool to rt and was stirred at this temperature overnight, leaving a solution with a volume of 1720 mL. A portion of this was taken (172 mL), and Deloxan THP-II resin (6.6 g, 72.5% w/w) was added and the mixture stirred at rt overnight. The resin was removed by filtration, washed with methanol (2 × 10 mL), and then water (150 mL) was added to the combined filtrates, causing crystallisation of the product. After stirring for 30 min, the solid was collected by filtration and dried under vacuum to leave biaryl **15** as a white solid, 9.06 g (87%). HPLC purity (conditions as above): 100 area %. Palladium level <2 ppm.

AR-C123196 Hydrochloride Salt (1a). A solution of imidazole (6.48 kg, 95.2 mol) in NMP (27.9 kg) was added to a suspension of carbonate oxalate salt **12a** (13.50 kg, 47.7 mol) in NMP (62.5 kg) at 13 °C, and the mixture was stirred for 2 h at 22−25 °C. The solid was collected by filtration and washed with NMP (18 kg), and the filtrates were combined to leave a solution of carbonate **12** (free base) in NMP. To this was added a solution of biaryl **15** (14.9 kg, 47.8 mol) in NMP (44.2 kg) followed by cesium carbonate (15.5 kg, 47.6 mol), and the mixture was heated to 100 °C. After 12 h at this temperature, the reaction mixture was cooled to 15 °C, and then ethyl acetate (126 kg) and water (324 kg) were added and the mixture stirred for 75 min. After settling, the layers were separated, and the aqueous layer was extracted with further ethyl acetate (106 kg). The organic extracts were combined to provide **26** as a solution in ethyl acetate, weight 204.1 kg.

This solution was washed with water (300 kg), and the layers were allowed to settle at 30 °C. The organic layer was separated off, concentrated hydrochloric acid (94.6 kg) was added to it and the mixture heated to 75 °C with stirring. After being maintained at this temperature for 4 h the reaction mixture was cooled to 55 °C over 1.5 h and maintained at this temperature for a further 3 h. The reaction mixture was then further cooled to 19 °C and held at this temperature for 13 h. Methanol (31 kg) was added and the mixture cooled to 13 °C. The resulting solid was collected in portions on a centrifuge, washed with methanol (20 kg) then dried under vacuum at 40 °C to leave AR-C123196 HCl salt (**1a**) as a white solid, weight 11.23 kg (53.5%). ^{1}H NMR δ 8.88 (1H, s), 8.79 (1H, d), 8.55 (1H, d), 8.03 (1H, dd), 7.69 (1H, br s), 7.62 (2H, d), 7.52 (1H, d), 7.39 (1H, d), 7.02 (2H, d), 3.95 (2H, d), 3.84−3.77 (1H, m), 3.08−2.87 (2H, m), 2.00−1.76 (2H, m). Enantiomeric purity by HPLC (Chiralcel OD, 4.6 mm × 250 mm at 25 °C, eluting with ethanol at 1.0 mL/min, 310 nm detection) >99.9 area %.

AR-C123196 (1). AR-C123196 HCl salt (**1a**) (6.0 kg, 13.6 mol) was charged to a reaction vessel followed by *N*-methylpyrrolidone (46.4 kg) and stirring started. Aqueous sodium hydroxide (1 M, 14.3 kg, 13.8 mol) was then added at a temperature of 19 °C, and the mixture was heated to 75 °C. After being maintained at 70−75 °C for 1 h, the resulting solution was filtered into a second vessel and the filter rinsed with hot (57 °C) *N*-methylpyrrolidone (4.6 kg). After holding at 73 °C for 15 min, the solution was cooled to 49 °C. Once at this temperature, methanol (14.5 kg) was added and cooling continued to 25 °C over a period of 3 h. Water (29.8 kg) was added to the cooled mixture (mildly exothermic), and stirring continued for 1 h during which time the temperature fell from 30 to 22 °C. The solid product was collected by filtration, washed with water (2 × 18 kg) followed by methanol (14.4 kg), and then dried under vacuum at 50 °C. AR-C123196 (**1**) was obtained as an off-white solid, 3.4 kg (62%). Purity by HPLC (Waters Symmetry C8, 4.6 mm × 150 mm at 40 °C, eluting with 10 mM aqueous NH_4OAc at pH 4.5/ MeCN at 1.5 mL/min, 310 nm detection): 97.2 area %. Palladium level 5 ppm. ^{1}H NMR δ 8.47 (1H, s), 8.40 (1H, m), 7.68−7.61 (5H, m), 7.50 (1H, d), 7.38 (1H, d), 7.33−7.29 (1H, m), 7.02 (2H, d), 5.08 (1H, d), 3.94 (2H, d), 3.86−3.73 (1H, m), 2.88−2.62 (2H, m), 1.93−1.65 (2H, m).

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(24) Oxford Asymmetry International became Evotec OAI and then Aptuit in November 2007.