Organic Process Research & Development **2008,** *12,* 1044–1059

Full Papers

Kepner-Tregoe Decision Analysis as a Tool To Aid Route Selection. Part 2. Application to AZD7545, a PDK Inhibitor

Jonathan D. Moseley,* David Brown, Catherine R. Firkin, Shelley L. Jenkin, Bharti Patel, and Evan W. Snape

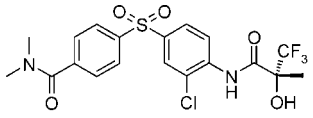
AstraZeneca, Process Research and Development, Avlon Works, Severn Road, Hallen, Bristol BS10 7ZE, UK

Abstract:

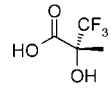
Kepner-Tregoe decision analysis was formally used as an aid to route selection, as outlined in the preceding paper. Over 40 paper routes were assessed for suitability for both immediate and longer term manufacture of AZD7545, a compound in the early stages of development. Eight routes were then investigated in full in the laboratory, and a further four in part, over a period of 3−4 months. From this exercise, the preferred long-term manufacturing route was identified before the first pilot scale manufacture had been completed. This route selection exercise worked well in this case where a large number of potential routes had to be considered using limited resources. It was also an effective means of bringing some long-term manufacturing issues to the fore at an early stage in development.

Introduction

AZD7545 was a pyruvate dehydrogenase kinase (PDK) inhibitor[1] designed to provide an oral treatment for type II diabetes[2] and was the first of a number of compounds to enter development from AstraZeneca's PDK project.[3] It was also the first compound in AstraZeneca upon which the Kepner-Tregoe decision analysis (KTDA) tool was formally used as an aid to route selection, as outlined in the previous paper.[4] Consequently, this tool provided much useful guidance on the route selection choice for AZD7545 whilst providing valuable learning with which to modify the process. Several of these improvements were incorporated for later compounds, as exemplified by the following paper.[5]



AZD7545 (**1**)



Chiral Acid (**2**)

At the time AZD7545 (**1**) entered development in December, 2000, there were two synthetic routes available for consideration: the one used by our medicinal chemistry colleagues to produce ∼200 g and a modification in use by a tactical contractor to produce the first kilogram for initial clinical trials. Both routes had significant disadvantages for long-term manufacture whilst being adequate in the short term.

A major drawback in both cases was the introduction early in the synthesis of the expensive contributory raw material, chiral acid (**2**). This had been required in the synthesis of ATP-sensitive potassium channel openers (for the treatment of urinary incontinence) on a previous Zeneca project,[6] for which several enzymatic resolutions had been developed.[7] Chiral acid (**2**) was commercially available for this project on large scale by an enzymatic resolution subsequently developed by Lonza.[8] This building block was expected to contribute 99% of the total raw materials costs for the first pilot plant scale manufacture (10 kg @ ≫£10k/kg, 2001 data), reducing to an estimated 50% at full scale manufacture (∼£1000/kg at tonne scale). (Cost contributions remained high at full scale in part because all the other raw materials were especially cheap; the KTDA process is therefore essentially unchanged). This was particularly critical as the expected API dosage was high (300 mg/day), resulting in a borderline cost of goods issue. Late introduction of chiral acid (**2**) would therefore clearly be advantageous. Late introduction was not necessary to preserve the chiral integrity of the enantiomeric centre since as a result of its quaternary nature it resisted racemisation. However, this did preclude the option to racemise and recycle the unwanted enantiomer in either the Lonza resolution process or later in the synthesis of AZD7545.

Consideration of the structure of AZD7545 reveals that it can be assembled in numerous ways (Scheme 1). To have investigated all of these potential routes in the laboratory was impractical as it would have required a high resource commitment. It was therefore necessary to assess the routes prior to laboratory work so that resource could be focused on the most promising ones. KTDA seemed an ideal method to decide this.

Kepner-Tregoe Decision Analysis

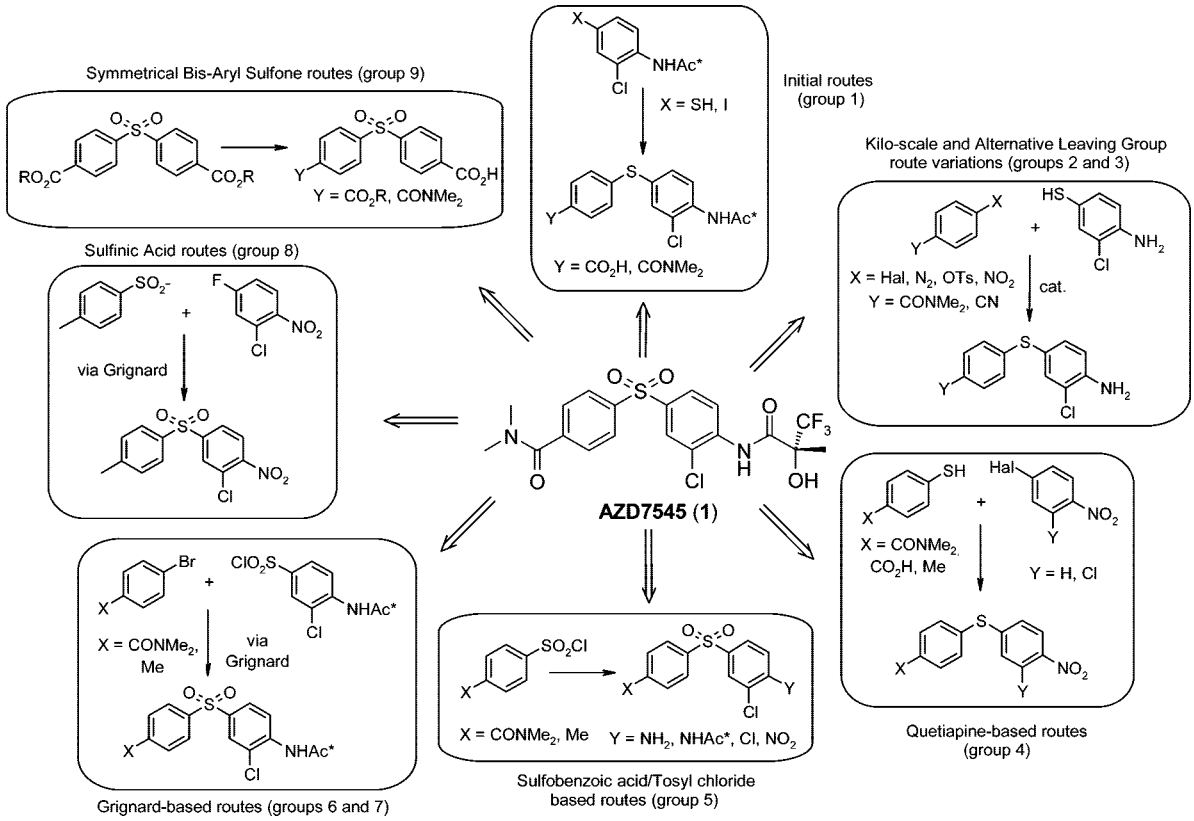
Decision Statement. The KTDA process has been outlined in the previous paper.[4] The important first task is to define a decision statement, which was as follows: "To identify routes most likely to succeed for full scale manufacture, for investigation in the short term (3−4 months), paying particular attention

* To whom correspondence should be addressed. E-mail: jonathan.moseley@astrazeneca.com.

(1) Butlin, R. J.; Nowak, T.; Burrows, J. N.; Block, M. H. PCT Int. Appl. WO 1999/9962506 A1.
(2) Mayers, R. M.; Leighton, B.; Kilgour, E. *Biochem. Soc. Trans.* **2005**, *33*, 367–370.
(3) Morell, J. A.; Orme, J.; Butlin, R. J.; Roche, T. E.; Mayers, R. M.; Kilgour, E. *Biochem. Soc. Trans.* **2003**, *31*, 1168–1170.
(4) Parker, J. S.; Moseley, J. D. *Org. Process Res. Dev.* **2008**, *12*, 1041–1043.
(5) Parker, J. S.; Bower, F.; Murray, P. M.; Patel, B.; Talavera, P. *Org. Process Res. Dev.* **2008**, *12*, 1060–1077.
(6) Ohnmacht, C. J.; Russell, K.; Empfield, J. R.; Frank, C. A.; Gibson, K. H.; Mayhugh, D. R.; McLaren, F. M.; Shapiro, H. S.; Brown, F. J.; Trainor, D. A.; Ceccarelli, C.; Lin, M. M.; Masek, B. B.; Forst, J. M.; Harris, R. J.; Hulsizer, J. M.; Lewis, J. J.; Silverman, S. M.; Smith, R. W.; Warwick, P. J.; Kau, S. T.; Yochim, C.; Dryoff, M. C.; Kirkland, M.; Neilson, K. L. *J. Med. Chem.* **1996**, *39*, 4592–4601.
(7) Crosby, J.; Holt, R. A.; Pittam, J. D. PCT Int. Appl. WO 97/38124 A2.
(8) Shaw, N. M.; Naughton, A.; Robins, K.; Tinschert, A.; Schimid, E.; Hischier, M.-L.; Venetz, V.; Werlan, J.; Zimmermann, T.; Brieden, W.; de Riedmatten, P.; Roduit, J.-P.; Zimmermann, B.; Neumüller, R. *Org. Process Res. Dev.* **2002**, *6*, 497–504.

10.1021/op800033c CCC: $40.75
Published on Web 10/28/2008

Scheme 1



to feasibility, cost and environmental issues in the long term." This reflected our desire to find a suitable long-term manufacturing route but recognized that we only had a short time for such investigations. We would therefore focus on those we thought most likely to give us a long-term manufacturing option.

Develop Objectives and Identify Musts and Wants. The objectives chosen from those listed previously[4] and identified as "must" criteria (with their pass criteria) were as follows:

- Safety, health and environment, taken as three separate but similar factors, in that no compromises could be made in these areas. Therefore no show-stoppers or major issues were permitted.
- Chemical feasibility, by which we meant the likelihood of success of any proposed chemical transformation. Some literature precedent, even if only by analogy, must be available.
- Raw materials, which were required to be available on a 10 kg scale within 6 months. This was necessary for the project to progress to its next milestone with a 10 kg manufacture in the pilot plant, since however good a proposed new route might be, it would be no use if the project failed to deliver its clinical targets on time.

These were identified as "must" criteria, which were essential to every route to be explored. Intellectual property (IP) was not included as a "must" in this first case study, although of course IP issues were taken into account when considering potential routes. This exemplifies in part how the KTDA exercise on AZD7545 served as a test-bed for later projects, and IP was formally included in following PDK compounds, for example.[5]

The "want" criteria were identified as follows (with weightings shown in parentheses):

- Accommodation (6)
- Chemical feasibility (10)
- Cost of goods (8)
- Environment (8)
- Number of stages (4)

The same objective can appear in both "must" and "want" categories as different levels of stringency can be required. For example, for environmental issues, a "must" requirement might be to have no stoichiometric heavy metals in the process; assuming catalytic heavy metals were acceptable below a certain threshold value, a "want" requirement would then be to reduce the loading as much as possible.

Having identified the "want" criteria, a weighting was applied to them as a score out of 10. The team agreed that chemical feasibility was the most important, which received a weighting of 10, while cost and environmental factors were scored highly at 8. Accommodation was significant but not overriding and so received a 6, and number of steps was given a 4, because chemical feasibility was felt to cover similar aspects (but see the conclusions for further discussion on the interplay between these two parameters). It is not worth scoring "wants" much below 4, because their contribution to the overall scores is low and serves only to average out the scores, thus lessening the discrimination observed between good and poor routes.

The quantification for the "wants" was as follows (also given in more detail in Table 1):

- Ease of accommodation into existing plant assets: a default score of 5 was given, with 1 point subtracted for each stage requiring special accommodation from

Table 1. **Scoring system for Wants**

Want	scoring system
accommodation	default score 5 −1 for each stage requiring special accommodation from standard pilot plant vessels (e.g., cryogenic, hydrogenation or pressure vessels)
chemical feasibility	default score normalised to 5 for best route known or estimated yield for each stage multiplied by confidence as assessed by rating below; total for all stages multiplied together and normalised to score of 5 for best route, all others pro rata score 10 for exact literature or AstraZeneca precedent score 8 for close literature precedent score 6 for a "better than even chance" score 4 for significant doubts, but some precedent score 2 for "one obscure paper suggests this is possible"
costs of goods	default score normalised to 5 for best route known or estimated yields for all stages after introduction of chiral acid multiplied together and normalised to score of 5 for best route, all others pro rata
environment	default score 5 −1 for each stage requiring special abatement or disposal (e.g., catalytic heavy metals, chlorination, iodine waste, oxidation)
number of stages	score 5 for 3 steps score 4 for 4 steps score 3 for 5 steps score 2 for 6 steps score 1 for 7 steps score 0 for 8 or more steps

standard pilot plant vessels (e.g., cryogenic, hydrogenation or pressure vessels).

- Chemical feasibility: for each stage, the known or expected literature yield was multiplied by the confidence that that yield could be achieved. So a known reaction would have a specific yield with a 100% confidence assigned, whereas a similar but not identical reaction might have a 60−80% confidence assigned to it. A more speculative reaction might score only 20−40% (more details are given in Table 1). This assessment was performed for every stage in the sequence and multiplied together to give an overall composite figure representative of yield and the confidence in achieving it for a given route. As with the cost of goods above, the highest scoring figure was given 5 points, with the others normalised against it accordingly. This procedure required considerable effort, although it is worth noting that the same reaction steps occurred at different points in many sequences, whilst the figures only had to be calculated once for each such reaction stage.
- Cost of goods: this was scored solely on the cost of the chiral acid (**2**). The combined estimated/known yield of all stages after the introduction of **2** was determined and normalised against the highest scoring yield, which was given 5 points, with the others scored pro rata accordingly. This apparently simple measure of cost was deemed appropriate due to the overwhelming contribution to the cost of goods from the chiral acid (and was further justified by the trivial cost of other raw materials).
- Environment: a default score of 5 was given, with 1 point subtracted for each environmental concern that could not be avoided.
- Number of stages: a default score of 5 was given for a three stage synthesis (not including the final crystallization), with 1 point deducted for every additional stage (but no negative scores were assigned beyond 8 steps).

The next step in the process was to evaluate all of the route ideas that had been generated previously, screening them through the "musts" and scoring the successful ones against the "wants". This data was easily gathered, calculated and tracked in a spreadsheet, a portion of which is shown in Table 2. Similar routes were gathered into clusters to help highlight where common issues might lie. For example, if one particular reaction step common to a cluster of routes could not be shown to work in practice, this would eliminate all of these routes, irrespective of their other virtues. On the other hand, if a speculative reaction was proven to be possible, this might open up several route options in a cluster of related routes and possibly indicate where the more successful strategies might lie. Generally, it was more helpful if the key reactions that needed investigation were near the start of each reaction sequence; less chemistry had to be undertaken before a definitive yes or no answer could then be determined.

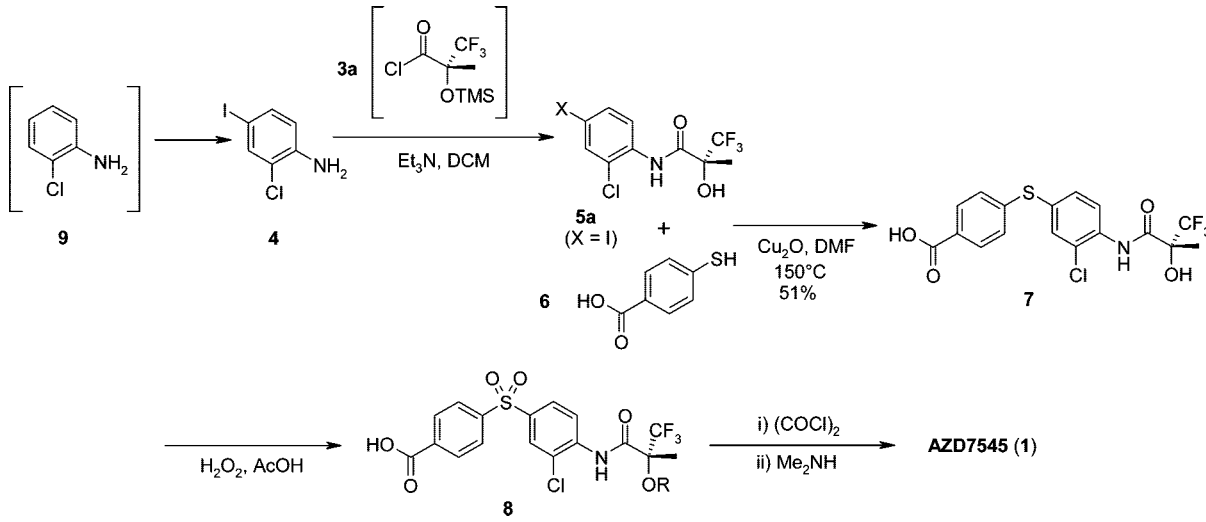
The scores from the "want" criteria ranged from 70−144 (for those routes that were scored). The medicinal chemistry route (Scheme 2, route 1.1) scored 95, which was towards the bottom end of the distribution, and was deemed to fail the must environmental and raw materials requirements. The second route (2.1) that the tactical contractor had quickly developed scored the highest initially with 144. By contrast, the final route that was chosen for later manufactures (route 3.4) scored only 130 initially, although this was towards the top end of the range and enough to be worth investigating. It is worth noting that more developed routes generally tend to score slightly low overall compared to "paper" routes, usually because their flaws are known (although they tend to score better for chemical feasibility); for undeveloped routes, many problems are often unseen until encountered in practice (or to use a military axiom, "no strategy of war survives the first day of action"). Some routes that obviously failed to meet several "must" criteria were simply not scored at all, on the assumption that they would be too low scoring even if the "must" criteria could be resolved; hence lower scores do not appear in the table. However, those

Table 2. **Initial KTDA data on 25 Jan 2001**

		Musts						Wants						
route no.	route description (name)	safety	health	environment	chemical feasibility	raw materials	go/no go	chemical feasibility, 10[a]	cost, 8[a]	environment, 8[a]	accommodation, 6[a]	numbers of steps, 4[a]	total score	initial rank
Initial Routes														
1.1	medicinal chemistry route	1	1	0	1	0	no	4.25	2.1	0	4	3	95	34
1.2	initial contractor's route	1	1	0	1	1	no	4.59	2.5	0	4	2	98	31
Campaign 2 Route Variations														
2.1	contractor's campaign 2 route	1	1	1	1	1	yes	5.00	4.5	4	3	2	144	**1**
2.2	with catalytic Pd	1	1	1	1	1	yes	4.40	4.5	4	3	2	139	**3**
2.3	with catalytic other metal	1	1	1	1	1	yes	3.00	4.5	4	3	2	124	**9**
2.4	nonmetal route	1	1	1	1	1	yes	3.00	4.5	5	3	2	132	**6**
2.5	with oxidation first	1	1	1	1	1	yes	3.56	5.0	4	3	2	134	**4**
2.6	nitro thiol route	1	1	1	1	1	yes	0.51	4.5	3	4	1	93	35
Alternative Leaving Group Variations														
3.1	diazonium LG	1	1	1	1	1	yes	1.20	4.5	4	3	1	102	25
3.2	tosylate LG	1	1	1	1	1	yes	0.86	4.5	5	5	1	119	12
3.3	nitro LG	1	1	1	1	1	yes	2.93	4.5	5	5	2	143	**2**
3.4	nitrile route	1	1	1	1	1	yes	2.05	4.5	5	5	1	130	**7**
3.5	nitro/diazo route	??[b]	1	1	??	1	??	not scored					n/s	40
Selected Other Route Options														
4.1	quetiapine-type best route	1	1	1	1	0	no	3.42	4.5	4	4	2	134	**4**
5.4	tosyl chloride and aniline	1	1	1	1	1	yes	1.07	5.0	3	4	3	111	16
5.6	typical tosyl chloride based route	1	1	1	1	1	yes	1.37	5.0	3	3	2	104	23
5.9	sulfobenzoic acid and aniline	1	1	1	1	1	yes	1.68	5.0	4	4	4	129	**8**
6.2	tolyl Grignard with protected amide	1	1	1	1	1	yes	1.96	2.0	4	4	3	103	24
7.2	protected aniline Grignard	1	1	1	1	1	yes	2.13	2.2	4	4	3	107	19
8.3	sulfinic acid (lowest scored route)	1	1	1	??	1	??	0.36	3.2	2	3	2	70	38
9.1	best bis-aryl sulfone route	1	1	1	1	1	yes	0.77	5.0	4	5	2	118	13

[a] Weighting. [b] Undecided/unknown.

Scheme 2



failing only one or two "must" criteria were scored if it was thought that resolving their "musts" might then reveal a promising route option.

Ideas for route options had been generated or gathered from a number of sources, most heavily within the project team and the local department, but also across the department at other sites, both nationally and internationally. Ideas from medicinal chemistry colleagues, which they had not had time to explore, were also taken into account, and a number of academics were consulted. However, most of the new ideas involved alternative syntheses of the expensive chiral acid unit, since this would have the greatest impact on the project; the challenge of AZD7545 itself was more one of efficiently combining the many possible subunits.

In total, the route generation exercise resulted in over 40 potential routes, which were grouped according to overall similarity or key chemical concept in the formation of AZD7545. Current resources were judged to allow 3−4 routes to be explored in detail within 3−4 months, after which time a decision about longer term manufacture (i.e., >10 kg) would need to be made. The default position would be further development of the 1 kg manufacturing route option ongoing at the tactical contractor, which was progressing well (route 2.1); any new route would have to be better than this. In fact, about 8 routes were investigated, and a number of other route options were briefly assessed by targeting reactions on key steps, which meant that overall 12 routes were assessed by laboratory work in some measure in the set time. It will be seen in the discussion below that the choice of which routes to work on was not driven completely by the KTDA scores; scientific experience and "chemical intuition" was still allowed to play a part so that the chemist's subjective judgment still had a role. However, KTDA provided the overall framework to guide the decision-making process.

As the laboratory work progressed and provided more accurate information about the chemical feasibility and yields, the values in the spread-sheet could be modified. In this way, the table existed as a living document, allowing it to further guide decision making and resource allocation in real project time. Given the similarity of several routes, a single piece of data could affect a number of routes. Furthermore, data from the tactical contractor's route 2.1 was particularly valuable for reassessing the group 2 routes. Negative results were often more helpful, because they could be used to eliminate routes definitively, whereas positive results invariably were not quite as positive as hoped, leaving a potential decision unresolved. Either way limited resources could be efficiently focused on those reactions which most needed to be proven or disproven.

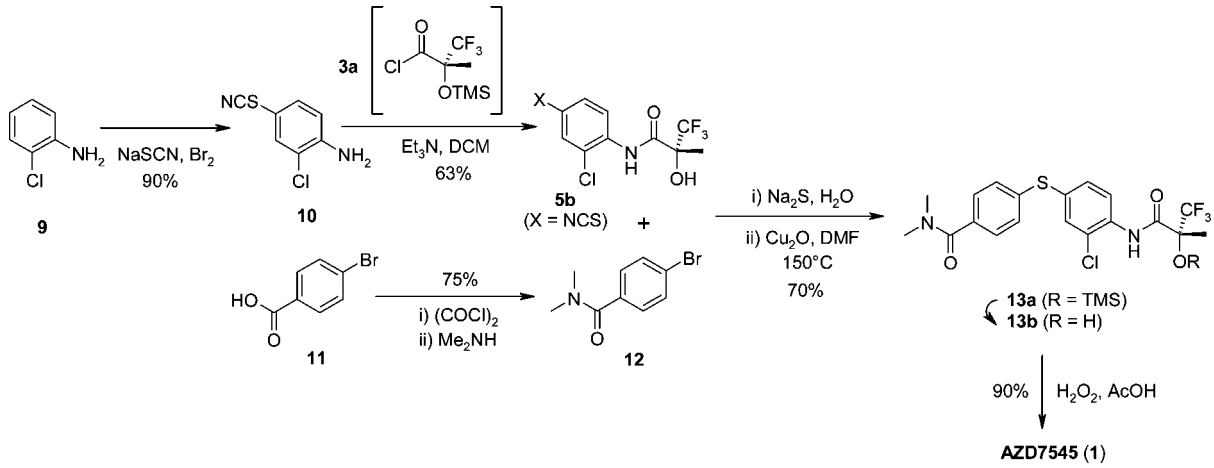
So far, this initial assessment had been a paper exercise. The results obtained meant that resource could be allocated to the most promising routes for further investigation in the laboratory. These will be discussed in their groups below, focusing mainly on the key steps in each sequence. However, some comments must be made on the initial route ideas before moving on to how the proposed route options fared against the K-T criteria chosen to assess them.

Results and Discussion

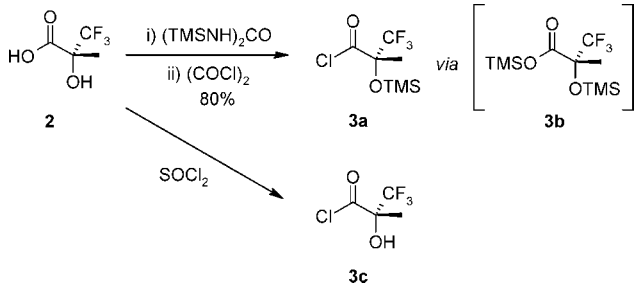
Initial Routes (Group 1). The medicinal chemistry route (Scheme 2, route 1.1) and a variation upon which the tactical contractor initially started (Scheme 3, route 1.2) scored only 95 and 98, respectively. Both of these scores were towards the bottom end of the distribution, and both were deemed to fail the "must" environmental requirements, mainly for the stoichiometric use of toxic metals in the Ullmann-type[9−11] sulfide coupling step (**5a** + **6** to give **7**). This was also a relatively high temperature reaction with a long reaction time, producing a moderate yield (51%) from a very dark reaction mixture after a difficult and dilute workup. Problems with the workup were not covered by the KTDA process, since they could not generally be anticipated in advance, and it was expected that ongoing process development would eventually provide a satisfactory workup procedure in most cases. Therefore, workups did not constitute show-stoppers in the KTDA process unless they were regarded as unworkable at laboratory scale. The iodide **4** was available in research quantities but would probably not have been available on the scale required for a 10

(9) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469.
(10) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428–2439.
(11) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337–2364.

Scheme 3



Scheme 4



kg manufacture and would have required an additional step from 2-chloroaniline (**9**) (and hence scored 0 for raw materials). The 4-mercaptobenzoic acid (**6**) was available but relatively expensive in absolute terms, although cheap compared to chiral acid **2**. Route 1.2 (Scheme 3) substituted the thiocyanate **10** (which did have to be prepared from **9**) for the iodide **4**, to give alternative coupling partner **5b**. This avoided the minor problem of iodine in the waste stream. It also avoided the thiophenol **6** by using the cheap acid **11** from which an earlier introduction of the dimethyl-substituted amide group gave benzamide **12**. This combination (**5b** + **12** to give **13**) was somewhat preferential in the main coupling step (70% yield), although the workup was still challenging. Finally, this route was also more convergent in adding the dimethylamide functionality in the subunit **12**, rather than leaving this trivial step to the last.

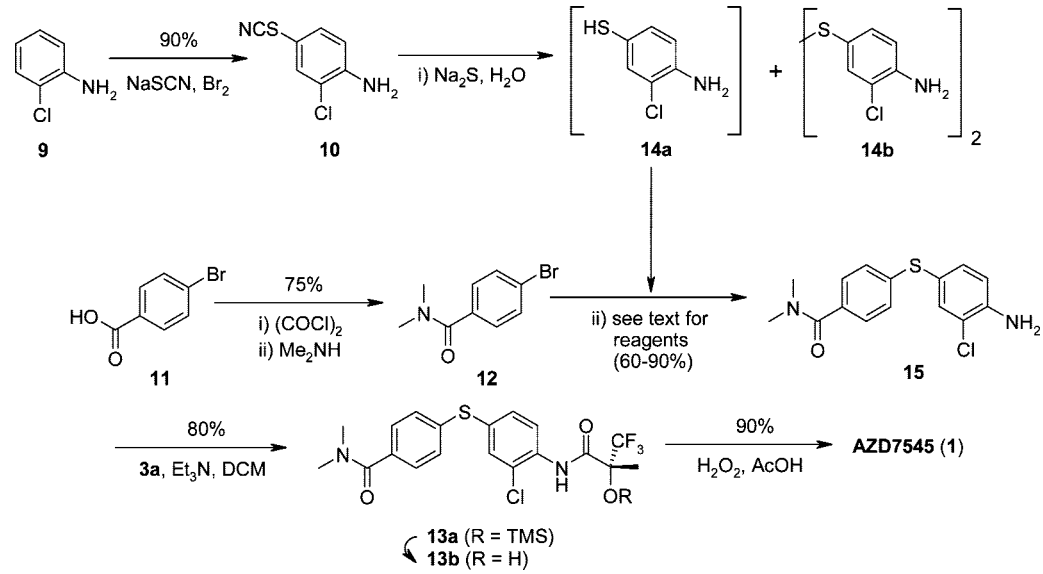
Finally, and ignoring the use of stoichiometric heavy metals that failed the "must" criteria, a reason for the low "want" scores was the early introduction of the chiral acid **2** in both cases. This was achieved through the bis-TMS-protected intermediate (**3b**) and activation as the acid chloride to give volatile **3a**, which could be isolated after distillation or more usually stored temporarily as a dichloromethane solution (Scheme 4). (The unprotected acid chloride **3c** was used successfully in later work for the final route chosen.) This added considerable cost to both routes, thus lowering their scores, and the less than complete conversion here (80% isolated yield), followed by other moderate yields in the key coupling step, further reduced the overall efficiency (although it will be recognized that medicinal chemistry routes are often designed for the facile synthesis of multiple analogues, not to be efficient for individual target molecules).

Kilo-Scale Route Variations (Group 2). The second major group of routes were variations on the one developed by the tactical contractor for the first 1 kg scale manufacture (Scheme 5, route 2.1). This route failed the environmental criteria[11] with the continuing use of stoichiometric Cu_2O (and dilute workup procedure). Furthermore, reduction of the thiocyanate **10** tended to result in significant quantities of the disulfide **14b**, up to 1:1 with sulfide **14a** in the early stages, which reduced the yield and complicated the workup. However, a major improvement was the step reorder so that protected chiral acid **3a** was introduced at the penultimate step to give protected sulfide anilide **13a**, which required only the final high-yielding oxidation of the sulfide to sulfone (with concomitant TMS-deprotection) to complete the synthesis. This considerably improved the cost score and the yield somewhat. If the environmental issue could be addressed, this would be a promising route. Literature precedent suggested that the key coupling step of thiocyanate **10** with bromobenzamide **12** to give **15** might be achievable with either Pd or other catalytic metals[9] or possibly without a catalyst at all.[12] This gave minor variations 2.2 to 2.4 (Scheme 5), which were deemed satisfactory on the environmental issues, and with much improved scores for cost and environment gave the other high scoring routes. Given that only the reagents of the key coupling step were different, they were effectively treated as one route option for investigation, since any solution would give a viable result. In practice, a low level of reaction was seen with several combinations of Pd sources, bases and solvents, but none of them were sufficiently promising to be worth investigating further, and these routes were parked as other options looked more promising. This was a good example of focusing on one key step in a cluster of several potentially good routes.

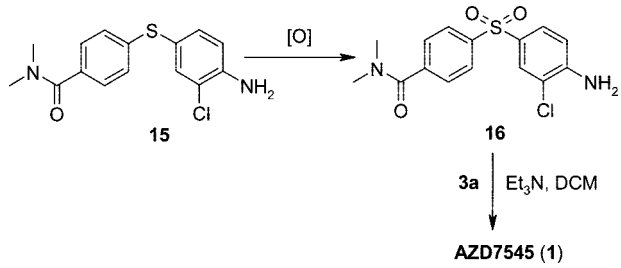
An even better potential alternative to the step order of routes 2.1−2.4 was to add the protected chiral acid **3a** as the very last step, giving route 2.5 with a score of 134 (Scheme 6, last steps only shown). However, this required the oxidation of the sulfide **15** to precede the final amide coupling reaction with **2**, which we knew would be unlikely to proceed selectively in the presence of the unprotected aniline group (i.e., without undergoing *N*-

(12) Sawyer, J. S.; Schmittling, E. A.; Palkowitz, J. A.; Smith, W. J. *J. Org. Chem.* **1998**, *63*, 6338–6343.

Scheme 5



Scheme 6

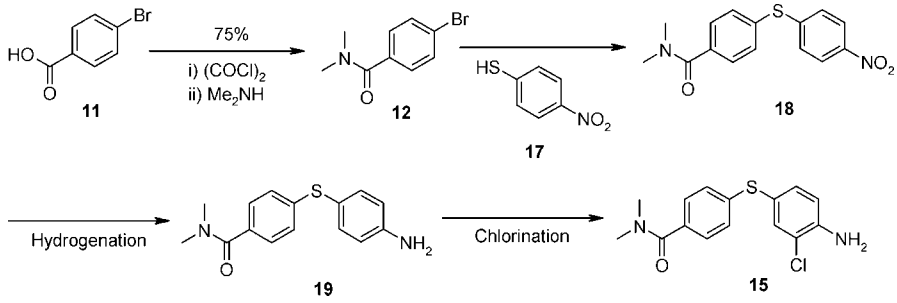


oxide formation at the aniline). Although the literature was far from encouraging, this was a good example of where a quick investigation of a single step was worth the investment of time for a potentially big gain. Using samples of **15** prepared from other routes, attempts to oxidize with either peracetic acid or oxone showed that there was no prospect of succeeding with this alternative route. Since it failed on chemical feasibility, it was quickly dropped. Only the analogous route to 2.1 was scored for this step reorder; if it had been successful, attention would then have focused on the analogous methodologies represented by routes 2.2−2.4.

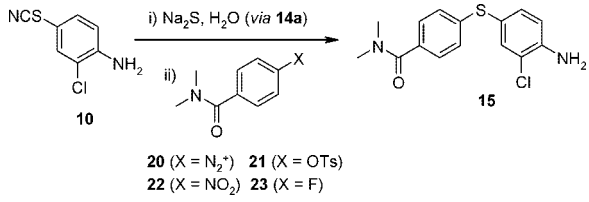
A final route in this cluster (Scheme 7, route 2.6) substituted the thiocyanate **10** for the commercially available 4-nitrothiophenol (**17**) to give the coupled product **18**. Assuming the coupling reaction could be realized, reduction of the nitro group would give **19**, the des-chloro analogue of **15**. Speculative chlorination of **19**, for which poly-chlorination might have been an issue, would give sulfide aniline **15**, which would be completed via **13a/b** to give AZD7545 as in the other related routes (Scheme 5). The low predicted chemical feasibility, along with some less desirable chemistries and the extra step, gave this route a score too low to consider (93), and no work on it was progressed.

Alternative Leaving Group Variations (Group 3). Another major group of higher scoring routes that passed the "must" criteria were those based on alternative leaving groups for the key coupling reaction with thiocyanate **10**. Rather than substitute the bromide in bromobenzamide **12**, diazo, tosyl, nitro and fluoro groups were proposed as the leaving groups in benzamides **20**−**23** (Scheme 8). The last part of each sequence was identical to those in Scheme 5 (from **15** onwards), but each earlier fragment required different steps to set up the appropriate leaving group, so they were clustered separately. The respective diazo- (**20**) and tosyl benzamides (**21**) could in principle be prepared easily in 2−3 steps. There was good literature precedent for the coupling step with **20**,[13] although with **21** it was much less encouraging, but both route scores were too low to consider (102 and 119, respectively). Substitution of the nitro group in **22** is also possible, although generally only with other strong electron-withdrawing groups present,[14] which gave this route (3.3) the second highest score (143). However, no coupling reaction between thiocyanate **10** and the known 4-nitrobenzamide (**22**)[15] (prepared in one step from 4-nitrobenzoic acid), with or without base, could be observed, and so this route failed

Scheme 7



Scheme 8

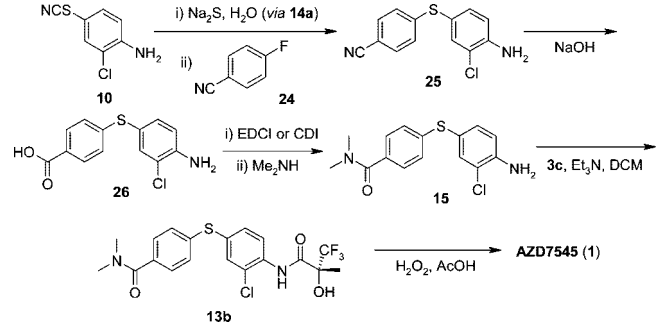


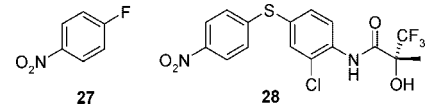
the feasibility test. Limited laboratory work was justified in this case by the high score and the fact that the key step was accessible as the second in the sequence. The route via the known 4-fluoro-dimethylbenzamide (**23**)[16] was not scored at this stage but prepared later after the success of route 3.4 had been established (vide infra). Using similar conditions from those used for bromobenzamide **12** and thiocyanate **10** (Cu_2O, DMF or NMP, >80 °C), an isolated crude yield of 46% was eventually obtained when tried, but by then route 3.4 was looking very promising.

An even better choice with which we were more confident of success used commercially available 4-fluorobenzonitrile (**24**). This route (Scheme 9, route 3.4) had a good but initially unexceptional score of 130, reduced by some concerns over chemical feasibility and a rather linear reaction sequence. But it held the promise of proceeding by a nonmetal containing S_NAr reaction,[17] which improved both the environmental factors[11,12] and the feasibility scores. This was successful at the first attempt, to give an LC conversion of 92% after only 1.5 h in NMP at 80 °C. Hydrolysis of the nitrile **25** was required to give acid **26**, which was derivatised to amide **15**, initially by EDCI coupling but later with CDI. The sequence proceeded in linear fashion but in simple steps so that the feasibility for these steps was eventually high. In common with the other group 3 routes, the cost criteria benefited from adding unprotected chiral acid chloride **3c** in the penultimate step to give **13b**, which as noted above had been established as the last possible point. With improvements to the coupling step, this developed from a promising route to the final route of choice, which will be discussed in more detail in a subsequent paper.

A possibly more advantageous analogue of **24** appeared to be 1-fluoro-4-nitrobenzene (**27**), which might be expected to be an even better coupling partner with thiol **14a** in the S_NAr reaction (route 3.5).[12] However, this would have required reduction of the nitro group to the amine and then diazotization or amide formation and then Beckman rearrangement to introduce the correct carboxylate/amide functionality, either of which options required too many extra steps and uncertain chemistry. Furthermore, the original aniline nitrogen in **28** would have required "protection" with the chiral acid portion to differentiate it from the other incipient aniline disguised as the nitro group. This was too early in the sequence to be economical, so for this and the other reasons above route 3.5 from **27** was neither scored nor investigated.

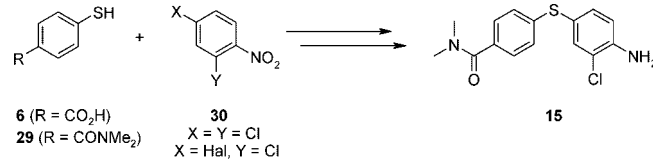
Scheme 9





"Quetiapine"-Based Routes (Group 4). Another group of routes essentially reversed the previous disconnection around the central sulfide, by using a sulfur nucleophile bearing the carboxylate (**6**) or amide functionality (**29**) to displace by S_NAr reaction a suitably substituted nitro-bearing compound **30** (Scheme 10). The nitro group would then be reduced to the aniline, with or without prior chlorination, to provide key sulfide aniline **15**. This route was based on analogous chemistry from a successful *ortho*-substituted example derived from an unrelated AstraZeneca compound (Quetiapine).[18] In fact only the first route, in which **30** had the correct substitution pattern (i.e., X = Y = Cl), scored highly enough (134) due to the similarity with Quetiapine chemistry to merit consideration. However, it was soon realized that there was insufficient discrimination between substitution at the *para* and *ortho* positions of the dichloride (**30**), and the preferred 4-fluoro-substituted compound (**46**, X = F, see Scheme 15) was not available at the time on the scale required. The other routes in this group required extra steps and relied on the uncertain regioselective chlorination noted for route 2.6 (Scheme 7), which was reflected in their lower scores (97−112). Attempts at selective chlorinations on other routes were similarly unsuccessful, and so this group was not investigated further.

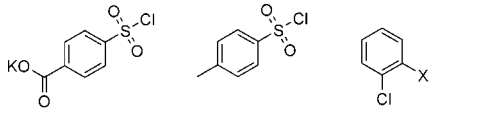
Scheme 10



4-Sulfobenzoic Acid/Tosyl Chloride-Based Routes (Group 5). Another large group of routes started from either readily available 4-sulfobenzoic acid potassium salt (**31**) or tosyl chloride (**32**). These routes had a number of common themes, generally relying on an aromatic Friedel−Crafts acylation of the sulfonyl chloride with a simple chlorobenzene, aniline or nitrobenzene (as a masked aniline) (**9**, **33a**−**d**) as the key step.

(13) Petrillo, G.; Novi, M.; Garbarino, G.; Dell'Erba, C. *Tetrahedron* **1986**, *42*, 4007–4016.
(14) For example, see: (a) Robert, J.; Anouti, M.; Bosser, G.; Parrain, J.-L.; Paris, J. *J. Chem. Soc., Perkin Trans.* **1995**, *2*, 1639–1644. (b) Zlotin, S. G.; Kislitsin, P. G.; Samet, A. V.; Serebryakov, E. A.; Konyushkin, L. D.; Semenov, V. V.; Buchanan, A. C.; Gakh, A. A. *J. Org. Chem.* **2000**, *65*, 8430–8438.
(15) Wenker, H. *J. Am. Chem. Soc.* **1938**, *60*, 1081.
(16) Schiemenz, G. P.; Stein, G. *Tetrahedron* **1970**, *26*, 200–2026.
(17) Tickner, A. M.; Huang, G. K.; Gombatz, K.; Mills, R. J.; Novack, V.; Webb, K. S. *Synth. Commun.* **1995**, *25*, 2497–2505.
(18) Murray, P. M.; Vaz, L.-M.; Ainge, D.; Harada, K.; Nishino, S.; Yoshii, K. PCT Int. Appl. US 2007/0203336 A1.

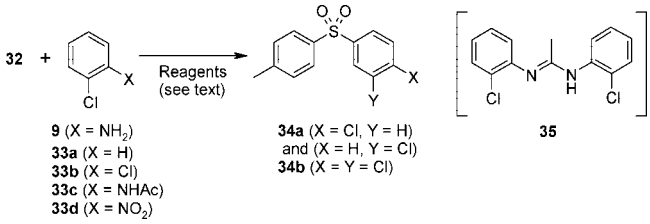
An advantage of these routes was that the sulfur atom was at the correct oxidation state, saving a step over the previously discussed routes above. The 4-sulfobenzoic acid was the preferred starting material, since whilst tosyl chloride avoided any difunctionalisation issues between the sulfonic and benzoic acids in **31**, the relatively inert methyl group would require oxidation at some stage to the benzoic acid. This meant swapping an easy oxidation (sulfide to sulfone) for a more difficult one, such that other features of these routes needed to be desirable to make them good options.



31 **32** **9, 33a-d** (X = Cl, NH_2, NHAc, NO_2)

In addition, the environmental burden of using stoichiometric Lewis acids as acylating agents was undesirable, although catalytic Lewis acids would be much more acceptable. These routes mostly scored in the middle range (100−120), although their short reaction sequences (generally four steps) and easily accessible, low-cost starting materials made them attractive (the highest scoring ones were generally based on **31** as the starting material). Given this large route cluster with some medium-high scores, it was felt some investigations were justified where the key Friedel−Craft acylation fell at the start of a sequence, such as shown in Scheme 11. For example, acylation of various

Scheme 11



chlorobenzenes (**9**, **33a**−**d**) with tosyl chloride (**32**) was quickly investigated using $FeCl_3$.[19] Whilst the protected acetamide **33c** gave the amidine dimer **35** and interaction of $FeCl_3$ with the unprotected aniline **9** resulted in a significant exothermic event (route 5.4, score 111), reaction with dichlorobenzene (**33b**) gave the desired sulfone **34b**[20] product in 45% crystallized yield after only 2 h at 100 °C (route 5.6, score 104). With only 5 mol % of Lewis acid, the reaction proceeded more slowly and failed to reach completion after extended period, even with fresh charges of $FeCl_3$. Reinvestigation of the "protected" aniline **33c** with **32** in the presence of the more potent $AlCl_3$ gave no reaction in dichloromethane but reacted preferentially with chlorobenzene (**33a**) when this was used as a solvent instead, to give complete conversion to **34a** but in a 2:1 mixture of isomers (assumed *para*:*meta*). Repeating the reaction of **32** in nitrobenzene (**33d**) gave no reaction with **33c** after 18 h at 100 °C. Since reactions of tosyl chloride and dichlorobenzene were too slow with $FeCl_3$ and too fast with $AlCl_3$, further Lewis acids (BF_3, CoF_2, CuI, MnF_2, PBr_3, $TiCl_4$) were investigated under a range of conditions between 80 and 120 °C in a systematic fashion by factorial experimental design (DoE strategy), but the original $FeCl_3$ was the only Lewis acid that gave clean product **34b** (in ~60% conversion). Work on other softer Lewis acids had not started when these routes were abandoned.

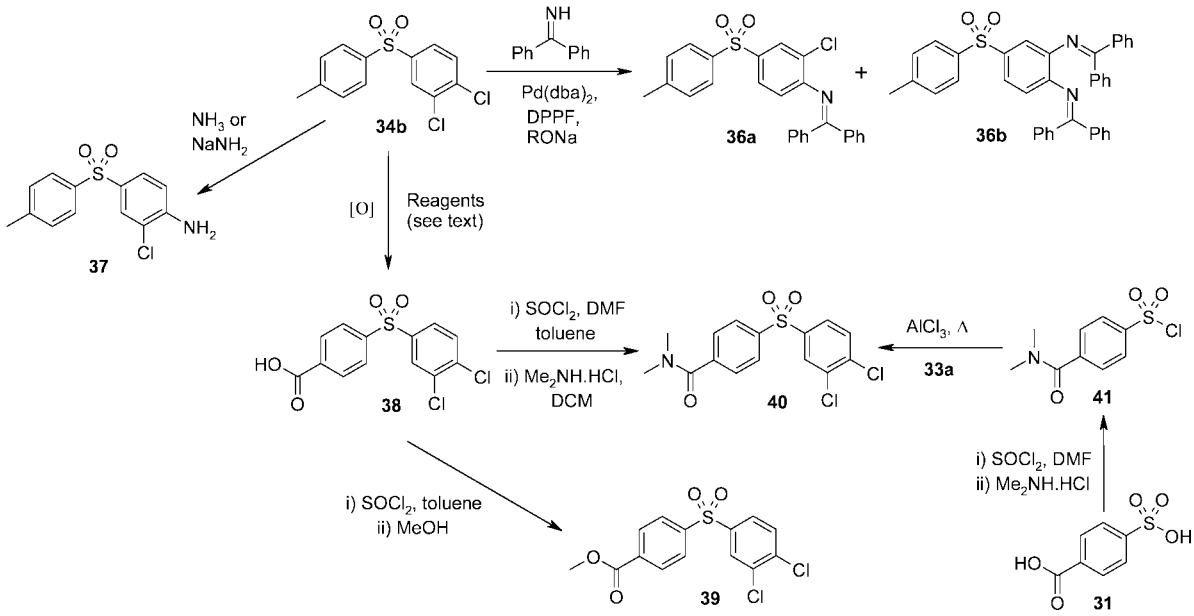
Introduction of the aniline functionality at the correct position of **34b** was another challenge that required solving. Use of benzophenone imine with 10 mol % Pd and the dppf ligand with sodium pentoxide as base in toluene gave complete conversion to two products, which proved to be an unresolvable mixture of the desired mono- to disubstituted benzophenone imines (**36a** and **36b**) in about 2:1 ratio (Scheme 12).[21] The problem appeared to be one of too great solubility, since once one benzophenone imine group had been introduced, the solubility of increased so much that the product **36a** reacted again in preference to the far less soluble dichloride **34b**. Other solvent (DMA and THF) and base (Cs_2CO_3) combinations were tried but to no avail. Obviously the use of benzophenone imine had very poor atom efficiency for the introduction of a single nitrogen atom. Forcing conditions in sealed tubes using either $NaNH_2$ or NH_3 as a more efficient source were also attempted but failed to give the desired **37**, as did using other sources of protected nitrogen equivalents such as acetamide and phthalimide groups.

Oxidation of the dichlorobenzyl sulfone **34b** to the benzoic acid sulfone **38** (continuation of route 5.6) was attempted with 5 mol% $RuCl_3$ and NaOCl under phase transfer conditions[22] and gave about 5% reaction, essentially only one turnover of the catalyst (Scheme 12). Speculative use of aqueous nitric acid failed to give any reaction, possibly due to solubility issues. However, stoichiometric use of $KMnO_4$ in 1 M NaOH gave complete conversion in 1 h at 100 °C to a new product that was assumed to be benzoic acid **38**.[23] Alternatively, $KMnO_4$ in aqueous *t*BuOH with 2.0 equiv of $KHCO_3$ gave complete and clean conversion after 24 h at 100 °C (aqueous *t*BuOH was found to aid solubility). The MnO_2 byproduct was easily filtered off, but the reaction was dilute and the workup problematic. The solubility of **38** was low, which hampered efforts to achieve conversion to the dimethyl amide **40** under standard conditions, and the result was difficult to confirm. However, further confirmation that benzoic acid **38** had been prepared was made by almost quantitative conversion to the methyl ester **39**, which had much greater, albeit still low, solubility in organic solvents. Once again, the full suite of solvents, bases and conditions was applied to **39** to introduce a nitrogen equivalent through the previously successful benzophenone imine chemistry,[21] which failed to work in this case despite increased organic solubility.

Conversion of the commercially available **31** to dimethyl amide **41** proceeded with standard reagents ($SOCl_2$, catalytic DMF, toluene, then dimethylamine·HCl) in 80% isolated yield to leave the sulfonyl chloride group intact (Scheme 12). Coupling this amide with $AlCl_3$ in 20 vol of dichlorobenzene (**33b**) revealed several new peaks after 4 h, including one

(19) Huismann, J. U.S. Patent 2,224,964, 1940.
(20) Zilberman, J.; Ioffe, D.; Gozlan, I. *Synthesis* **1992**, 659–660.
(21) Wolfe, J. P.; Åhman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367–6370.
(22) Sasson, Y.; Zappi, G. D.; Neumann, R. *J. Org. Chem.* **1986**, *51*, 2880–2883.
(23) Fatiadi, A. J. *Synthesis* **1987**, 85–127.

Scheme 12

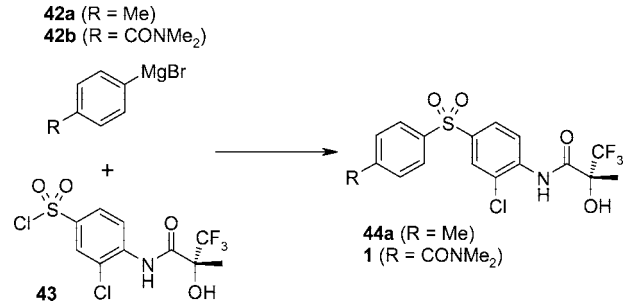


corresponding to the previously tentatively identified dimethylamide sulfone **40** (route 5.9, score 129). This thus established a connectivity between the two original starting materials, **31** and **32**. However, no further work was conducted due to the lack of time.

In summary, all the Friedel−Craft-based routes offered (on paper at least) short syntheses from cheap commercially available starting materials, and the highest scoring ones justified the effort invested in them. The key acylation step was accessible at the start of the syntheses, and the benzoic oxidation proved easier to achieve than anticipated. Furthermore, a high level of connectivity was shown between the various routes, including from sulfobenzoic acid **31**, which allowed a large area of overlapping reaction space to be investigated efficiently. However, all of these routes broke down due to the failure to introduce any worthwhile nitrogen atom selectivity into the aromatic ring, largely as a result of the low solubility of the dichloride **34b**, which was an otherwise accessible and stable intermediate.

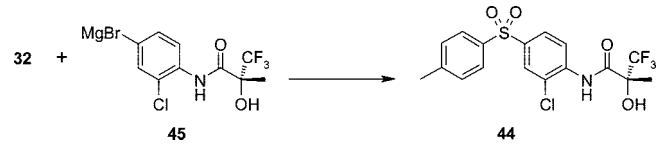
Grignard-Based Routes (Groups 6 and 7). The key step in these proposed routes relied upon a Grignard coupling with a sulfonyl chloride, for which there was some precedent.[24] The Grignard reagent could be either the magnesium Grignard of bromobenzamide (**42b**) or tolyl magnesium bromide (**42a**), which would require oxidation of the methyl group in product **44** (Scheme 13; cf. **34a/b** in Scheme 11); however, this latter transformation had been proven from related work above (see group 5 route discussion). Grignard attack was required on the sulfonyl chloride functionality in the coupling partner, which effectively also required the protected aniline functionality to be compatible with the Grignard reagent. Without resorting to a protection−deprotection sequence, the obvious protecting group was the chiral acid fragment, giving compound **43** (which coupled with **42b** would give **1** directly) (Scheme 13, group 6 routes). However, this required introducing the chiral acid at the start of the sequence to protect the aniline functionality, which was obviously undesirable, whilst leaving the aniline unprotected was judged to be unfeasible.

Scheme 13



The group 7 routes simply reversed this strategy by making the Grignard reagent of the protected aniline **45** and coupling that with tosyl chloride (**32**) to also give **44** (Scheme 14, group 7 routes). Again, the use of the unprotected aniline was judged to be unfeasible, whilst use of the chiral acid as the protecting group so early in the synthesis was undesirable. All of these routes scored well on environmental and plant accommodation factors (AstraZeneca has suitable pilot plant facilities and experience for cryogenic Grignard-type reactions) and were moderately short sequences. However, those routes that passed the "must" criteria for feasibility did not score highly in this area under "wants", and their cost scores were also moderate.

Scheme 14



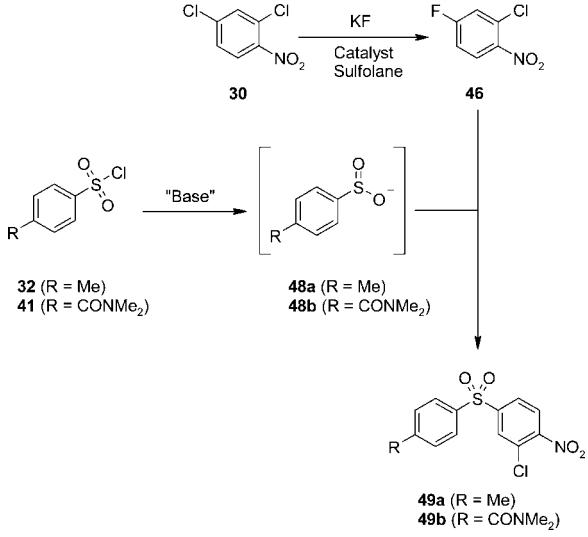
Given the concerns over their feasibility and their moderately low overall scores (103−116 for those scored), no laboratory work was undertaken on them. However, it should be noted that this work largely preceded publication of the Knochel-type

(24) Gilman, H.; Fothergill, R. E. *J. Am. Chem. Soc.* **1929**, *51*, 3501–3508.

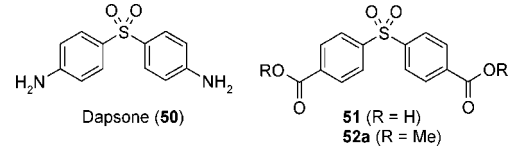
Grignard chemistry, which might now make both group 6 and 7 routes viable alternatives.

Sulfinic Acid Routes (Group 8). These three routes had as their key step the formation of the sulfinic acid anion (**48a/b**), which was to be used as the nucleophile in an S_NAr displacement of 2-chloro-4-fluoronitrobenzene (**46**), available by halogen exchange[25] from cheap and commercially available 2,4-dichloronitrobenzene (**30**) (Scheme 15). Oxidation and dimethylamide formation from **49a**, followed by reduction of the nitro group and addition of the chiral acid gave route 8.1 or, with these steps paired the opposite way round, route 8.3. Route 8.2 used the preformed dimethylamide sulfinate anion (**48b** from **41**) to give another variation (**49b**). Although these routes passed all the "must" criteria and scored well on cost, overall they scored towards the bottom end of the range (70−101), mainly due to a concern over their chemical feasibility, although environmental issues and longer reaction sequences also contributed. Given the low K-T scores, they were not investigated even though the key steps were near the beginning of the synthesis; only a limited number of routes could be investigated, and the larger group 5 routes were chosen instead.

Scheme 15

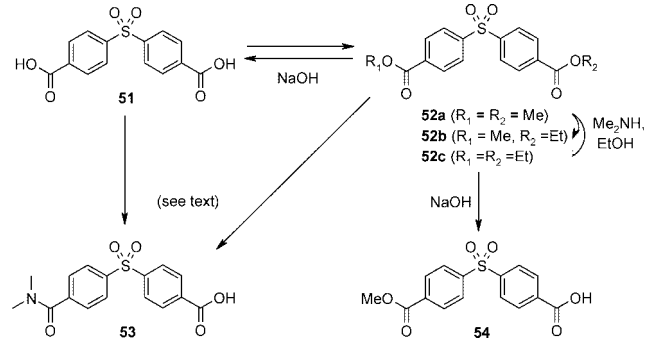


Symmetrical Bis-aryl Sulfone Routes (Group 9). These routes were initially inspired by the idea of using the commercially available antibacterial agent, Dapsone,[26] (**50**) as a starting material for AZD7545 (a late suggestion, not incorporated into the initial KTDA process, was to rely on a statistical monodiazotisation and then displace the diazo group with a halide, followed by a Pd-catalysed carbonylation).[27] Even so, some other related symmetrical difunctional molecules were also commercially available on large scale and at low cost, which looked like attractive targets, particularly the 4,4′-sulfonylbis(methyl) benzoate (**52a**) and its parent diacid, 4,4′-sulfonyldibenzoic acid (**51**), although the diester was only available in 90% strength. If these could be differentially functionalized, then the routes might be viable. The K-T analysis gave the best route (9.1) a medium score of 118 initially. However, given that this cluster of routes (9.1−9.4) was distinctly different from other clusters and the raw materials were cheap and commercially available, and if the regioselectivity issues could be investigated early on in the process (which we thought they could), then some investment of effort would be justified. We decided to investigate them further on this basis.



A simple amide-ester exchange of the dimethyl ester (**52a**) with Me_2NH/ethanol in DMF could not be made to work under standard or forcing conditions, and resulted only in ester exchange to the mono and diethyl esters (**52b/c**) (Scheme 16). Treatment with a large excess of aqueous Me_2NH solution in NMP gave a product tentatively identified as the desired amide ester (**53**). However, this did not coelute on LC with the previous sample made (prepared by methanol quench of the acid chloride derived from the amide acid **56a**; see below). Monohydrolysis from diester **52a** to acid ester **54** was also unsuccessful, giving mainly the completely hydrolysed diacid **51**. Further work on these approaches was stopped at this point, due to the timing of the project. Given the problems with the solubility of these compounds and the inability to address the regioisomers issues, these routes did not look as promising as first hoped.

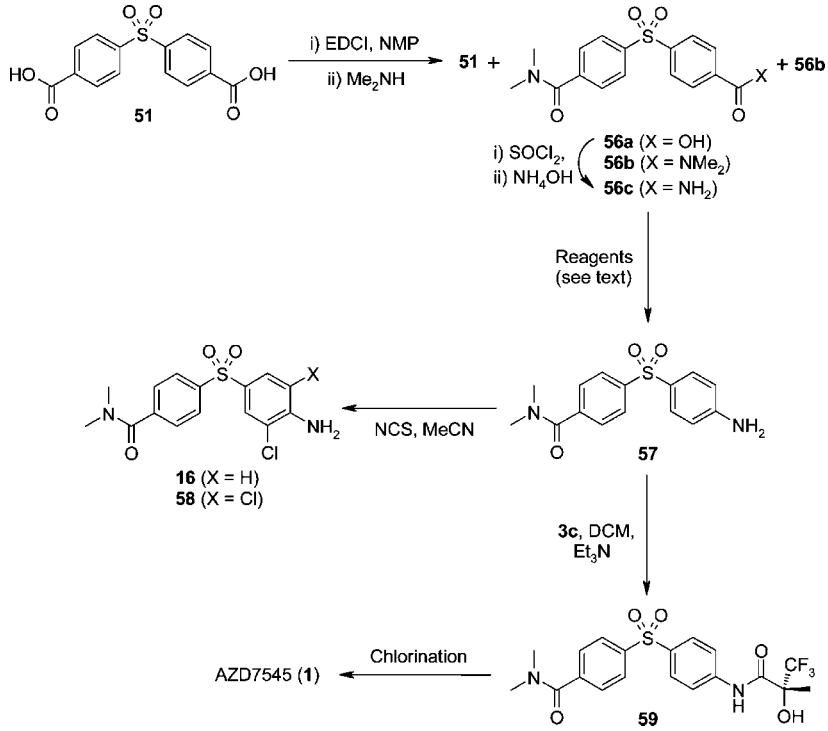
Scheme 16



The diacid **51** was prepared initially on laboratory scale by complete saponification of the diester **52a** but was also potentially available on scale from a commercial source. Attempted formation of the monoamide acid with thionyl chloride and dimethylamine was unsuccessful. However, using EDCI coupling of Me_2NH in NMP with diacid **51** gave a largely statistical mixture of unreacted diacid, desired amide-acid (**56a**) and doubly reacted diamide **56b** in ~3:4:2 ratio, respectively (Scheme 17). The isolated yield of **56a** was only 30% due to problems with the purification and relatively high losses to the aqueous NMP liquors. Conversion to the primary amide **56c** under standard conditions ($SOCl_2$, NH_4OH, NMP) appeared to be nearly quantitative, but again high losses to the liquors resulted in a yield of only 35%. Various standard reagents to achieve the Hofmann rearrangement all failed. For example, alkaline NaOCl at 80 °C gave diacid **51**, presumably by base

(25) Yoshida, Y.; Kimura, Y.; Tomoi, M. *Chem. Lett.* **1990**, 769–772.
(26) *The Merck Index*, 14th ed.; O'Neil, M. J., Ed.; Merck and Co., Inc.: Whitehouse Station, NJ, 2006.
(27) Earley, W. G.; Oh, T.; Overman, L. E. *Tetrahedron Lett.* **1988**, 3785.

Scheme 17



hydrolysis;[28] bromine in NaOH gave no reaction;[29] as did NaOBr generated in situ and other reagents. However, the use of $BzMe_3NBr_3$ did give a 35% yield of the desired aniline **57**.[30] An initial attempt to introduce chlorine using NCS in acetonitrile[31] gave a 3:2 mixture of products by LC, later confirmed by spectroscopy as the desired mono- and undesired dichloroamines (**16** and **58**), in an overall 30% isolated yield. Addition of the chiral acid portion to aniline **57** to give **59** might have tempered the reactivity sufficiently to give the desired monochloride (i.e., **1**), but similar chemistry had proven more difficult than expected when attempted by our medicinal chemistry colleagues. Furthermore, the route selection phase of the project had run out of time by this stage. Total time spent on these stages, which had been plagued by solubility and isolation issues, was about 3−4 months. Overall, whilst there was some scope for improving these stages, unresolved regioisomer ratios combined with low solubility and poor yields throughout meant that considerable effort would be required to resolve these issues. Consequently, no further work was conducted on these route options.

Conclusions

In summary, KTDA worked well in this first case to focus limited resources on the investigation of potential new manufacturing routes where a large number of potential route options existed. The use of the spreadsheet (Table 2) as a living document kept resources appropriately focused on promising avenues of investigation, and allowed new data to be incorporated into the analysis without having to restart the whole procedure. However, since this was the first example, some learning points were made:

•The "must" criteria were generally easy to decide and assess, as they have to provide clear-cut yes/no answers. However, the failure to include IP was an oversight (although it had subconsciously been taken into account), and this was rectified in all following examples.[5]

•Cost of goods. The approximation of using solely the cost of chiral acid **2**, in combination with the expected yields through the syntheses, worked well in this case where cost of goods was a major issue. However, we were fortunate that the cost of chiral acid was such a dominant factor and could be used in this way. In the more typical case, determining the cost is likely to be much more complicated (although it is likely that a small number of raw materials and reagents will account for much of the cost so that worthwhile approximations can still be made). In other cases, the dosage may be low or the therapeutic gain high (e.g., for oncology projects), such that the cost of goods can largely be ignored.

•Chemical feasibility. The calculation to try and assess the yield and confidence of achieving it was the only parameter that was too complicated in this KTDA exercise. Chemical feasibility had been given the highest weighting in the "wants" criteria and so was judged worth assessing in this way. In retrospect, this procedure was too complicated and time-consuming and not always of value, depending on what the data was based on. Known figures based on exact or similar reactions were probably worthwhile; those where a more subjective judgment was required (even though this was performed as a team exercise) were probably of much less value. In future projects it was decided to use a simple tally of the number of stages and apply a higher weighting to this to compensate. This procedure has been found to be

(28) Harvey, I. W.; McFarlane, M. D.; Moody, D. J.; Smith, D. M. *J. Chem. Soc., Perkin Trans.* **1988**, *1*, 1939–1943.
(29) Lalezari, I.; Lalezari, P. *J. Med. Chem.* **1989**, *32*, 2352–2357.
(30) Kajigaeshi, S.; Asano, K.; Fujisaki, S.; Kakinami, T.; Okamoto, T. *Chem. Lett.* **1989**, 463–464.
(31) Nickson, T. E.; Roche-Dolson, C. A. *Synthesis* **1985**, 669–670.

Table 3. **Final KTDA data on 04 May 2001**

route no.	route description (name)	musts: chemical feasibility	musts: raw materials	go/no go	initial score	initial rank	final score	change in score	final rank[a]
Initial Routes									
1.1	medicinal chemistry route	1	0	no	95	34	98	+3	n/a
1.2	initial contractor's route	1	1	no	98	31	98	0	n/a
Campaign 2 Route Variations									
2.1	contractor's campaign 2 route	1	1	**yes**	144	**1**	144	0	**2**
2.2	with catalytic Pd	1	1	**yes**	139	**3**	139	0	**3**
2.3	with catalytic other metal	1	1	**yes**	124	**9**	124	0	**5**
2.4	nonmetal route	1	1	**yes**	132	**6**	132	0	**4**
2.5	with oxidation first	0	1	no	134	**4**	58	−78	n/a
2.6	nitro thiol route	1	1	**yes**	93	35	93	0	n/r
Alternative Leaving Group Variations									
3.1	diazonium LG	1	1	**yes**	102	25	106	+4	n/r
3.2	tosylate LG	1	1	**yes**	119	12	119	0	n/r
3.3	nitro LG	0	1	no	143	**2**	114	−29	n/a
3.4	nitrile route	1	1	**yes**	130	**7**	146	+16	**1**
Selected Other Route Options									
4.1	quetiapine-type best route	1	0	no	134	**4**	124	−10	n/a
5.4	tosyl chloride and aniline	0	1	no	111	16	100	−11	n/a
5.6	typical tosyl chloride based route	1	1	**yes**	104	23	111	+7	n/r
5.9	sulfobenzoic acid and aniline	0	1	no	129	**8**	112	−17	n/a
6.2	tolyl grignard with Protected Amide	1	1	**yes**	103	24	105	+2	n/r
7.2	protected aniline Grignard	1	1	**yes**	107	19	108	+1	n/r
8.3	sulfinic acid (lowest scored route)	??	1	??	70	38	71	+1	n/a
9.1	best bis-aryl sulfone route	1	1	**yes**	118	13	114	−4	n/r

[a] n/a = not applicable; n/r = not ranked.

a better guide for the level of effort required,[5] given that certainty cannot be known in any case.

These modifications were applied to the following PDKi project, along with other factors specific to those compounds.[5]

In retrospect, we felt that the KTDA process had led us to the correct routes. Leaving aside the "must" criteria, which some "paper" routes clearly failed when investigated in the laboratory, the summary of "wants" scores were generally a good guide. For example, both of the first two medicinal chemistry routes (1.1−1.2) scored low against process chemistry criteria used for the KTDA. However, what was essentially a step reorder in the tactical contractor's improved route (2.1), maintained its high score throughout the process, justifying its use for the 10 kg campaign and consideration for future manufacture. Variations on this (routes 2.2−2.6) were clearly justified, as were the similar group 3 routes. The eventual best route (3.4) chosen for the following pilot plant scale manufacture did end up with the highest score, albeit essentially equivalent to the kilo-scale route (2.1). However, other aspects such as robustness and ease of workup identified route 3.4 as significantly better overall. These factors were not scored by KTDA (the ease of workup for example could not have been known), but KTDA did highlight this route as one of the better ones, and it is gratifying that this route was genuinely the highest scoring at the end of the process based on the initial parameters chosen. Other routes (such as the promising route 3.3) could not be made to work and so dropped out of the process at an early stage.

The scores for the sulfobenzoic acid/tosyl chloride routes (group 5) and the symmetrical bis-aryl sulfone routes (group 9) suggested they were not really good enough to investigate, and they did not improve over the period, as shown in Table 3. Both groups of routes failed largely due to regiochemistry and solubility issues, the latter of which were not (and perhaps could not have been) foreseen. Thus the group 5 routes failed the "must" chemical feasibility criteria, which the group 9 routes passed in principle, but in practice the lack of beneficial solubility removed the possibility to resolve the failings of the regioselectivity. In both cases though, investigation was still felt to be justified because the key steps lay at the beginning of the synthesis and represented alternative chemical approaches to the same target molecule.

It is noteworthy that the eventual route chosen for long-term manufacture (3.4) was the only route that significantly improved its score (to 146), whilst most other routes either failed "must" criteria or tended to decline in their scores. The contractor's second route (2.1) did maintain its place, which indicated this too was a viable long-term alternative.

Finally, regarding the time requirements of the process (other than literature searching, which would have been performed anyway), the team of six invested about 4 h for the initial meeting. After this, the lead chemist probably invested a couple of days to process the data. The spreadsheets had to be composed from scratch in this first instance, but once prepared, the monitoring process was simple, and later projects benefited from the initial development effort. This approach has been reused about half a dozen times locally (in full) and in abbreviated form more widely. It is more useful on projects with a large number of route options; the effort involved (which must be admitted is substantial) is repaid less on more constrained targets where the route options may be more obviously limited (e.g., by competitor IP, raw materials availability, structure of the molecule). However, there is also value

in getting the team to accept ownership of the decision-making process, so there are additional benefits in all cases.

Summary. Overall, the use of KTDA for route assessment led to the selection of a new route for the pilot plant campaign (10 kg) and longer term manufacture (>100 kg), which will be discussed in more detail in a subsequent paper. In conclusion, the route selection exercise worked well in this case where a large number of potential routes were to be considered using limited resources. It was also an effective means of bringing some long-term manufacturing issues to the fore at an early stage in development.

Experimental Section

General Note. Because of the nature of this project, it is neither practical nor profitable to reproduce here the full experimental detail for each reaction attempted. The experimental procedures that follow are therefore representative of those reaction steps that were reproduced more often and on larger scale, generally from the group 2 and 3 route options. In a similar vein, physical and spectral data is not included since products of various qualities (and in some cases uncertain identities) were taken through reaction sequences to prove a particular point. If that reaction sequence was then discarded, time did not permit complete characterizations to be obtained. Full data is available for the more thoroughly investigated group 2 and 3 routes, and this will be reproduced in full in a following manuscript. Full experimental details can in any case be found for the early (group 1) routes in the medicinal chemistry patent.[1] Procedures are given for the most reliable processes on large laboratory scale at an early phase in the KTDA process.

General Procedures. Reaction mixtures and products were analysed by reverse phase HPLC on Hewlett-Packard 1050 or 1100 instruments, generally with an eluent of acetonitrile/water mixtures at a flow rate of 1.0−1.5 mL/min and a wavelength of 230−254 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 400 spectrometer at 400 and 100.6 MHz, respectively, with chemical shifts given in ppm relative to TMS at $\delta = 0$. Electrospray (ES^+) mass spectra were determined on a Micromass LCT with time-of-flight. Analytical TLC was carried out on commercially prepared plates coated with 0.25 mm of self-indicating Merck Kieselgel 60 F_{254} and visualised by UV light at 254 nm. Preparative scale silica gel flash chromatography was carried out by standard procedures using Merck Kieselgel 60 (230−400 mesh).

Preparation of Thiocyanate (10). [**Important note:** the following description is given as typical of a laboratory-scale preparation of thiocyanate **10** at the beginning of the project during the route exploration stage and was safe in our hands on this scale. **There is a significant interaction between bromine and alcohols as noted in Bretherick**,[32] **and the procedure reported here should (preferably) not be reproduced at all and certainly not be scaled up further.** A safe alternative procedure will be reported in a planned later manuscript]. 2-Chloroaniline (**9**) (50.0 g, 392 mmol) was dissolved in methanol (500 mL, 10 vol) and cooled to 0 °C, and sodium thiocyanate (63.6 g, 784 mmol, 2.0 equiv) added in two portions with stirring (a 2−3 K exotherm was observed on this scale in the laboratory). In a separate reactor vessel, sodium bromide (30.0 g, 291 mmol, 0.75 equiv) was added to methanol (150 mL, 3.0 vol) and cooled to 0 °C with stirring. Bromine (65.8 g, 412 mmol, 1.05 equiv) was added slowly to the second reaction vessel with stirring. (**Caution:** a 20 K exotherm was observed on this scale in the laboratory.) Both reaction mixtures were recooled to 0 °C, and the bromine/methanol solution was added slowly to the first reaction mixture (thiocyanate/aniline) over 1.5 h with stirring, maintaining the temperature at 0−5 °C. The combined reaction mixture was allowed to warm to 20 °C over 2−3 h. Water (1000 mL, 20 vol) was added slowly with stirring, resulting in an 8 K exotherm, and a dense precipitate about halfway through the addition. The mixture was stirred for 1.5 h, and then solid sodium bicarbonate (70 g, 833 mmol, 2.1 equiv) was added in portions (**Caution:** vigorous effervescence; CO_2 released). Once the effervescence had subsided, toluene (500 mL) was added, and the mixture was stirred for 30 min and then filtered to remove excess sodium bicarbonate. Methanol was distilled from the solution under partial vacuum (40 °C at 250 mmHg) until 500 mL of distillate had been collected. Further toluene (500 mL) was added, and the distillation was repeated, collecting another 500 mL of distillate. The lower aqueous phase was removed, and water was added, stirred for 20−30 min, and then separated off. The residual toluene phase was concentrated to 3 vol (150 mL) by distillation, whereupon a solid crystallized. The reaction liquors were cooled to 0 °C, and the solid was isolated by filtration and dried to give the title compound as an off-white to pale yellow solid in typically 75−90% yield and 95% purity (as determined by HPLC).

Preparation of 4-Bromobenzamide (12). [Note: the medicinal chemistry route and early work on the KTDA were conducted using oxalyl chloride instead of thionyl chloride, but the latter became the preferred method during the KTDA route selection process. Ironically, oxalyl chloride was preferred again for larger scale manufactures]. 4-Bromobenzoic acid (**11**) (50.0 g, 249 mmol), toluene (417 mL), and NMP (2.1 mL, 21.6 mmol 0.087 equiv) were charged to a nitrogen-flushed vessel and heated to 60 °C with stirring. Thionyl chloride (31.1 g, 261 mmol, 1.05 equiv) was added dropwise over 15−30 min (caution: gas evolution), and the reaction mixture stirred at this temperature for 6 h and then cooled to 0 °C for 30 min. Dimethylamine in ethanol (89 mL of a 33% solution (5.6 M), 498 mmol, 2.00 equiv) was added smoothly over 1 h maintaining the temperature below 5 °C and then stirred for 2 h before warming to RT. The reaction mixture was quenched with aqueous HCl (560 mL of a 1.0 M solution), carefully at first, and then mixed thoroughly for 30 min once the addition of HCl was complete before settling. The lower aqueous phase was separated off, and the organic phase was washed with water (250 mL). After removal of the water wash, the reaction liquors were heated to 40 °C, and the volume was reduced to 3 vol (~150−200 mL) by distillation of toluene at reduced pressure. The reaction mixture was cooled again to 0 °C, and after 2 h at this temperature, the crystalline product was isolated by filtration and dried in a vacuum oven at RT to give the known compound **12** as a low melting waxy solid in typically 75% yield and >95% purity as determined by HPLC.

(32) *Bretherick's Handbook of Reactive Chemical Hazards*, 6th ed.; Urban, P. G., Ed.; Butterworth-Heinemann: Oxford, 1999; Vol. 1.

Preparation of Sulfide Aniline (15). Thiocyanate (**10**) (4.0 g, 21.6 mmol) was dissolved in DMF (80 mL, 20 vol) with stirring. In a separate vessel, sodium sulfide nonahydrate ($Na_2S \cdot 9H_2O$) (6.24 g, 26.0 mmol, 1.20 equiv) was dissolved in water (20 mL, 5.0 vol) with stirring (**Caution:** an 18 K exotherm was observed on this scale in the laboratory). This alkaline solution was added to the first reaction mixture over 10 min, resulting in a 2−3 K exotherm on this scale. The reaction mixture was heated to 50 °C for 2 h and then concentrated to 10 volumes (40 mL) by distillation to drive off the residual water (as determined by Karl Fischer measurement). The distillate was replaced with fresh DMF (40 mL, 10 vol). Copper(I) oxide (0.31 g, 2.16 mmol, 0.10 equiv) and 4-bromobenzamide (**12**) (4.94 g, 21.6 mmol, 1.00 equiv) were added, followed by further DMF (80 mL, 20 vol), and the reaction mixture heated to 150 °C for 6 h. If >75% sulfide aniline was detected by HPLC, with <5% of **12** and dimeric **14b**, the reaction mixture was cooled to 40 °C and filtered through a pad of Celite (if not, heating continued until these criteria were met). Water (540 mL, 135 vol) was added slowly to the dark brown filtrate over 30 min (an 18 K exotherm was observed on this scale in the laboratory), and the reaction liquors were then reheated to 50 °C for 1 h, before cooling back to 0 °C for 2 h, during which time a brown solid had formed. The product was isolated by filtration and dried in a vacuum oven at 40 °C to give the title compound **15** as a brown solid in typically 60−70% yield and ∼90% purity as determined by HPLC. This subsequently had to be recrystallised from ethyl acetate for further use.

Preparation of TMS-Protected Chiral Acid Chloride (3a). Chiral acid **2** (45.0 g, 285 mmol), dichloromethane (675 mL), and DMF (0.56 mL, 7.2 mmol 0.025 equiv) were charged to a nitrogen-flushed vessel and stirred for 10 min. Bis-TMS urea (75.7 g, 370 mmol, 1.30 equiv) was added in portions over 15 min, and the reaction mixture was stirred at RT for 4−8 h until >95% conversion of the di-TMS-protected intermediate had formed (by GC). The reaction mixture was filtered to remove the insoluble urea precipitate that had formed, and the resulting solid was washed twice with dichloromethane (298 mL each). The washes were added to the reaction liquors and charged to a second nitrogen-inerted vessel and cooled to 0 °C. In a separate vessel, oxalyl chloride (29.8 mL, 342 mmol, 1.20 equiv) was dissolved in dichloromethane (90 mL) and then added to the reaction mixture over 15−30 min. The reaction mixture was stirred at 0 °C for 2 h, allowed to warm to RT over 2 h, and stirred at RT for 2 h. If the reaction was >95% complete by GC, the mixture was filtered to remove any residual urea that had formed and stored cold in a sealed vessel. Alternatively, **3a** could be isolated neat after distillation under reduced vacuum at 175−250 mbar and 30 °C (to remove dichloromethane but avoid loss of the volatile product) as a pale yellow oil. The strength of the dichloromethane solution was assayed against a purified sample. The typical overall yield was 80%.

Preparation of Crude TMS-Protected Sulfide Anilide (13a). Sulfide aniline (**15**) (100 g, 326 mmol) was dissolved in dichloromethane (220 mL, 2.2 vol) and triethylamine (131 mL, 95.3 g, 942 mmol, 2.90 equiv) and cooled to 0 °C. TMS-protected acid chloride (**3a**) (105 g in 2000 mL of dichloromethane, 422 mmol, 1.30 equiv), prepared shortly before required use, was added over 1 h keeping the temperature below 5 °C. The reaction mixture was allowed to warm to RT over 6 h, and then dichloromethane was distilled off, collecting ∼920 mL distillate. Aqueous HCl (1300 mL of a 2 M solution) was added, and the reaction mixture was stirred for 30 min. The lower organic phase was separated off, and further water was added (1300 mL) and stirred for 30 min. The organic phase was separated off again and concentrated to dryness to give the title compound as a sticky solid/gum in typically 75−80% yield, which was used without further purification.

Preparation of Crude AZD7545 (1). Glacial acetic acid (150 mL, 1.5 vol) was used to wash crude TMS-protected sulfide anilide (**13a**) (325 mmol scale) into a reaction vessel containing further glacial acetic acid (400 mL, 4.0 vol). Hydrogen peroxide (35 wt % solution, 307 mL) was added, and the reaction mixture was heated to 90 °C for 3 h. Water (1330 mL, 13.3 vol) was then added over 30 mnutes, and the reaction mixture was cooled to RT. Dichloromethane was added (2050 mL, 20.5 vol), and the reaction mixture was stirred for 30 min before separating off the lower organic phase. This was washed with sodium bicarbonate solution (2050 mL) for 30 min, separated, and washed with water (2050 mL) for 30 min before being separated off again. The organic phase was concentrated to dryness to give crude AZD7545 as a sticky solid/gum in typically 75−80% yield and >90% purity as determined by HPLC.

Preparation of Friedel−Crafts Product (34b).[19] Iron(III) chloride (8.6 g, 53.2 mmol, 1.05 equiv) was added to a dried nitrogen-purged reaction vessel fitted with a condenser, mechanical stirrer and acidic gas scrubbing apparatus. Tosyl chloride (**32**) (10.2 g, 56.0 mmol, 1.10 equiv) was added under a nitrogen purge, followed by dichlorobenzene (**33b**) (7.5 g, 51.0 mmol). The reaction mixture was heated to 100 °C with mechanical stirring, during which time acidic gases were released. After 2 h, all of **33b** had been consumed. The reaction mixture was cooled slightly, aqueous sodium hydroxide was added (1 N, 25 mL), and the mixture reheated to 100 °C briefly to destroy any excess **32** remaining. The reaction mixture was cooled to RT, ethyl acetate (100 mL) and water (75 mL) were added, and extractionwas attempted, which had a poor phase separation. Sodium chloride (20 g) was added, and the mixture was shaken vigorously, but the separation did not improve, so the mixture was filtered through a pad of Celite, which gave two clear phases. The organic phase was washed with dilute brine (50 mL), separated, dried over $MgSO_4$, and concentrated to dryness under reduced pressure to give a yellow-brown oil that crystallized on standing. (15.6 g). The crude product was recrystallised from hot MTBE (100 mL) and iso-hexane (60 mL) to give the title compound **34b** as a yellow-brown solid (4.8 g, 31%).[20] A second crop was obtained from the mother liquors (2.2 g, 14%), giving an overall yield of recrystallised **34b** of 7.0 g (45%).

Preparation of Benzoic Acid (38). Friedel−Crafts product (**34b**) (6.03 g, 20.0 mmol), potassium permanganate (15.8 g, 100 mmol, 5.0 equiv) and potassium bicarbonate (4.0 g, 40.1 mmol, 2.0 equiv) were charged to a reaction flask followed by

tert-butanol (22 mL) and water (22 mL). The resultant purple solution was heated to 100 °C (**caution:** vigorous effervescence initially) for 24 h to give a colourless solution and a sticky dark solid. The reaction mixture was cooled to RT, sand (25 g) was added, and the mixture was filtered. The residual sand/MnO_2 solid was rinsed with *tert*-butanol/water (1:1, 50 mL), and the combined filtrates were filtered through a small pad of Celite to remove final traces of MnO_2 to give two clear phases. This reaction solution was used to investigate several alternative workup procedures involving acid and base washes, extractions, and crystallisations. The overall yield of the title compound **38** obtained as a solid was 5.8 g (88%) by these various techniques.

Acknowledgment

J.D.M. thanks Danny Levin for helpful discussions at the start of this project and Kepner-Tregoe for their support in presenting this case history.

Received for review February 14, 2008.

OP800033C