Organic Process Research & Development **2009,** *13,* 303–309

Process Development and Scale-Up of a PPARγ Agonist: Selection of the Manufacture Route

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Abstract:

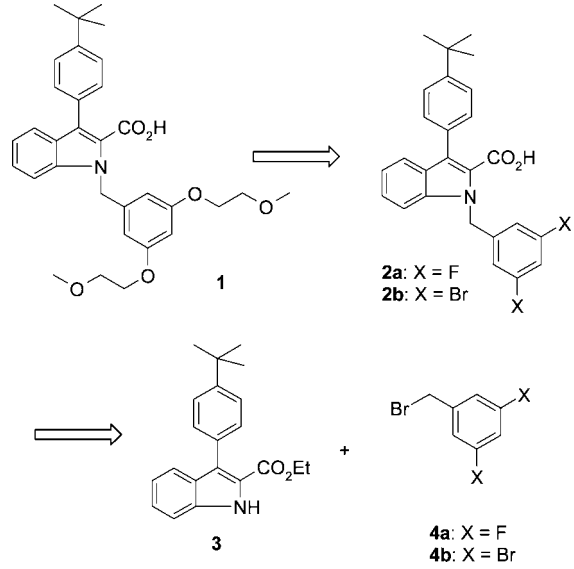
Two short, high-yielding routes to the selective PPARγ agonist GSK376501A were developed and carried out on scale. The key bond -forming reaction in each synthesis was the substitution of a 3,5-difluoro or 3,5-dibromo aryl intermediate with 2-methoxyethanol. A nucleophilic aromatic (S_NAr) substitution reaction under basic conditions was developed for the aryl fluoride substrate. The 3,5-dibromo aryl halide intermediate required copper-catalyzed conditions to achieve substitution of the second bromide. In addition, a 2-methoxyethanol decomposition pathway to generate methanol and ethylene oxide under basic reaction conditions as well as its effect on impurity formation, was elucidated. Both the difluoro and dibromo intermediates were considered as the basis for the final route of manufacture. The difluoro substrates were chosen due to straightforward chemistry, controllable impurity profile, and ease of fluoride removal.

Introduction

Activation of the nuclear receptor, peroxisome proliferator activated receptor gamma (PPARγ), has been shown to enhance insulin sensitivity and reduce plasma glucose levels, which have made it an attractive target for treatment of type 2 diabetes mellitus (T2DM). [1] Full agonists of the PPARγ receptor such as rosiglitazone and pioglitazone have been widely used to treat T2DM; however, potential side effects have limited their efficacy in some patient populations. Data in preclinical animal models suggest that selective PPARγ modulators (SPPARMγ) may provide the enhanced insulin sensitivity required for effective treatment of T2DM while avoiding or greatly diminishing the undesired side effects observed in some patients treated with a PPARγ full agonist.[2] GSK376501A (**1**) is a SPPARMγ molecule in development in our laboratories.[3]

Scheme 1 illustrates a convergent route to **1** which begins with the reaction of ethyl 3-[4-(1,1-dimethylethyl)phenyl]-1*H*-indole-2-carboxylate (**3**) with a commercially available dihalobenzyl bromide (**4a**, **4b**). The key transformation in the synthesis is an aryl halide displacement on **2a** or **2b** with 2-methoxyethanol. The final step is the recrystallization of intermediate grade **1** (**IG-1**) to generate final active pharmaceutical ingredient (API) (**1**).

Scheme 1. **GSK376501A retrosynthesis**



Both potential manufacture route starting materials (**4a** and **4b**) were carried through to final API on large scale in comparable overall yield (82%) and with comparable raw materials costs. The decision regarding which dihalo intermediates to utilize would be based on the development of efficient, high-yielding conditions for the coupling reaction and aryl halide displacement. Moreover, impurity generation, process simplicity, and waste stream differences would need to be taken into consideration.

The Stage 1 development work was initially performed using difluoro starting material **4a**, which was coupled to indole **3**, a synthesis of which has been carried out in our laboratories and described previously[4] (Scheme 2). Original reaction conditions utilized Cs_2CO_3 in DMF at elevated temperature to generate **5a**, followed by hydrolysis with 50% NaOH to yield **2a**. However, scale-up of these conditions highlighted potential mixing issues, as it was difficult to suspend the solid Cs_2CO_3 with overhead stirring, resulting in inconsistent reaction times and reaction stalling.

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10.1021/op800211c CCC: $40.75
Published on Web 12/05/2008

Scheme 2. **Stage 1**

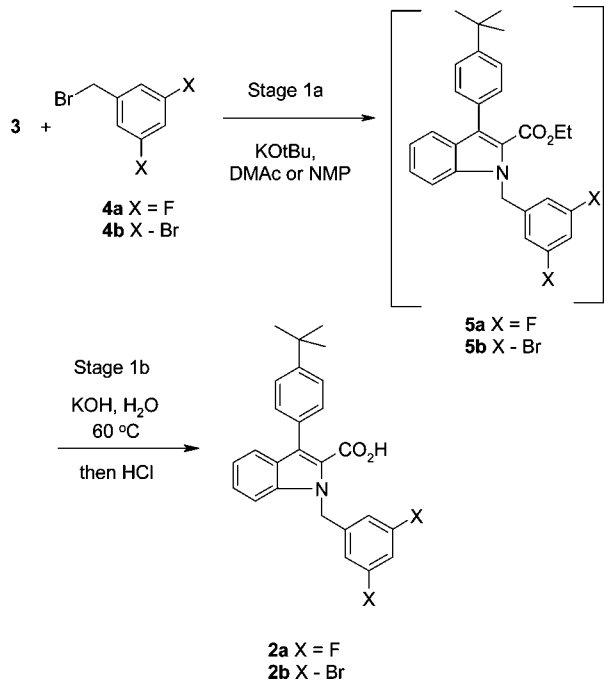


Table 1. **Solvent screen results using KOtBu and KOH for Stage 1**

entry	solvent	4a equiv	5 (HPLC area %)	2a (HPLC area %)
1	DMAc	1.0	85	87
2	NMP	1.0	90	96
3	DME	1.0	83	9
4	MTBE	1.0	74	36
5	MeCN	1.0	94	13
6	NMP[a]	1.0	82	90
7	DMAc	1.2	89	96

[a] Scale-up of conditions identified in screen.

Therefore, alternate bases were considered, and KOH, which provided 97% conversion to **2a**, was initially identified as promising. However, because of the potential for hydrolysis of **3** prior to the coupling reaction and the fact that the acid of **3** will not react with **4a**, a better choice of base for Stage 1a proved to be KOtBu. In DMF with KOtBu, the coupling was complete in 2 h at room temperature. The advantage of using KOtBu in place of high-molecular weight and relatively expensive Cs_2CO_3 was a homogeneous reaction mixture, which resulted in consistent, reproducible reaction times and obviated the need for mixing studies that would have been required on the heterogeneous reaction mixture if Cs_2CO_3 were to be used.

With optimized Stage 1a conditions in hand, we next turned our attention to Stage 1b, saponification of ethyl ester **5a**. A switch from 50% NaOH to aqueous KOH (1.2 equiv in 2 vol water at 60 °C) not only resulted in consistent Stage 1b reaction times but also prevented the precipitation of **2a** as a gummy solid during the isolation, which was an issue when NaOH was used.

The final Stage 1 variable examined was the effect of solvent on reaction performance using the KOtBu/KOH base system (Table 1). In all cases, **3** and KOtBu were premixed prior to addition of **4a**; which decomposes upon exposure to basic conditions. While Stage 1a proceeded with good conversion in numerous solvents, especially MeCN (entry 5), Stage 1b proceeded well in only *N,N*-dimethylacetamide (DMAc) and *N*-methylpyrrolidine (NMP), with NMP giving superior results (entries 1 and 2). Scale-up of the NMP conditions (entry 6), however, demonstrated that NMP remained in isolated **2a**, (up to 18 wt %) even when large volumes of water were used to wash the solid. Therefore, the reaction in DMAc was examined more closely, and an increase in the equivalents of **4a** (from 1.0 to 1.2) resulted in improved reaction performance in DMAc (Table 1, entry 7).

The Stage 1 product (**2a**) could be isolated from the reaction mixture by precipitation upon the addition of water followed by concentrated HCl. However, this resulted in a tendency for **2a** to form large lumps that were difficult to remove from fixed equipment. This issue was resolved by the slow addition of reaction mixture to 6 N HCl with maximum stirring in the reaction vessel.[5] The optimized reaction conditions and reverse addition were successfully carried out on 200-gal scale in 97% yield, and **2a** was generated as a free-flowing solid that could easily be drained from the reactors.

Not surprisingly, **4b** proved to have reactivity very similar to that of **4a** in Stage 1 (Scheme 2), and reaction conditions and workup were developed to synthesize **2a** successfully generated **2b.** Optimization work for the dibromo substrate included an increase in the amount of KOH (2.5 equiv) to achieve consistent hydrolysis reaction times and a solvent change to NMP. NMP provided a better yield (97% with NMP vs 84% with DMAc) and removal of NMP from the isolated solid could be easily accomplished when either a normal or reverse addition was used to precipitate the product. The optimized reaction conditions performed well to generate **2b** on 50-L scale.

The Stage 1 development and scale-up work demonstrated that both **2a** and **2b** could be generated in an analogous manner. Therefore, both were progressed into Stage 2 where the reaction conditions required for the aryl halide displacements differentiated the intermediates, and it was determined **2a** had significant advantages over **2b**.

Stage 2. Synthesis of IG-1 via Difluoro Intermediate 2a. Our approach to the synthesis of **IG-1** via **2a** involved an aryl fluoride displacement under basic conditions with the potassium alkoxide of 2-methoxyethanol (Scheme 3). As expected, the displacement of one fluoride to generate **6a** was facile since the fluoride in the Ar-5 position activates the ring towards the S_NAr reaction. Displacement of the second fluoride, on the now deactivated ring, proved to be more challenging; however, reaction conditions for the displacement of aryl fluorides on deactivated rings, similar to those previously developed in our laboratories,[6] could be employed on this system to generate intermediate grade **1** (**IG- 1**) (Table 2).

First generation conditions to synthesize **IG-1** via **2a** involved treatment of 2-methoxyethanol (20 equiv) with KOtBu (18 equiv) in toluene. Starting material **2a** was then added as a solution in toluene and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-

(5) It was later discovered that the reaction could be performed in NMP, and a reverse addition allowed for easy removal of NMP from the isolated material.

(6) Kim, A.; Powers, J. D.; Toczko, J. F. *J. Org. Chem.* **2006**, *71*, 2170.

Scheme 3. **Stage 2**

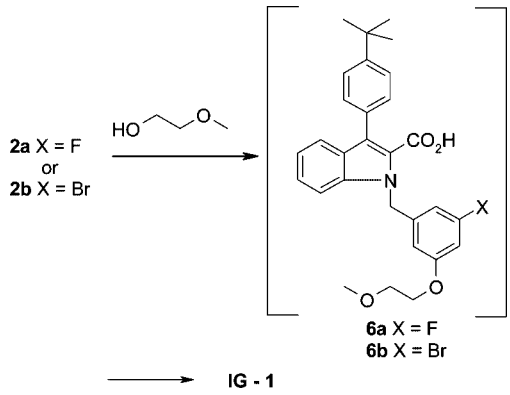


Table 2. **Optimization of fluoride displacement reaction**

entry	alcohol (equiv)	KOtBu (equiv)	temp (°C)	time (h)	yield (%)
1	20	18	80	12	80
2	5	4	110	12	76[a]
3	7	6	110	3	83

[a] Volume of alkoxide formation reaction reduced by 10−20% prior to addition of **2a** solution.

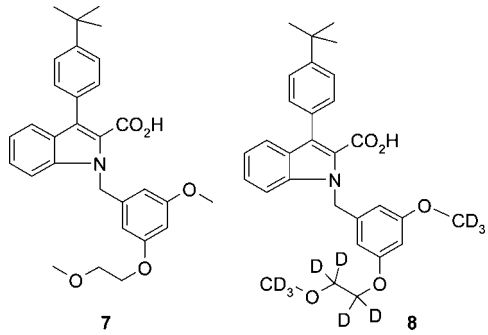


Figure 1. **Methoxide displacement impurity.**

pyrimidinone (DMPU) to the alkoxide solution with additional heating at 80 °C for 12 h (entry 1). The high alkoxide loading and long cycle time for the displacement were deemed necessary in order to keep the reaction temperature at 80 °C and still achieve complete conversion. At the time, we thought the lower temperature was required in order to minimize a byproduct which was tentatively identified as decarboxylated **1**. While not ideal, the advantage of the first generation process was its operational simplicity, and these conditions were successfully carried out on 50-L scale. Further development efforts focused on maintaining the operational simplicity while lowering the alkoxide loading. First, however, the structure of the purported decarboxylated impurity needed to be confirmed.

Mass spectrometric analysis and the synthesis of a marker showed that the impurity was, in fact, not decarboxylated product, but rather methoxy analog **7** (Figure 1) (*vide infra*). Since decarboxylation appeared not to be a major side reaction, we could now explore higher reaction temperatures. By increasing the reaction temperature, we reasoned that equivalents of base and alcohol could be significantly lowered, and this was indeed the case.

Second-generation conditions in the toluene/DMPU solvent system with a dramatically lower alkoxide loading were developed (Table 2, entry 2).[7] However, a distillation step after alkoxide generation and prior to addition of the **2a** solution was necessary to reduce the reaction volume in order to achieve complete consumption of intermediate **6a** at these lower equivalents. Although these conditions accomplished the goal of lowering alkoxide loading and were successful at 50-L scale, the distillation step increased both complexity and the cycle time of the process.

Third-generation conditions eliminated the distillation and reduced cycle times by reducing the toluene volume during the alkoxide formation and slightly increasing alkoxide equivalents, with complete conversion to **IG-1** in 3 h (Table 2, entry 3). Although the alkoxide loading was still rather high, it was deemed that these conditions were a good compromise between alkoxide loading versus cycle time and process simplicity.

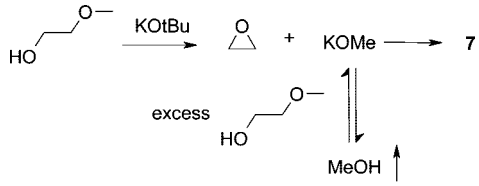
The final issues in the reaction development were in the workup and isolation. On pilot-plant scale, to avoid generation of HF and potentially etching glass-lined reactors, fluoride levels needed to be <20 ppm before the reaction mixture could be acidified. Therefore, highly efficient and effective workup conditions needed to be developed to remove the fluoride generated during the reaction, and a series of brine washes on the reaction mixture proved to be extremely effective. On laboratory scale, three washes at room temperature brought the fluoride in the organic layer to <0.5 ppm. The organic layer could then be heated to 60 °C and neutralized with 6 N HCl,[8] followed by addition of heptane to crystallize **IG-1**. Further development work focused on minimizing emulsion issues during the brine washes and ensuring that **IG-1** did not crystallize out of solution during the HCl wash. By increasing the temperature of the brine washes to 60 °C and diluting the organic layer with additional toluene prior to 6 N HCl addition, both the emulsion and crystallization issues were addressed. A final wash of **IG-1** with iPrOH removed any residual DMPU that was present in the isolated solid.[9] Optimized reaction and workup conditions were carried out on 100- and 200-gal scale in 83−85% yield. [10]

In the long term, the high volumes of brine required for fluoride removal could be an issue in regard to waste stream disposal; therefore, preliminary work, focused on reducing fluoride levels by filtration of KF and/or CaF_2 salts, was carried out. In laboratory-scale experiments, it was demonstrated that filtration of the reaction mixture, followed by treatment of the filtrate with aqueous $CaSO_4$ and filtration of the resulting CaF_2 salts reduced fluoride levels in the organic layer to <20 ppm. Acidification and isolation of **IG-1** could be performed as before.

Concurrent with reaction optimization work, experiments were performed to identify the source of impurity **7**. Understanding and controlling the factors that influence its formation

(7) Minimizing the amount of 2-methoxyethnaol used in the process was important from a green chemistry perspective since the compound is a tetratogen and reproductive hazard.
(8) Elevated temperature was required to keep **IG-1** in solution during the wash.
(9) ^{1}H NMR was used to monitor DMPU levels in isolated product.
(10) In some batches, a fourth brine wash was required to meet the <20 ppm target. This was likely due to a rag layer at the organic/aqueous interface during the phase splits that was retained in the reactor until the final wash.

Scheme 4. **Generation of Impurity 7**



were particularly important since **7** had been identified in final API synthesized by all processes at variable levels (0.3% to 1.1 area %).

The obvious first variable examined was the possibility that MeOH was present in the 2-methoxyethanol starting material. GC analysis of numerous 2-methoxyethanol batches showed that, in some cases, small amounts of MeOH were present, whereas in others none was detected. Surprisingly, when a MeOH-free lot was used in Stage 2, **7** was still observed by HPLC.

Based on these results, it seemed probable that MeOH was being generated over the course of the reaction, likely through the decomposition of 2-methoxyethanol (Scheme 4). Careful GC monitoring of the reaction mixture confirmed that MeOH is indeed produced during alkoxide formation. Additionally, ethylene oxide, the other decomposition product of 2-methoxyethanol, was detected using headspace GC/MS during alkoxide generation. Further evidence that the methoxide was generated from decomposition of 2-methoxymethanol was provided by treatment of **2a** with $CD_3OCD_2CD_2OD$. Mass spectrometric analysis indicated that **8** (Figure 1) was generated.

With a good understanding of the source of **7**, we next turned out attention to identifying the variables that control its formation. Both reaction temperature and nitrogen sweep were examined in a series of small-scale reactions at 80 and 110 °C, both in sealed tubes and with a nitrogen sweep.

At both temperatures **7** was generated; however, the sealed experiments showed higher levels of impurity than those with a nitrogen sweep (2−4 area % higher at 110 °C, and ∼1 area % higher at 80 °C)[11] The importance of nitrogen sweep was further confirmed on pilot-plant scale where it was demonstrated, with a static nitrogen blanket on the reactor headspace, levels of **7** in isolated **IG-1** were 1.7 area %. When performed with a headspace nitrogen sweep, levels of **7** in isolated **IG-1** were 0.13 to 0.65 area %.

Stage 2. Synthesis of IG-1 via Dibromo Intermediate 2b. Our initial approach to the synthesis of **IG-1** via intermediate **2b** was to perform the aryl bromide displacement under basic conditions similar to those employed for **2a**. However, while the displacement of the first bromide to generate **6b** was facile, conversion of **6b** to **IG-1** required very forcing conditions (20 equiv of alkoxide, toluene/DMPU, 65 h).[12]

We therefore turned our attention to metal-catalyzed processes to promote aryl bromide displacement on **6b**. Initially, the best procedure involved isolation of **6b**, followed by a copper-catalyzed reaction in DMF/DME using CuI (0.7 equiv), KOtBu (5.5 equiv), and 2-methoxyethanol (9 equiv) at 100 °C.

(11) The reactions carried out at 80 °C did not achieve complete conversion.
(12) The displacement reaction was also evaluated on the corresponding dichloro substrate. The reaction did not proceed to completion despite high alkoxide loadings and long cycle times.

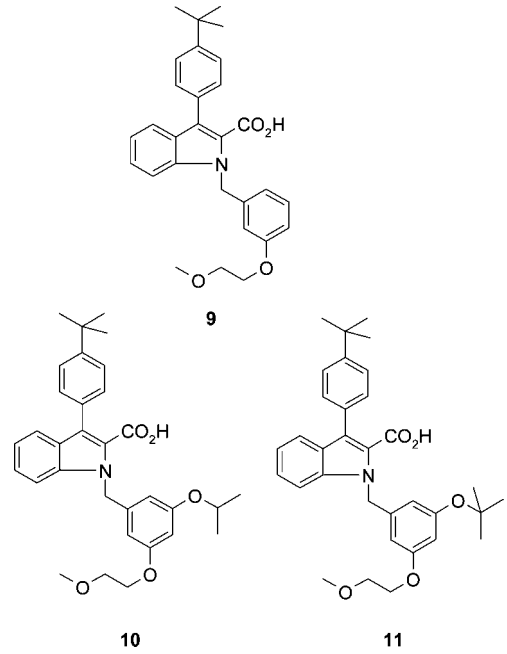


Figure 2. **Potential impurities generated in Stage 2 with 2b input.**

These conditions provided **IG-1** (74%) in addition to a desbromo impurity (**9**) (Figure 2). Although promising, the reaction required high copper loading for good conversion, and a significant amount of **9** (∼8 area %) was present. Additionally, we wanted to telescope both aryl bromide displacements into a single reaction, and when the above conditions were performed using **2b** as input material, incomplete conversion was observed after 17 h of reaction time. These reaction conditions, however, provided a good starting point with which to use design of experiments (DoE) to quickly and efficiently optimize the chemistry (Table 3).

The DoE studies started with a solvent and base screen, with the goal of maximizing formation of **IG-1** and minimizing **9**. Additionally, impurity **7** would be monitored since it was also generated under the reaction conditions. Solvents and bases were varied, while holding CuI (0.7 equiv) and 2-methoxyethanol (10 equiv) constant. Starting material **2b** was added to all reactions as a solution in DMF, since previous experiments in DME and DMAc demonstrated the copper-catalyzed reaction would not proceed in good conversion without it. The results of the screen indicated sodium *tert*-pentoxide was the best base, and the best solvents were diglyme and iPrOAc, which showed complete consumption of **2b** with no **6b** present (Table 3, entries 1 and 2). However, in iPrOAc, mass spectrometric analysis indicated a side product (**10**) (Figure 2), resulting from addition of isopropyl alkoxide to the aryl ring, was present. Because of the undesired side product, we chose to progress the diglyme/DMF solvent system into the next screen.

A second set of experiments was devised with the goal of optimizing reagent loadings and investigating the reaction space to determine if varying the reagent equivalents affected the generation of **9**. The amounts of 2-methoxyethanol, sodium *tert*-pentoxide, CuI, and temperature were varied while holding solvent (diglyme/DMF) constant. The DoE data, followed by a small number of single experiments, identified the best

Table 3. **Optimization of bromide displacement**

entry	solvent	sodium *tert*-pentoxide (equiv)	CuI (equiv)	alcohol (equiv)	temp (°C)	time (h)	**IG-1** (HPLC area %)	**9** (HPLC area %)	**10/11** (HPLC area %)
1	diglyme/DMF	6	0.7	10	90	16	88.7	2.1	NA
2	iPrOAc/DMF	6	0.7	10	90	16	72.0	5.4	**10**7.7
3	diglyme/DMF	7	0.1	8	90	2	88.2	1.1	NA
4	iPrOAc	7	0.1	8	80	3.5	82.6	2.1	**10**8.2
5	tBuOAc	7	0.1	8	85	12	90.6	1.1	**11**2.1
6	diglyme/DMF[a]	7	0.1	8	90	2	84.4	3.1	NA

[a] Scale-up of optimized conditions.

conditions as sodium *tert*-pentoxide (7 equiv), CuI (0.1 equiv),[13] and 2-methoxyethanol (8 equiv) (Table 3, entry 3). Moreover, under all conditions screened, the level of **9** impurity was <2.5 area %, and impurity **7** was present at levels comparable to those observed in the S_NAr reaction of **2a**.

With optimized reagent loadings in hand, a final set of experiments was carried out using the conditions in a variety of solvents without DMF. Interestingly, in the absence of DMF, the only solvents that provided good conversion to **IG-1** were iPrOAc and tBuOAc.[14] However, the corresponding alkoxide addition products were also generated (Table 3, entries 4 and 5). While changing to a less water-miscible solvent was attractive due to the expanded options for reaction workup, we chose to advance the diglyme/DMF solvent system for scale-up because it eliminated the potential for solvent addition impurities (Table 3, entry 6).

Upon completion of the reaction in diglyme/DMF, **IG-1** was isolated by cooling to 80 °C followed by the addition of iPrOH and water to dissolve the salt of the product, which had precipitated out of solution during the reaction. The inorganic solids were filtered off, and acidification of the filtrate resulted in crystallization of **IG-1**. The optimized reaction conditions and workup were carried out on 50-L scale in 75% yield.[15]

While our goals of optimizing the generation of **IG-1** and minimizing impurity **9** were accomplished and the process performed well on scale, utilizing **2b** in the manufacture route had several drawbacks including variability in levels of impurity **9** and potential long-term issues with dissolved copper levels in the waste stream.

Impurity **9** arises from reductive dehalogenation, a known side reaction in many copper-catalyzed processes.[16] With our substrate, the amount of **9** produced is highly variable, depending on the choice of base and solvent. For example, when NaOtBu is used in place of sodium *tert*-pentoxide in digylme/DMF, very high levels of **9** are observed (27 area %). However, in iPrOAc, **9** is present in ~2 area % (in addition to solvent-related impurity **11** in 13 area %) whether sodium *tert*-pentoxide or NaOtBu is used as the base. Therefore, although the formation of **9** appears to be controlled under the sodium *tert*-pentoxide, DMF/diglyme conditions, if future work required a solvent or base change, the impurity levels could also change. This is a particularly important consideration since **9** is not completely removed in the final recrystallization step.

In the reaction workup, >95% of the copper is filtered out of the reaction as a solid; however, dissolved copper levels in the waste stream would likely need to be lowered if the process progresses into a manufacturing setting. While Stage 2 can be carried out with lower CuI loadings, the resulting reaction rates are slower. Slower reaction rates are not ideal since experiments have indicated some variability in reaction time with the 0.1 equiv CuI loading, and in some cases the reaction required up to 3 h to proceed to completion. Changing the workup will be the most prudent solution to further reduce dissolved copper in the waste stream; however, the majority of the copper is precipitated from the solution using the current process, and reducing levels further, while maintaining minimal workup unit operations, will be difficult.

For these reasons, it was determined that the difluoro intermediate **2a** would be the optimal choice for incorporation into the final route of manufacture, and **IG-1**, synthesized via the fluoride displacement chemistry, was carried into the Stage 3 recrystallization studies.

Stage 3. Crystallization of IG-1. The Stage 3 recrystallization converts the intermediate grade **1** (**IG-1**) to final API (**1**) and was incorporated into the synthesis to ensure control over final API particle formation. Only a single anhydrous crystal form of **1** had been identified; therefore, recrystallization studies focused on throughput, mobility of the slurry upon crystallization of **1**, and the effect of impurities on the crystallization.

A small-scale solvent screen identified five promising solvents for the recrystallization: n-propanol, methyl isobutyl ketone (MIBK), MeOH, toluene, and 2-butanone. Two-point solubility data (Figure 3), volume of solvent required for dissolution, and the calculated expected yield were obtained (Table 4).

In the case of 2-butanone, reasonable yields could not be expected; therefore, it was eliminated from further study. Moreover, MeOH was eliminated due to the high number of volumes required for dissolution. A scale-up experiment using n-propanol required additional solvent volumes to facilitate mobility of the thick slurry. Because the throughput would be significantly decreased, n-propanol was also eliminated, and further work focused on toluene and MIBK.

Solubility curves in toluene and MIBK were generated using high purity **1** (>99 area %), and the data showed effective

(13) The reaction could tolerate as little as 0.05 equiv of CuI, with a reaction time of 4 h. The reaction also performs well with $Cu(OAc)_2$ as the catalyst.

(14) Toluene, THF, DMPU, 2-methoxyethanol, diglyme, NMP/diglyme all proceeded in <55% conversion.

(15) Copper levels in isolated **IG-1** were <1 ppm.

(16) (a) Lindley, J. *Tetrahedron.* **1984**, *40*, 1433. (b) Bacon, R. G. R.; Rennison, S. C. *J. Chem. Soc. (C)* **1969**, 308. (c) Bacon, R. G. R.; Rennison, S. C. *J. Chem. Soc. (C)* **1969**, 312. (d) Keegstra, M. A.; Peters, T. H. A.; Brandsma, L. *Tetrahedron.* **1992**, *48*, 3633.

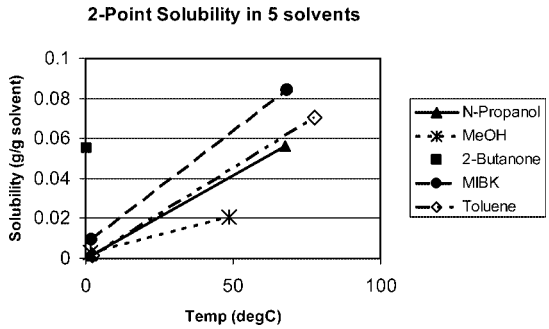


Figure 3. **Recrystallization. Two-point solubility data.**

Table 4. **Recrystallization screen results**

	temp range (°C)	dissolution volumes	yield[a] (%)
n-PrOH	2.0−68	22	98
MeOH	1.5−49	61	85
MIBK	1.9−68	15	89
toluene	2.2−78	16	98

[a] Calculated.

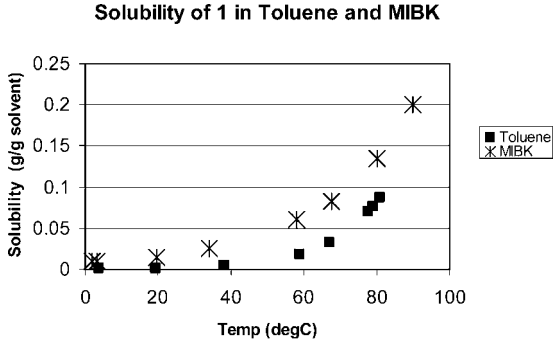


Figure 4. **Solubility curves in toluene and MIBK using high purity (>99 area %) 1.**

dissolution at 80 °C could be achieved with 15 volumes of toluene or 9 volumes of MIBK (Figure 4). Additionally, yields of >95% upon isolation at 0 °C were expected under these conditions, and both solvents gave a mobile slurry upon cooling to 0 °C. Using these set solvent volumes, metastable zone widths (MSZWs) for both solvents were approximated for these conditions by fully dissolving the solid, then cooling until the solids spontaneously nucleated. Both solvents had large MSZWs, 17 °C in toluene and 26 °C in MIBK, which indicated a wide temperature range for seeding.

At this point, both solvents were still considered good candidates for the final recrystallization, with MIBK at a small advantage due to slightly better throughput. Yields for both solvents using the best conditions were 94−96%, and experiments to examine the effect of impurities present in **IG-1** were necessary to make the final decision.

A batch of **IG-1** was selected and tested with both toluene and MIBK (Table 5). It was observed that a drop in the purity of **IG-1** (from >99 to 96−97 area %) had a noticeable effect on the solubility in MIBK, greatly increasing the solubility throughout the temperature range. This caused the seeds to dissolve, and the yield at 0 °C was much lower than the expected at 95%. Solubility in toluene was not greatly affected by the impurities, and the same dissolution volume, seed

Table 5. **Effect of Impurities on Recrystallization Yield**

	IG-1 input: 96.9 area %	
	yield (%)	purity (area %)
toluene	95	98.2
MIBK	84	98.7

window, and yield were employed as when pure **1** was used. As a result, in order to ensure a robust process regardless of variation in the impurity profile of the **IG-1**, toluene was selected as the solvent of choice for the crystallization.

Conclusions

Two efficient, high-yielding syntheses of GSK376501A were developed and carried out on scale. The key step in both syntheses was the development of conditions for the Stage 2 aryl halide displacement reaction, and the data collected during development and scale-up were used to select the API manufacture route.

The Stage 2 reaction conditions required for the conversion of **2b** into **IG-1** had several drawbacks including control of impurity profile and the presence of low levels of copper in the waste stream which would be unacceptable in the long term.

For intermediate **2a**, Stage 2 is a straightforward aryl fluoride displacement that is operationally simple, highly reproducible, and has performed well on a variety of scales ranging from 20 L to 200 gal. The workup is extremely effective in removing the fluoride generated in the reaction, and the impurity profile of **1** synthesized via **2a** has been consistent and controllable once the variables affecting the generation of impurity **7** were understood. For these reasons, the difluoro intermediates were selected for incorporation into the final route of manufacture.

Experimental Section

Recrystallization of 1-[(3,5-Bis{[2-(methyloxy)ethyl]oxy}-phenyl)methyl]-3-[4-(1,1-dimethylethyl)phenyl]-1H-indole-2-carboxylic Acid (1). A reaction vessel was charged with **IG-1** (50.0 kg, 1.00 equiv) followed by toluene (630 kg, 14.5 vol) and heated to 78−87 °C. When dissolution was observed, the reaction mixture was cooled to 70−74 °C, and a slurry of **IG-1** seeds in toluene (100 g of GSK376501A in 1.0 kg of toluene) was added. The reaction mixture was stirred for 1 h and then cooled to 0 °C over 2.5 h. The solids were filtered off, and the cake was washed with cold toluene (43.5 kg, 1.00 vol × 2) and dried under vacuum to give 49.0 kg (98% yield, 99.37 area %) of **1**.

^{1}H NMR: δ 1.34 (s, 9H), 3.25 (s, 6H), 3.57−3.59 (t, 4H, J = 4.5 Hz), 3.98−4.00 (t, 4H, J = 4.0 Hz), 5.75 (s, 2H), 6.23 (s, 2H), 6.39 (s, 1H), 7.11−7.14 (t, 1H, J = 7.5 Hz), 7.29−7.35 (ddd, 1H, J = 0.9, 7.0, 8.3 Hz), 7.38−7.49 (m, 4H), 7.48−7.51 (m, 1H), 7.58−7.61 (d, 1H, J = 8.5 Hz), 13.1 (s, 1H).

Preparation of 1-[(3,5-Bis{[2-(methyloxy)ethyl]oxy}-phenyl)methyl]-3-[4-(1,1-dimethylethyl)phenyl]-1H-indole-2-carboxylic Acid (IG-1). *Fluoride Displacement.* A reaction vessel was charged with KOtBu (80.5 kg, 6.00 equiv), toluene (130.5 kg, 3.00 vol), and 2-methoxyethanol (63.5 kg, 7.00 equiv). After the mixture was heated to 80 °C for 30 min, a solution of **2a** (50.0 kg, 1.00 equiv) in DMPU (106 kg, 2.00 vol) and toluene (22 kg, 0.50 vol) was added. The reaction

mixture was heated at 110 °C for 3 h and then cooled to 60 °C. Toluene was added to bring the reactor contents to ~10 vol. The solution was then washed at 60 °C with 5% brine (250 kg × 3) followed by 6 N HCl (165 kg, 3.30 vol). Heptane (170 kg, 3.00 vol) was added to the organic layer, and the reaction mixture was cooled to 0 °C over 1.5 h and stirred for several hours. The solids were filtered off, and the cake was washed with iPrOH (60 kg, 5.0 vol) and dried under vacuum to give 52.8 kg (83% yield, 99.14 area %) of **IG-1**.

Preparation of 1-[(3,5-Bis{[2-(methyloxy)ethyl]oxy}-phenyl)methyl]-3-[4-(1,1-dimethylethyl)phenyl]-1H-indole-2-carboxylic Acid (IG-1). *Bromide Displacement.* A reaction vessel was charged with sodium *tert*-pentoxide (2.8 kg, 7.0 equiv), CuI (70 g, 0.10 equiv), and diglyme (8.0 L, 4.0 vol). 2-Methoxyethanol (2.2 kg, 8.0 equiv) was added, maintaining the reaction temperature below 55 °C. The reaction mixture was heated to 55 °C for 30 min, and a solution of **2b** (2.0 kg, 1.0 equiv in 4.0 L, 2.0 vol DMF) was added. The slurry was heated at 90 °C for 2 h and then cooled to <80 °C. Water (2.0 L, 1.0 vol) and iPrOH (10 L, 5.0 vol) were added and stirred at 60 °C for 30 min. The solids were filtered off, and the filtrate was warmed to 60 °C. A solution of 6 N HCl (10 L, 5.0 vol) was added, and the slurry was cooled to 20 °C over 1.5 h and stirred overnight. The solids were filtered off, and the cake was washed with a water/iPrOH mixture (10.6 L, 5.30 vol water, 5.4 L, 2.7 vol IPA) and dried under vacuum to give 1482 g (76% yield, 96.7 area %) of **IG-1**.

Preparation of 1-[(3,5-Difluorophenyl)methyl]-3-[4-(1,1-dimethylethyl)phenyl]-1H-indole-2-carboxylic Acid (2a). A reaction vessel was charged with DMAc (292 kg, 8.00 vol)[17] followed by **3** (38.8 kg, 1.00 equiv), and the solution was added to a second reactor containing KOtBu (16.3 kg, 1.20 equiv) and stirred at 20 °C for at least 45 min. 3,5-Difluorobenzyl bromide (**4a**) (29.9 kg, 1.20 equiv) was then added, and the reaction mixture was stirred at 20 °C for 1.5−2 h. A solution of KOH (12.2 kg, 1.80 equiv KOH in 79.3 L, 2.0 vol water) was added slowly, maintaining a reaction temperature of 20 °C. The reaction mixture was heated to 60 °C for 1 h and then slowly added to 6 N HCl (198 kg, 4.50 vol) at 60 °C. The slurry was cooled to 20 °C and held at least 6 h. The solids were filtered off, and the cake washed with water (77.6 L of reactor rinse followed by a direct cake wash with 116.4 L), and dried under vacuum to give 48.9 kg (97% yield, 97.23 area %) of **2a**.

^{1}H NMR: δ 1.34 (s, 9H), 5.86 (s, 2H), 6.77−6.78 (d, 2H, J = 6.3 Hz), 7.10−7.17 (m, 2H), 7.33−7.36 (t, 1H, J = 7.8 Hz), 7.40−7.49 (m, 4H), 7.49−7.51 (d, 1H, J = 8.9 Hz), 7.59−7.61 (d, 1H, J = 8.3 Hz), 13.0 (s, 1H).

Preparation of 1-[(3,5-Dibromophenyl)methyl]-3-[4-(1,1-dimethylethyl)phenyl]-1H-indole-2-carboxylic Acid (2b). A reaction vessel was charged with **3** (3.0 kg, 1.0 equiv), KOtBu (1.26 kg, 1.20 equiv), and NMP (15 L, 5.0 vol) and stirred at 20 °C for 45 min. Add a solution of **4b** (3.65 kg, 1.20 equiv) in NMP (7.5 L, 2.5 vol) was added and the reaction mixture was stirred at 20 °C for 1−2 h. After heating to 60 °C, aq. KOH (1.31 kg, 2.50 equiv in 6 L, 2 vol water) was added, maintaining the reaction temperature below 65 °C and the reaction mixture was heated at 60 °C for 1 h. The reaction mixture was added to 6 N HCl (13.8 L, 4.60 vol) at 60 °C over 1 h, and cooled to 20 °C. The solids were filtered off, and the cake was washed with water (12 L, 4.0 vol then 18 L, 6.0 vol), and dried under vacuum to give 5.65 kg (112% yield, 97.57 area %)[18] of **2b**.

^{1}H NMR: δ 1.35 (s, 9H), 5.82 (s, 2H), 7.14−7.17 (t, 1H, J = 7.1 Hz), 7.30−7.31 (d, 2H, J = 1.6 Hz), 7.34−7.38 (t, 1H, J = 7.1 Hz), 7.39−7.49 (m, 4H), 7.50−7.52 (d, 1H, J = 8.0 Hz), 7.62−7.64 (d, 1H, J = 8.4 Hz), 7.73−7.74 (t, 1H, J = 1.8 Hz), 13.1 (s, 1H).

Acknowledgment

We thank David Black, John Grimes, Byron Johnson, Eric Kraft, Mark Saulter, and Hamid Shafiei (GlaxoSmithKline, Analytical Sciences) for NMR, mass spectrometry, ICP-OES, and ion chromatography support.

Supporting Information Available

Characterization and purity data for compounds **1**, **IG-1**, **2a**, **2b**. Characterization data for compounds **7**, **8**, **9**, **10**, **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review August 29, 2008.

OP800211C

(17) After DMAc addition, the batch was analyzed for water content. For safety reasons, water levels needed to be <0.1% prior addition of the solution to KOtBu. This also minimized the risk of hydrolysis of the indole starting material.

(18) The high yield is likely due to inorganic solids that were isolated with the product. This material was used in the subsequent stage on 50-L scale which performed as expected. In small-scale experiments contamination of the product inorganic solids was not observed.