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Article

Development and Scale-Up of an Asymmetric Synthesis of AZD8186 Using the Fukuyama Modification of the Mitsunobu Reaction

Peter R. Moore,* James C. Muir, Jerome Dubiez, Kevin W. Leslie, Paula Tomlin, Marc McCormick, Sophie L. Janbon, Philip Cornwall, Per Ryberg, and Robert Berg

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ABSTRACT: A large-scale asymmetric synthesis has been developed for the kilo-lab manufacture of AZD8186. The process initially employs a regioselective Heck coupling in water to provide the starting aromatic ketone. This ketone is reduced asymmetrically under ruthenium-catalyzed transfer hydrogenation conditions to provide a chiral alcohol in high enantiomeric purity. The key synthetic step then requires the reaction of this chiral alcohol with the activated derivative of 3,5-difluoroaniline under the Mitsunobu reaction conditions. The common issues associated with the use of the Mitsunobu reaction, such as removal of triphenylphosphine oxide and reduced diisopropyl azodicarboxylate (DIAD) by-products, have been eliminated through crystallization of the relevant intermediates.

KEYWORDS: *asymmetric synthesis, Mitsunobu reaction, Fukuyama modification, transfer hydrogenation, Heck reaction, pi3kβ inhibitor*

INTRODUCTION

AZD8186 (Figure 1) is a phosphoinositide-3-kinase β (pi3kβ) inhibitor currently undergoing clinical development at AstraZeneca for the treatment of breast and prostate cancer.[1,2] Due to an increasing demand for drug substance (to support both initial Full Good Laboratory Practice (FGLP) toxicology and Phase 1 clinical trial studies), a robust multi-kilogram route to compound **1** was sought.

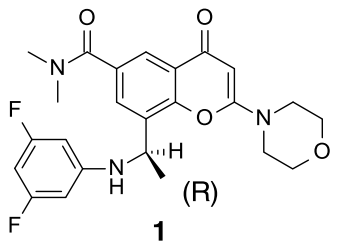

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Figure 1. Structure of AZD8186.

RESULTS AND DISCUSSION

The original discovery chemistry route to AZD8186 is shown in Scheme 1.[2] Although this route proved sufficient for delivery of multigram quantities of drug substance, a number of issues with this approach required further development to facilitate future scale-up activities. First, the route is not stereoselective, and the target amine **6** is delivered as a racemic mixture. This mixture may be resolved by chiral chromatography, with an associated substantial reduction in overall yield. Second, the incorporation of the ketone moiety into compound **3** required the use of a Stille cross-coupling and the use of a vinyl stannane.[3] Organotin reagents are known to possess toxicity issues and would not be amenable to future scale-up.[4] Other issues included the use of PBr_3 and the application of environmentally unfriendly chlorinated solvents. Considering all of the above issues, an alternative approach was sought for realizing a medium-scale synthesis (>10 kg) of AZD8186.

Initially, a number of routes were investigated, including further development of the existing medicinal chemistry route and the use of the Leuckart−Wallach[5] reaction for incorporation of an amine from ketone **3**. However, these investigations met with little success due to the poor reactivity of the aniline with ketone **3** under the reductive amination conditions. Scheme 2 outlines an alternative retrosynthetic approach to provide AZD8186 as a single enantiomer. It was envisaged that the Mitsunobu reaction[6] of the chiral (*S*)-alcohol **7** with an appropriately activated difluorinated aniline (Fukuyama modification)[7] would establish the required (*R*)-stereochemistry in the product by simple inversion of stereochemistry. The required (*S*)-alcohol **7** could be then derived by asymmetric reduction of the known ketone **3**.[8] Due to the good literature precedent for asymmetric reduction of acetophenone derivatives such as **3** and its ready availability, this strategy was investigated further.

As outlined above, the first issue to resolve was the large-scale manufacture of ketone **3** without recourse to the use of toxic stannanes. The Heck reaction[9] was considered as an alternative approach to the ketone through use of a vinyl ether as a cross-coupling partner. However, initial investigations under Heck coupling conditions using bromide **2** highlighted

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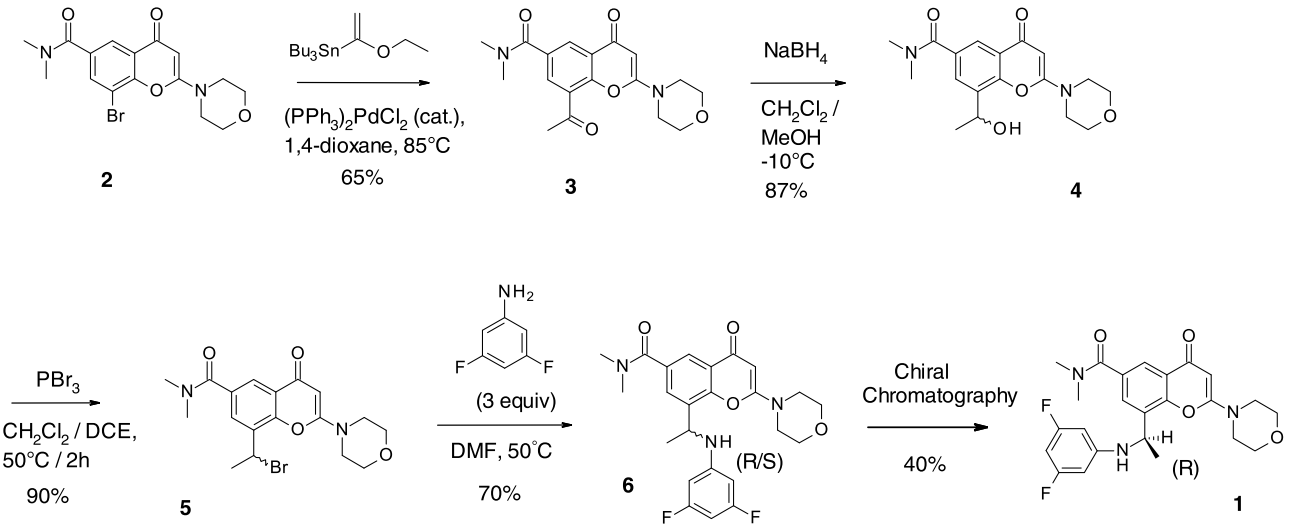
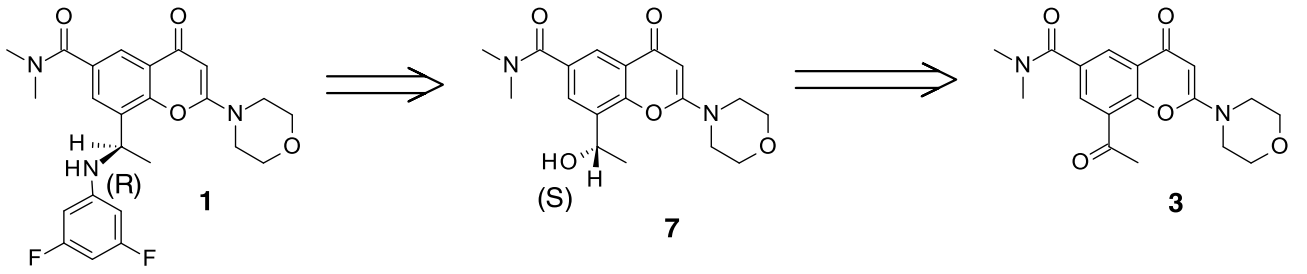
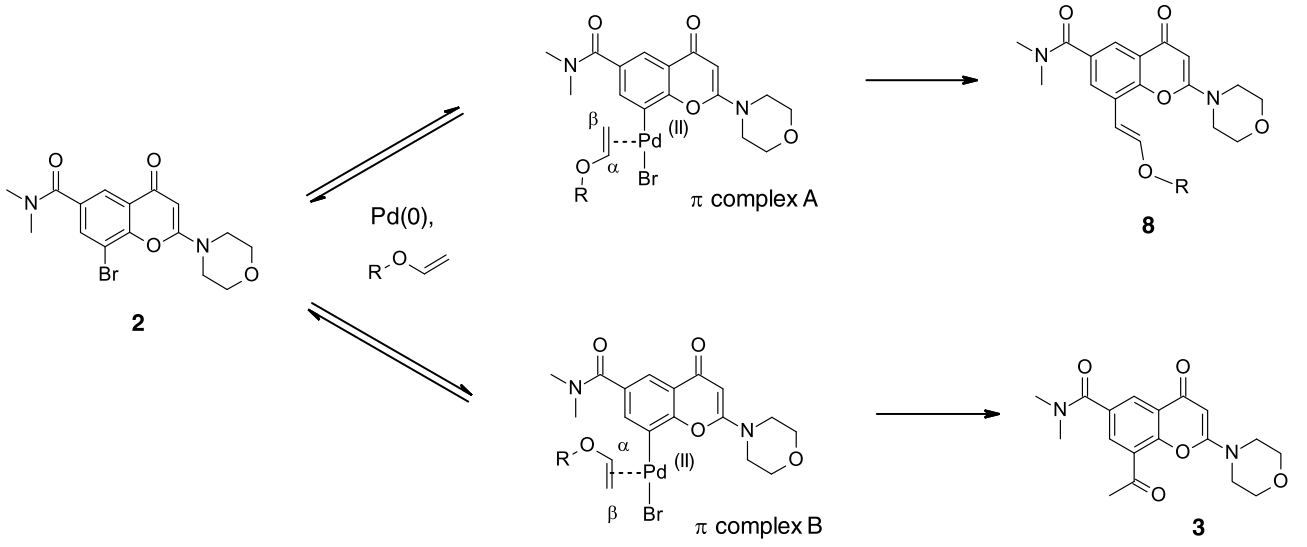
Scheme 1. Original Discovery Chemistry Route to AZD8186



Scheme 2. Alternative Retrosynthetic Approach to AZD8186 from Ketone 3 Utilizing the Mitsunobu Reaction



Scheme 3. Initial Outcome of the Heck Reaction of Bromide 2 with Substituted Vinyl Ethers



an issue of regioselectivity (Scheme 3). Reaction with various vinyl ethers provided a mixture of the required ketone **3** and the undesired enol ether **8**. Formation of these mixtures was ascribed to poor regiocontrol in formation of the intermediate π complexes A and B (Scheme 3).[10] With mixtures of the π complexes A and B formed during the reaction, subsequent collapse of these complexes provided both the required α-arylated product (ketone **3**) and the undesired β-arylated impurity (enol ether **8**).

In lieu of these initial results, a suitable procedure for formation of ketone **3** exclusively was sought. Previous literature precedent suggested that use of reaction conditions that favor a more cationic reaction pathway could deliver the required α-product (Scheme 4).

A targeted screening of reaction conditions directed by the previous work of Larhed et al. was undertaken.[11] This screening work led to the development of a process in water that delivered the required ketone exclusively (Scheme 5).

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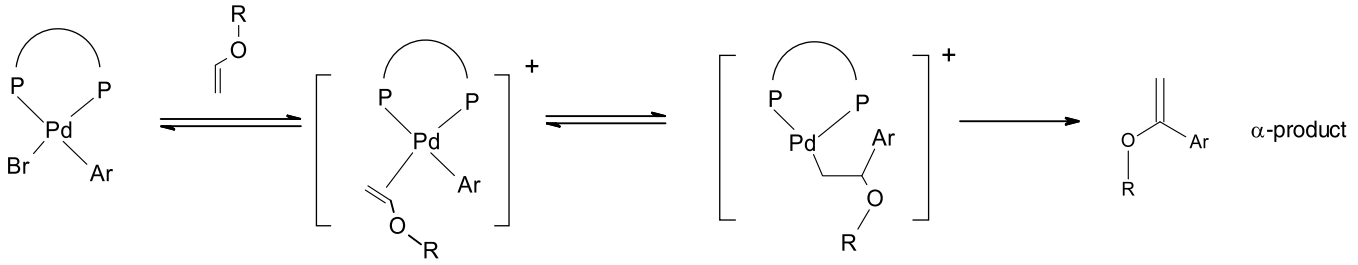
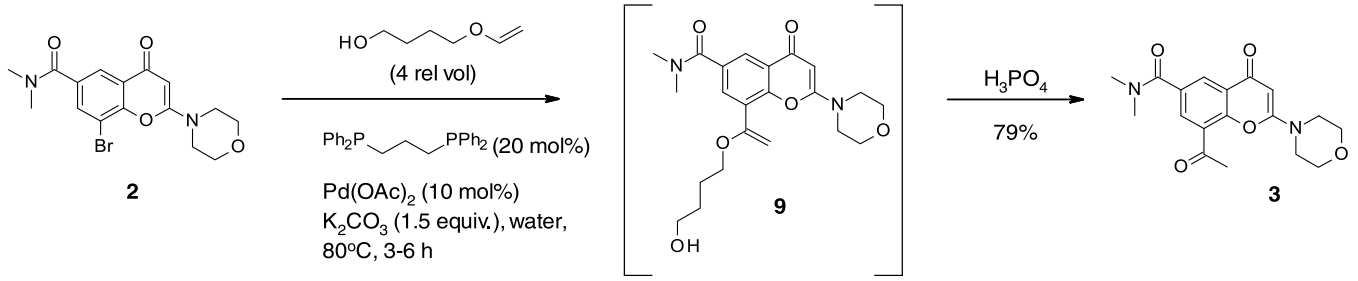
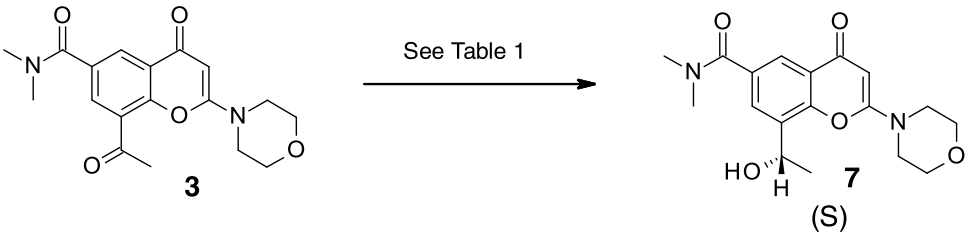
Scheme 4. Formation of the Desired α-Product through Cationic Heck Reaction[11]



Scheme 5. Successful Formation of Ketone 3 via a Modified Heck Reaction



Scheme 6. Asymmetric Reduction of Ketone 3



The initial reaction of bromide **2** with 4-(vinyloxy)butan-1-ol in the presence of palladium(II) acetate and 1,3-bis(diphenylphosphino)propane as a ligand provided the enol ether **9** in excellent yield and selectivity. This intermediate ether **9** was not isolated but converted directly to the required ketone **3** by the action of phosphoric acid. Metal scavenging was not required as part of the workup, and a controlled crystallization allowed for isolation of the product in good yield and excellent quality. The scalability of the above process was demonstrated on a 4 kg batch scale to deliver >15 kg overall of the required ketone **3** in 79% yield and 97% w/w assay (residual Pd = 50 ppm).

With access to multi-kilogram amounts of ketone **3** now established, a reduction method was sought to provide the required chiral (*S*)-alcohol **7** on a large scale (Scheme 6).

Initial screening work demonstrated that the desired transformation was readily achieved using ruthenium catalysis. In all cases, reaction under transfer hydrogenation conditions proceeded with complete conversion and excellent stereocontrol (Table 1).[12]

In agreement with the literature,[13] further work demonstrated that an (*S*,*S*) ligand on ruthenium provided the desired (*S*)-alcohol **7**.[14] Before further development of the reaction was pursued, an initial assessment of the commercial availability of the (*S*,*S*)-type ruthenium catalysts was made. This assessment advocated the use of the Ru(Cymene)(*S*,*S* MsDPEN)Cl system based on both cost and lead time of the catalyst.

Table 1. Initial Screening Results for Asymmetric Transfer Hydrogenation of Ketone 3[a]

catalyst	reaction time (h)	conversion (%)	enantiomeric excess[b]
Ru(Cymene)(*S*,*S* MsDPEN)Cl	4	100	>98% ee
Ru(Mesitylene)(*S*,*S* MsDPEN)Cl	18	100	>98% ee
Ru(*R*,*R*-teth-TsDPEN)Cl	1	100	>98% ee
Ru(Cymene)(*R*,*R* CsDPEN)Cl	1	100	>98% ee

[a]Note that all reactions were performed in dimethyl sulfoxide (DMSO) or dimethylformamide (DMF) using $Et_3N{\cdot}HCO_2H$ as the hydrogen source. [b]As determined by chiral high-performance liquid chromatography (HPLC) analysis.

Initial trial reactions of the asymmetric reduction using this catalyst in a number of suitable solvents such as ethyl acetate (EtOAc), tetrahydrofuran (THF), and 2-methyltetrahydrofuran (2-MeTHF) at 60 °C highlighted an issue of solubility. In these solvents, the reaction mixture did not form a solution but remained as a slurry throughout, with both starting ketone and product alcohol out of the solution. Also, despite the addition of a large excess of reducing agent, the reaction did not proceed to completion (3−5% unreacted ketone remaining), suggesting that some occlusion of the starting material may have occurred by the product. However, in each case, the enantiomeric excess (ee) of the product alcohol was found to be excellent (>99% ee).

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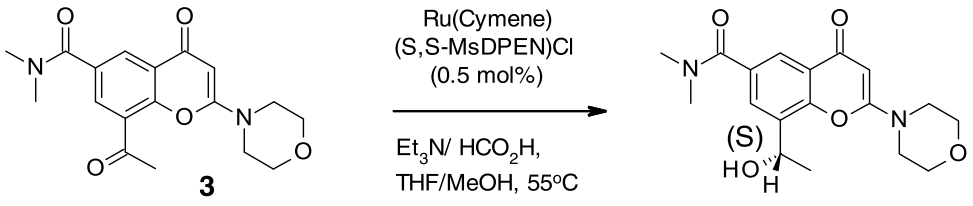
Scheme 7. Optimized Reaction Conditions for Asymmetric Reduction of Ketone 3

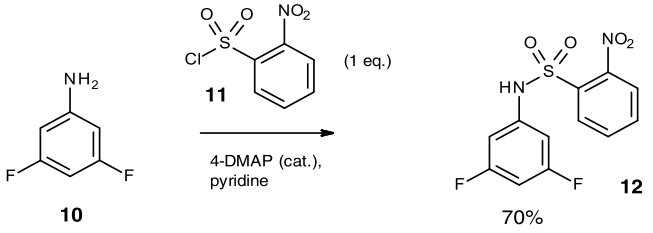


Further investigations (see the Supporting Information) using more polar solvent systems showed that a solution could be formed at the reaction temperature. Use of methanol provided a solution throughout the course of the reaction; however, the optical purity of the isolated product was found to be considerably lower. In the event, a 1:1 mixture of THF/MeOH provided optimum reaction conditions. A complete solution was formed during the reaction, and on cooling, the product alcohol crystallized from solution. Further cooling and addition of methyl *tert*-butyl ether (MTBE) to the reaction mixture allowed for isolation of alcohol **7** in excellent yield and enantiomeric excess (see Scheme 7).

With optimized reaction conditions now identified, the asymmetric reduction of ketone **3** proceeded as planned in manufacture, delivering 12 kg of the required (*S*)-alcohol in excellent chemical (99% w/w assay) and optical purity (>99.5% ee).

Our focus then turned to the stereocontrolled incorporation of difluoroaniline in AZD8186. Alkylation via the Mitsunobu reaction would require initial activation (through reduction of pK_a) of the aniline.[7] Further investigation found that the corresponding 2-nosylate derivative (calculated pK_a = 5.2) performed most effectively in the reaction. Other activated aniline derivatives (NBOC and NCOCF$_3$) failed to react.[15] The nosylated derivative **12** was readily prepared, as shown in Scheme 8, through the reaction of 3,5-difluoroaniline with 2-nitrobenzenesulfonyl chloride in pyridine with 4-dimethylaminopyridine as the catalyst.

Scheme 8. Preparation of the Nosylate Derivative 12



During the course of our investigations, it was identified that solid 2-nitrobenzenesulfonyl chloride **11** had given a positive result in the Köenen test, which is one of the UN tests used to determine whether a material is a Class 1 explosive for transport.[16] This classification would have restrictions on the future sourcing, use, and storage of this material. Further work by AstraZeneca has shown that the corresponding 4-nitrobenzenesulfonyl chloride does not have explosive properties. The 4-nitro analogue of compound **12** (Figure 2) has been prepared in a similar manner to that outlined above and undergoes the transformations outlined in this article. Thus, the 4-nitro analogue was utilized in later campaigns.[17]

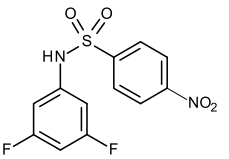


Figure 2. 4-Nitro analogue of compound 12.

Inspection of the literature[6] and initial small-scale experiments suggested that the reaction of the nosylate **12** with the chiral alcohol **7** would be best achieved through slow addition of diisopropyl azodicarboxylate (DIAD) to a solution of the alcohol **7**, sulfonamide **12**, and triphenylphosphine (Ph$_3$P) at 0 °C in a suitable solvent. The reaction mixture is then allowed to warm to 20 °C and agitated for 24 h to completion. To optimize the reaction conditions in the minimum time, a design of experiments (DoE) approach was used (see the Supporting Information). The DoE was a mixed level design investigating both the levels of the reagents combined with the solvent type and reaction concentration (Table 2). A quarter fraction of the total number of possible experiments was completed, plus three centerpoints as follows.

Table 2. FED Parameters Investigated for Optimization of the Mitsunobu Reaction[a]

	Ph$_3$P (equiv)	DIAD (equiv)	sulfonamide **12** (equiv)	solvent type	solvent (relative volumes)
low	1.0	1.0	1.0	MeCN EtOAC	8
mid	1.25	1.25	1.25	toluene 2-MeTHF	14
high	1.5	1.5	1.5		20

[a]MeCN was used as the centerpoint solvent. The following variables were fixed: chiral alcohol **7**, 1.0 equiv; DIAD addition time, 10 min; temperature of DIAD addition, 0 °C; and temperature for hold, 20 °C.

A number of recommendations for optimization of the reaction were inferred from this DoE:

- The reaction required equivalent charges (1.5 equiv) of Ph$_3$P and DIAD to maximize the yield and quality of the product.
- The nosylate charge has no impact on the reaction. Therefore, the nosylate **12** would be charged at 1.1 equiv.
- Acetonitrile is the preferred solvent.
- Lower volumes of the solvent have a positive impact on yield and quality of the product.

Also, during the course of the studies, it was observed that the product sulfonamide **13** crystallized from acetonitrile, providing the product in excellent purity and free from associated phosphine and reduced DIAD byproducts. Further

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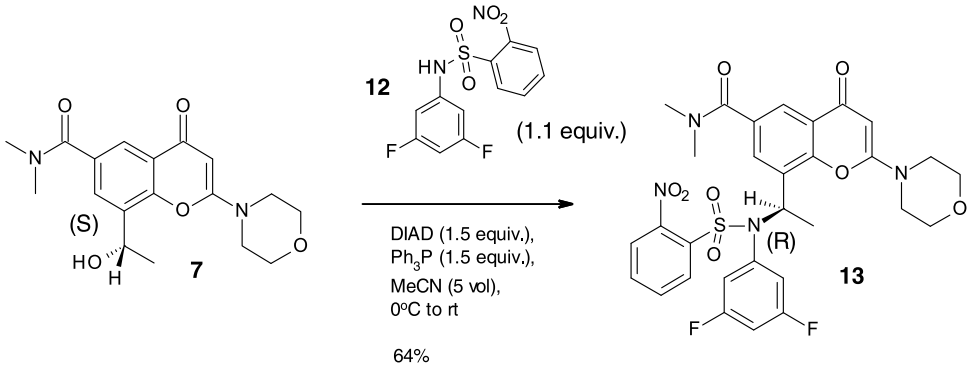
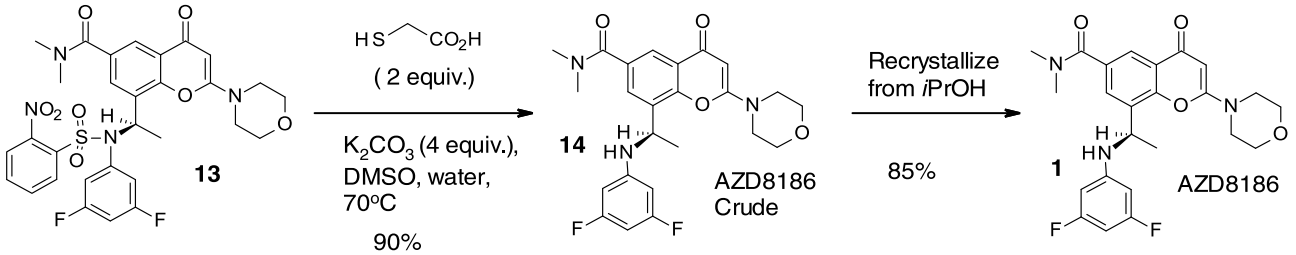
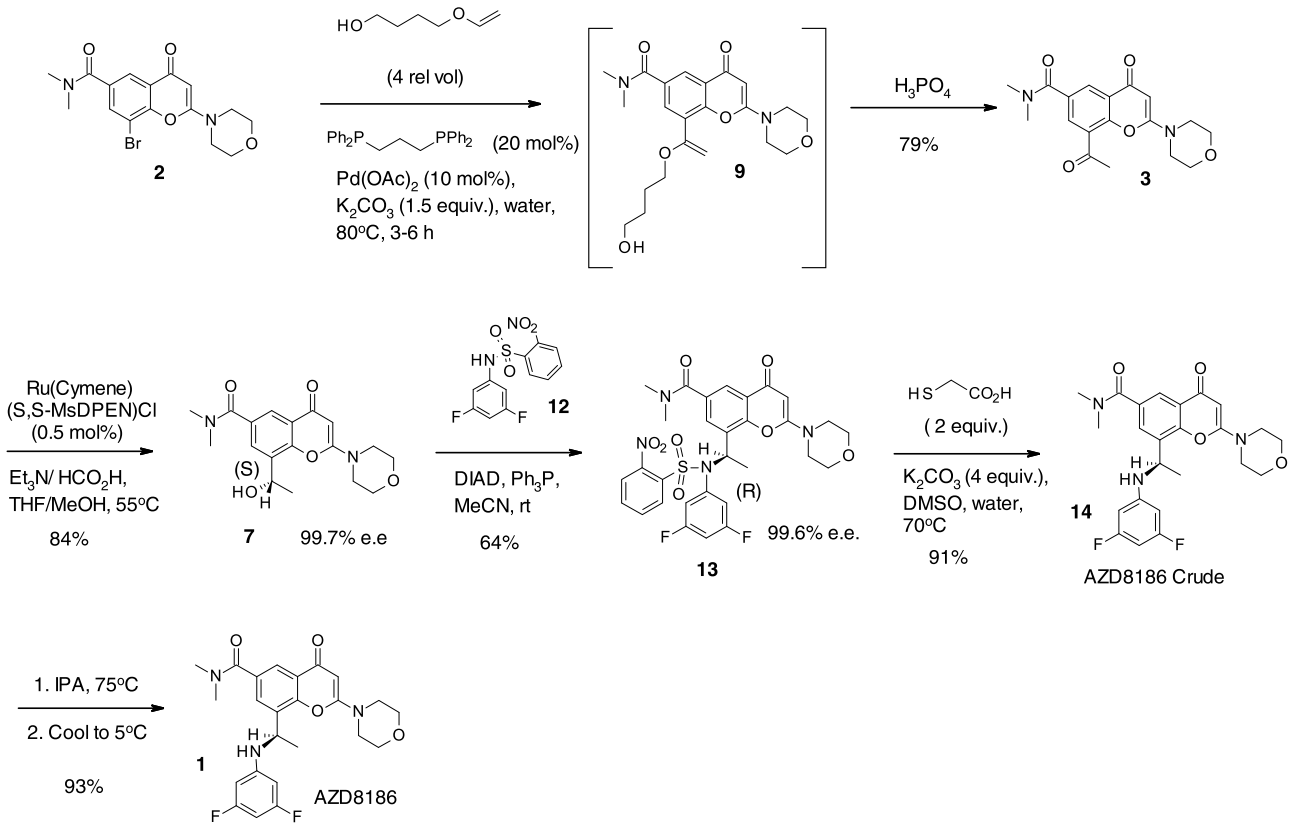
Scheme 9. Synthesis of Sulfonamide 13



Scheme 10. Removal of the Nosylate Group and Final Recrystallization



Scheme 11. Campaign 2 Manufacturing Route for AZD8186



development provided the following procedure for large-scale preparation of the sulfonamide **13** (Scheme 9).[17]

Again, this procedure performed as expected in manufacture, delivering 13.6 kg of sulfonamide **13** through a four batch strategy in good yield (64%), quality (99% w/w assay) and optical purity (>98% ee). Residual triphenylphosphine oxide and reduced DIAD impurities were retained in the mother liquors, obviating the need for chromatography.

The final step in the synthesis of AZD8186 required the removal of the nosylate activating group from sulfonamide **13**. For this transformation, thioglycolic acid (as originally described by Fukuyama[7]) in the presence of a suitable base

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was investigated. In the event, slow addition of thioglycolic acid to a hot solution of the sulfonamide **13** and potassium carbonate (4 equiv) in a mixture of dimethylsulfoxide and water resulted in the efficient removal of the nosylate group (Scheme 10). Subsequent addition of AZD8186 seed and water followed by a cooling crystallization allowed for ready isolation of AZD8186 by simple filtration from the aqueous reaction mixture. The thioglycolic acid byproduct was retained in the basic aqueous mother liquors. This procedure performed exceptionally well in manufacture, providing >13 kg of AZD8186 Crude in excellent yield (>90%), quality (98% w/w), and optical purity (>99% ee). Final recrystallization of the AZD8186 Crude from isopropanol provided the target AZD8186 as a white crystalline solid in excellent yield (93%) and quality (99% w/w assay)— see Scheme 10.

■ CONCLUSIONS

An enantioselective route has been developed for the large-scale manufacture of AZD8186 (Scheme 11). This new route to the active pharmaceutical ingredient (API) commences with a regioselective Heck coupling in water to provide the starting aromatic ketone. The manufacture then utilizes a ruthenium-catalyzed asymmetric hydrogenation, followed by a stereoselective Mitsunobu reaction with an activated aniline. Critical to the success of this approach is the use of the nosylate derivative of 3,5-difluoroaniline (pK_a = 5.3) in the Mitsunobu reaction. Furthermore, the Mitsunobu product was isolated by simple crystallization from the reaction mixture, thus obviating the need for chromatographic removal of triphenylphosphine oxide and reduced DIAD. Final deprotection of the nosylate group was achieved with thioglycolic acid to provide AZD8186 in good overall yield (31%) and optical purity (99% ee) starting from amide **2**. This new stereocontrolled manufacturing route to AZD8186 provides numerous benefits over the original medicinal chemistry route, including the following:

- An increase in overall yield from starting bromide **2** (31 versus <10%).
- Eliminating the need for chromatography by crystallization of relevant intermediates.
- Removal of toxic tin chemistry by application of a modified Heck reaction.
- Use of more environmentally friendly solvents.

Establishment of this new manufacturing route to AZD8186 has allowed the project to meet key deadlines for drug substance delivery, facilitating the initial Phase I clinical development of the pi3kβ oncology program at AstraZeneca.

■ EXPERIMENTAL METHODS

General. All of the reactions were performed in dry vessels under an atmosphere of dry nitrogen unless otherwise stated. All reagents and solvents were used as received without further purification unless otherwise specified.

*Synthesis of 8-Acetyl-N,N-dimethyl-2-morpholino-4-oxo-chromene-6-carboxamide (**3**).* To a 100 L large-scale glass-lined reactor under a nitrogen atmosphere were added bromide **2** (5.50 kg, 14.30 mol), potassium carbonate (2.99 kg, 21.63 mol), bis-(1,3-diphenylphosphino)propane (1.19 kg, 2.89 mol), palladium acetate (323.90 g, 1.44 mol), hydroxybutyl vinyl ether (33.52 kg, 288.54 mol), and water (27.50 L, 1526.50 mol). The reaction mixture was heated under nitrogen to 80 °C until the formation of ketone **3** was complete. The reaction mixture was cooled to 20 °C and screened through a glass fiber filter paper. The aqueous layer was discarded from the resultant filtrates. The remaining organic layer was filtered through a pad of diatomaceous earth. The filtrates were allowed to settle over 20 min, and any resulting aqueous layer was discarded. The resulting organic extracts were concentrated under reduced pressure (30 mbar pressure at a batch temperature of 13 °C rising to 90 °C) so that approximately 16.50 L of the distillate was collected. After adding 1,2,4-trichlorobenzene (52.25 L, 418.98 mol), the reaction mixture was concentrated again under reduced pressure (30 mbar pressure and batch temperature of 80−86 °C) so that a further 58 L of the distillate was collected. The residue was cooled to 30 °C, then water (27.50 L, 1526.48 mol) and 6.8 M phosphoric acid (2.34 L, 15.91 mol) were added, and the reaction mixture was heated to 35 °C until the formation of ketone **3** was complete. The reaction mixture was filtered, and the filtrate was allowed to settle over 20 min. The lower dark organic phase was discarded. Isobutanol (27.50 L, 297.25 mol) and 18.1 M sodium hydroxide (840.73 mL, 15.87 mol) were added to the retained lower phase, and the mixture was stirred at 25 °C for 10 min. The stirring was stopped, and the mixture was allowed to settle over a minimum of 15 min. The lower aqueous layer was separated off, and the aqueous layer was extracted with further isobutanol (27.50 L, 297.25 mol). The combined isobutanol extracts were concentrated under reduced pressure (100 mbar and 35−40 °C) so that 27.50 L of the distillate was collected. The contents of the vessel were adjusted to 55 °C, and methyl *tert*-butyl ether (22.00 L, 185.11 mol) was added. The mixture was ramp-cooled to 0 °C with stirring over at least 1 h, and the desired ketone **3** was collected by filtration. The solids were washed with methyl *tert*-butyl ether (11.00 L, 92.56 mol) and dried to constant weight at 50 °C to provide ketone **3** (4.03 kg, 11.34 mol, 79% yield, Q NMR 97% w/w) as a white crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.11 (d, J = 2.3, 1H), 8.08 (d, J = 2.3, 1H), 5.60 (s, 1H), 3.72 (m, 4H), 3.57 (m, 4H), 3.00 (s, 3H), 2.94 (s, 3H), 2.68 (s, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 196.9, 173.6, 168.2, 162.1, 150.6, 132.6, 131.9, 127.0, 127.0, 123.2, 86.0, 65.2 (2C's), 44.6 (2C's), 39.0, 34.9, 30.2. HRMS (ESI): $[M + H]^+$ m/z calcd for C18H21N2O5, 345.1445; found, 345.1447.

*8-[(1S)-1-Hydroxyethyl]-N,N-dimethyl-2-morpholino-4-oxo-chromene-6-carboxamide (**7**). Formation of Triethylammonium Formate Solution (Vessel 1).* To a 20 L large-scale glass-lined reactor (Vessel 1) under a nitrogen atmosphere were added tetrahydrofuran (4.82 L, 59.28 mol), methanol (1.21 L, 29.80 mol), and triethylamine (1.07 L, 7.68 mol), and the mixture was cooled to 5 °C with agitation under a nitrogen atmosphere. Formic acid (484.80 mL, 12.84 mol) was then added dropwise over 10 min, allowing the mixture to warm to 20 °C. The mixture was then agitated at 20 °C to be used directly in the next stage (see below).

Asymmetric Reduction (Vessel 2). To a 100 L large-scale glass-lined reactor (Vessel 2) were added ketone **3** (4.02 kg, 11.67 mol), Ru(*S*,*S*-MsDPEN)(Cymene)Cl (32.63 g, 58.37 mmol), tetrahydrofuran (25.73 L, 316.43 mol), and methanol (6.50 L, 160.60 mol), and the contents of the vessel were degassed (×4). The contents were agitated under a nitrogen atmosphere and heated to 55 °C. The triethylammonium formate solution (formed as above in Vessel 1) was then added dropwise to Vessel 2 over a minimum of 90 min. Tetrahydrofuran (4.02 L, 49.40 mol) was then added to Vessel 1, and the remaining contents of Vessel 1 were added to

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Vessel 2. The contents of Vessel 2 were agitated at 55 °C for a minimum of 1 h. Vessel 2 was seeded with alcohol **7** (2.40 g, 7.00 mmol), and the contents were agitated at 55 °C for a further 30 min. The contents of Vessel 2 were then cooled to 40 °C over 1 h. The contents of Vessel 2 were distilled at 40 °C and 400 mmHg until approximately 14 L of the distillates was collected. Methyl *t*-butyl ether (12.06 L, 101.47 mol) was then added to Vessel 2 over a minimum of 1 h. The contents of Vessel 2 were cooled to 20 °C over 2 h and agitated at this temperature for a minimum of 2 h. The resulting solid was filtered under reduced pressure, and the filter cake was washed with methyl *t*-butyl ether (10.05 L, 84.56 mol). The solids were dried under a stream of nitrogen and then in a vacuum oven to constant weight to provide the chiral alcohol **7** (3.45 kg, 9,87 mol, 84% yield; Q NMR 99% w/w) as a white crystalline solid.

Enantiomeric purity: 99.72%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.78 (d, J = 2.3, 1H), 7.75 (d, J = 2.3, 1H), 5.55 (s, 1H), 5.46 (s, 1H), 5.21 (q, J = 6.4, 1H), 3.73 (m, 4H), 3.51 (m, 4H), 3.02 (s, 3H), 2.94 (s, 3H), 1.40 (d, J = 6.4, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 174.6, 169.2, 161.9, 149.8, 135.6, 132.2, 127.6, 121.9, 121.6, 86.0, 65.2, 62.5, 44.3, 38.9 (2C's), 34.8 (2C's), 24.09. HRMS (ESI): $[M + H]^+$ m/z calcd for $C_{18}H_{23}N_2O_5$, 347.1601; found, 347.1596.

*8-[(1R)-1-{(3,5-Difluorophenyl)[(2-nitrophenyl)sulfonyl]-amino}ethyl]-N,N-dimethyl-2-(morpholin-4-yl)-4-oxo-4H-chromene-6-carboxamide (**13**).* To a 100 L large-scale glass-lined reactor vessel under a nitrogen atmosphere were added chiral alcohol **7** (3.75 kg, 10.7 mol), *N*-(3,5-difluorophenyl)-2-nitrobenzenesulfonamide **12** (3.78 kg, 11.79 mol), triphenylphosphine (4.22 kg, 16.08 mol), and acetonitrile (<0.02% water, 18.56 L, 354.04 mol), and the mixture was stirred under a nitrogen atmosphere at 20 °C for 30 min. The mixture was cooled to 3 °C and held at this temperature for 10 min. Diisopropyl azodicarboxylate (3.26 kg, 15.76 mol) was then added dropwise at a rate to maintain the temperature of the reaction at <10 °C during the addition. The reaction was held at <10 °C for 30 min before being heated to approximately 20 °C over 30 min. The reaction mixture was then held at this temperature for 24 h with agitation under a nitrogen atmosphere. The resulting slurry was heated to 48 °C over 30 min and held at this temperature for approximately 30 min with agitation. Isopropyl acetate (44.60 L, 380.44 mol) was then added at a constant rate over 30 min while maintaining the temperature of the slurry at 48 °C. The slurry was held at 48 °C with agitation for 1 h and then cooled to 20 °C over 4 h with agitation and held at 20 °C for a further 18 h. The final slurry was filtered under reduced pressure, and the filter cake was washed with isopropyl acetate (7.50 L, 63.98 mol). The resulting solids were dried in an oven to constant weight to provide the chiral aniline **13** as a white solid (4.45 kg, 6.86 mol, 64% yield; Q NMR 99% w/w).

Enantiomeric purity: 98.6%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (m, 1H), 7.90 (m, 1H), 7.83 (d, J = 2.0, 1H), 7.78 (m, 2H), 7.36 (m, 1H), 7.10 (d, J = 2.2, 1H), 6.62 (m, 2H), 6.28 (q, J = 7.1, 1H), 5.61 (s, 1H), 3.72 (m, 4H), 3.65 (m, 2H), 3.55 (m, 2H), 2.90 (s, 3H), 2.65 (d, J = 1.5, 3H), 1.65 (d, J = 7.0, 3H). 13C NMR (DMSO-d_6, 101 MHz): 174.3, 168.4, 162.1, 161.8 (2C's), 150.3, 147.6, 136.0, 135.4, 132.4, 132.1, 130.5, 130.0, 129.8, 127.2, 124.3, 123.5, 122.7, 116.4 (2C's), 105.6, 86.4, 65.4 (2C's), 51.6, 44.7 (2C's), 38.5, 34.6, 19.0. HRMS (ESI): $[M + Na]^+$ m/z calcd for $C_{30}H_{29}F_2N_4O_8S$, 643.1669; found, 643.1676.

*AZD8186 Crude: 8-[(1R)-1-(3,5-Difluoroanilino)ethyl]-N,N-dimethyl-2-morpholino-4-oxo-chromene-6-carboxamide (**14**).* To a 100 L large-scale glass-lined reactor vessel were added chiral aniline **13** (4 kg, 6.22 mol), potassium carbonate (3.44 kg, 24.90 mol), and dimethylsulfoxide (32.00 L, 447.23 mol). Water (1.6 L, 88.81 mol) was then added, and the contents of the flask were agitated and degassed (×5) under a nitrogen atmosphere. Thioglycolic acid (1.15 L, 865.48 mol) was then added dropwise at a rate to maintain the contents of the vessel at <30 °C throughout the addition. The contents of the vessel were heated at 60 °C for approximately 3 h. AZD8186 seed (2.40 g, 5.14 mmol) was then added to the vessel and water (32 L, 1776.27 mol) was added dropwise over approximately 45 min, maintaining the vessel contents at approximately 60 °C. The contents of the vessel were cooled to 20 °C with agitation over 4 h and held at this temperature for a further 14 h. The contents of the vessel were filtered under reduced pressure. More water (12 L, 666.10 mol) was added to the vessel and agitated at 20 °C for 5 min. The contents of the vessel were discharged onto the filter cake, and the cake was pulled dry under reduced pressure. The filter was washed with water (12 L, 666.10 mol), and the filter cake was dried under reduced pressure. The resulting solids were dried in a vacuum oven to constant weight to provide AZD8186 Crude **14** as a white crystalline solid (2.91 kg, 6.22 mol, 90.7% yield; Q NMR 98% w/w).

Enantiomeric purity: 100.00%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.82 (d, J = 2.2, 1H), 7.55 (d, J = 2.2, 1H), 6.96 (d, J = 6.7, 1H), 6.22 (m, 1H), 6.16 (m, 2H), 5.61 (s, 1H), 5.02 (m, 1H), 3.74 (m, 4H), 3.57 (m, 4H), 2.95 (s, 3H), 2.74 (s, 3H), 1.52 (d, J = 6.7, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 174.6, 169.1, 163.3 (2C's), 162.2, 151.1, 150, 132.2 (2C's), 127.5, 122.6, 122.3, 95.4 (2C's), 90.8, 86.2, 65.3 (2C's), 46.4, 44.4 (2C's), 38.8, 34.9, 21.6. HRMS (ESI): $[M + H]^+$ m/z calcd for $C_{24}H_{26}F_2N_3O_4$, 458.1886; found, 458.1893.

AZD8186 Recrystallization. Vessels 1 and 2 were 100 L large-scale glass-lined reactors.

To Vessel 1 was added AZD8186 Crude **14** (7.29 kg, 15.54 mol), followed by isopropyl alcohol (92.40 L, 1208.51 mol), and the mixture was heated with agitation under a nitrogen atmosphere to 75 °C and held at this temperature for 1 h. The contents of the vessel were then filtered hot into Vessel 2, which was already maintained at a temperature of 65 °C.

The contents of Vessel 2 were cooled with agitation under a nitrogen atmosphere to 55 °C and held at this temperature for another 1 h with agitation. To Vessel 2 was added AZD8186 Pure seed **1** (6.40 g, 13.84 mol), and the contents of Vessel 2 were agitated at 55 °C for another 1 h. The contents of Vessel 2 were cooled to 5 °C over 3 h and maintained at this temperature for a further 18 h. The contents of Vessel 2 were filtered under reduced pressure. Isopropyl alcohol (14.21 L, 185.91 mol) was then added to Vessel 2, and the contents were agitated at 5 °C for 10 min. The contents of Vessel 2 were discharged onto the filter cake, and the filter cake was pulled dry under vacuum. The solids were then dried in a vacuum oven at 40 °C to constant weight to provide AZD8186 Pure **1** (6.67 kg, 14.41 mol, 92.75% yield; Q NMR 99% w/w) as a white crystalline solid.

■ ASSOCIATED CONTENT

Supporting Information

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Further information regarding the development of the asymmetric hydrogenation conditions; details regarding the DoE for optimization of the Mitsunobu reaction; ^{1}H and ^{13}C NMR spectra for compounds **3**, **7**, **13**, and AZD8186; and the chiral HPLC method for determining optical purity of AZD8186 (PDF)

AUTHOR INFORMATION

Corresponding Author

Peter R. Moore − *Early Chemical Development, Pharmaceutical Sciences, R&D BioPharmaceuticals, AstraZeneca, Macclesfield SK10 2NA, U.K.;* orcid.org/0000-0001-7274-4218; Phone: +44 1625 512406; Email: peter.moore@astrazeneca.com; Fax: +44 1625 433744

Authors

James C. Muir − *Chemical Development, Pharmaceutical Technology & Development, Operations, AstraZeneca, Macclesfield SK10 2NA, U.K.*

Jerome Dubiez − *Early Chemical Development, Pharmaceutical Sciences, R&D BioPharmaceuticals, AstraZeneca, Macclesfield SK10 2NA, U.K.*

Kevin W. Leslie − *Chemical Development, Pharmaceutical Technology & Development, Operations, AstraZeneca, Macclesfield SK10 2NA, U.K.*

Paula Tomlin − *Chemical Development, Pharmaceutical Technology & Development, Operations, AstraZeneca, Macclesfield SK10 2NA, U.K.*

Marc McCormick − *Early Chemical Development, Pharmaceutical Sciences, R&D BioPharmaceuticals, AstraZeneca, Macclesfield SK10 2NA, U.K.*

Sophie L. Janbon − *Early Chemical Development, Pharmaceutical Sciences, R&D BioPharmaceuticals, AstraZeneca, Macclesfield SK10 2NA, U.K.;* orcid.org/0000-0001-7908-8292

Philip Cornwall − *Early Chemical Development, Pharmaceutical Sciences, R&D BioPharmaceuticals, AstraZeneca, Macclesfield SK10 2NA, U.K.*

Per Ryberg − *Chemical Development, Pharmaceutical Technology and Development, Operations, AstraZeneca, 15185 Södertälje, Sweden*

Robert Berg − *Chemical Development, Pharmaceutical Technology and Development, Operations, AstraZeneca, 15185 Södertälje, Sweden*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.oprd.1c00133

Author Contributions

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Notes

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ABBREVIATIONS

pi3kβ, phosphoinositide-3-kinase β; FGLP, Full Good Laboratory Practice; API, active pharmaceutical ingredient; DoE, design of experiments; MTBE, methyl *tert*-butyl ether; 2-MeTHF, 2-methyltetrahydrofuran; THF, tetrahydrofuran; EtOAc, ethyl acetate; MeOH, methanol

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(14) Successful synthesis of the required (*R*)-enantiomer of AZD8186 using the methodology outlined in this paper confirmed that the alcohol **7** was of (*S*)-configuration. The Mitsunobu reaction of alcohol **7** with nosylate **12** proceeding through clean inversion of stereochemistry.
(15) (a) It was assumed that the corresponding NBOC and $NCOCF_3$ derivatives of 3,5-difluoroaniline failed to react in the Mitsunobu reaction, as their calculated pK_a values of 12.3 and 8.5 are substantially higher than the corresponding nosylated derivative (pK_a ∼ 5.2). These results correspond with previously observed findings of the dependency of successful inversion reaction with the dissociation constant of the acidic reactant. See Dodge, J. A.; Trujillo, J. I.; Presnell, M. Effect of the Acidic Component on the Mitsunobu Inversion of a Sterically Hindered Alcohol. *J. Org. Chem.* **1994**, *59*, 234−236. and (b) Hughes, D. L.; Reamer, R. A. The Effect of Acid Strength on the Mitsunobu Esterification Reaction: Carboxyl vs Hydroxyl Reactivity. *J. Org. Chem.* **1996**, *61*, 2967−2971.
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(17) Note: Further studies showed that the corresponding 4-nitro analogue of sulfonamide 12 also provided a crystalline product under the described Mitsunobu conditions. Again the 4-nitro analogue of compound 13 could be crystallised from the reaction mixture to provide the product in high yield and quality.

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