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Process Development and Scale-up of AG035029

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Abstract:

A practical process for the synthesis of PPARγ agonist AG035029 was developed which involved six steps along the longest linear path. The process development utilized automated technology and computational chemistry extensively to accelerate the speed of the project in the areas of catalyst screening, reaction optimization, mechanistic studies, and polymorph control.

Introduction

AG035029 is a potent PPARγ agonist developed at Pfizer for potential treatment of type II diabetes. In the U.S. 17 million people have type 2 diabetes mellitus (T2D), and the worldwide number is estimated to be over 100 million. The cost related to T2D in the U.S. is estimated at over $120 billion annually. Approximately 60% of diabetic patients do not reach the treatment goal of HbA1c < 7% using the currently available therapeutics as mono- or polypharmacy. Glitazones (TZDs) are commercially successful PPARγ agonists; however, there is significant room for improvement in their safety/efficacy profile.[1] **AG035029** (Figure 1)is a non-TZD PPARγ agonist with weak cross activity for PPARα. Based on animal models, it is expected that **AG035029** might differentiate itself from the currently marketed TZDs with respect to potency and possibly lipid control. In order to support toxicity studies and clinical studies, the material demands of the project escalated exponentially in a very short period of time such that 10 kg of drug substance were needed to proceed to Phase 1 study. In addition to classical process chemistry techniques, the use of a variety of automated technologies coupled with input from computational chemistry experiments allowed development of a synthetic route to this deceptively simple compound in a rather short period of time. We present the combined results of these studies in this manuscript to demonstrate the advantages of a multidisciplinary approach to chemical process development.

Results and Discussion

Evaluation of the Medicinal Chemistry Synthesis. The synthetic route employed by the medicinal chemistry team (Scheme 1) was evaluated to gain insights and to identify potential hurdles to scale-up. Although the route is linear and all the intermediates and API were isolated by chromatography, most of the transformations proceeded in acceptable yield and several intermediates are crystalline when the purity is high. Importantly, it was revealed early in the development that the penultimate intermediate (**10**) is a workable solid that could be purified by recrystallization, which provided a good control point for the purity of the **AG035029**. However, two major issues still remained. The Jacobsen indazole synthesis[2] involved intermediate formation of a hazardous diazonium salt, and the synthesis is long and inefficient.

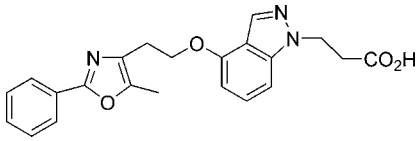

Figure 1. **AG035029.**

An alternative indazole formation method reported in the literature[3] was evaluated for suitability. Unfortunately, due to the difference in substitution patterns, the high efficiency was not achieved on our substrate. Jacobson indazole synthesis appeared to be superior in terms of efficiency. A calorimetric study of the Jacobsen indazole synthesis revealed that no significant exotherm or off-gassing occurred in the process. This was in agreement with the proposed mechanism[2] of the reaction in which the diazonium salt does not accumulate; it is consumed as it is produced. After careful study and consideration, it was felt that the risks involved in the Jacobsen indazole synthesis could be managed.

Two further issues were factored into our initial approach to the project. Soon after the project was initiated, a vendor was identified to provide compound **4** in large quantities (50 kg), although at substantial cost. Because of the low efficiency of a linear route, the high price of **4** mandated the introduction of this piece at a later stage in the synthesis. Further, differential scanning calorimetry data suggested that phenyl oxazole containing intermediates in the linear route employed by Discovery tend to be high-energy compounds; early introduction of the phenyl oxazole group should be avoided for production safety considerations. These two key factors necessitated the study of a more convergent approach to **AG035029**.

Convergent Route to AG-035029. A more convergent route was easy to envisage (as shown in Scheme 2) and was quickly reduced to practice. The synthesis started from compound **11**, a readily commercially available material. The

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(1) Schoonjans, K.; Auwerx, J. *The Lancet* **2000**, *355*, 1008.

(2) Troendlin, F.; Werner, R.; Ruechardt, C. *Chem. Ber.* **1978**, *111*, 367−78.

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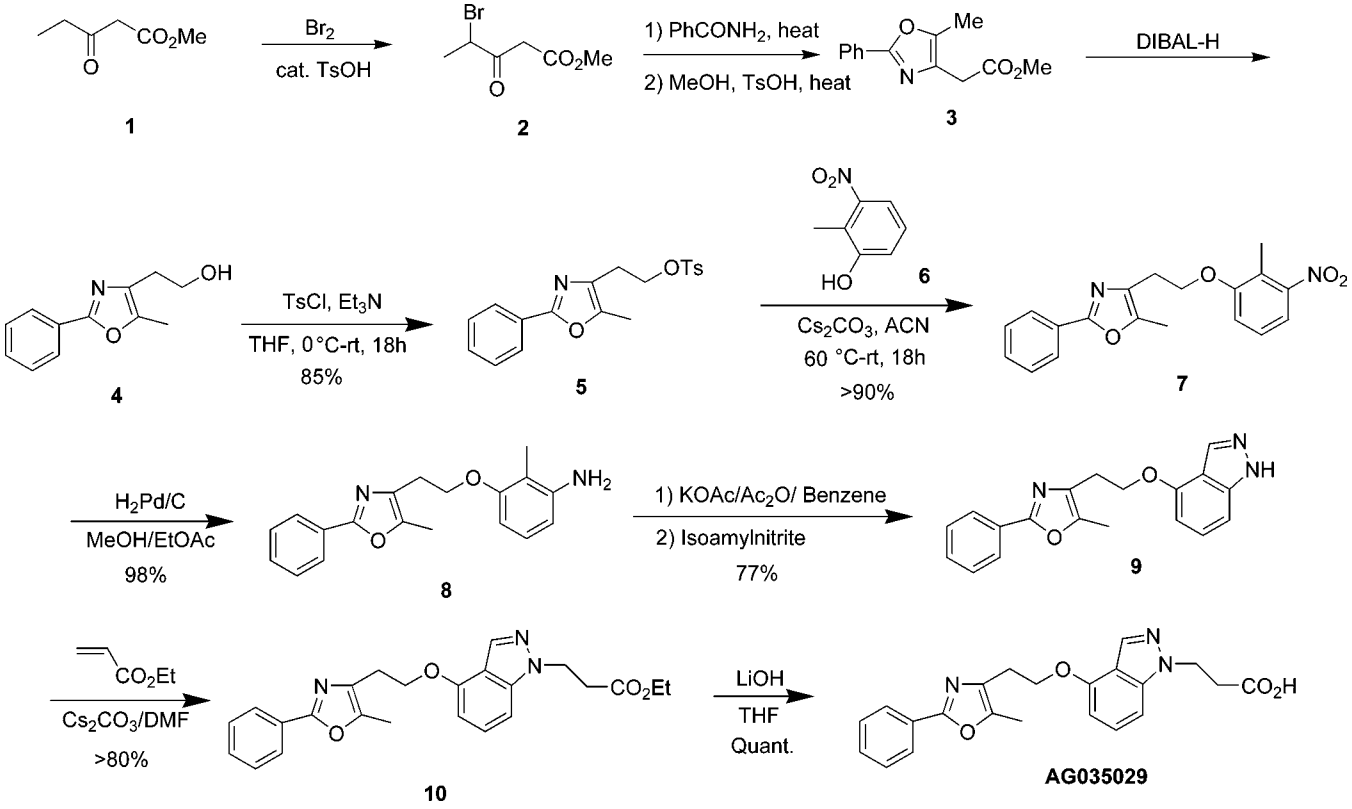
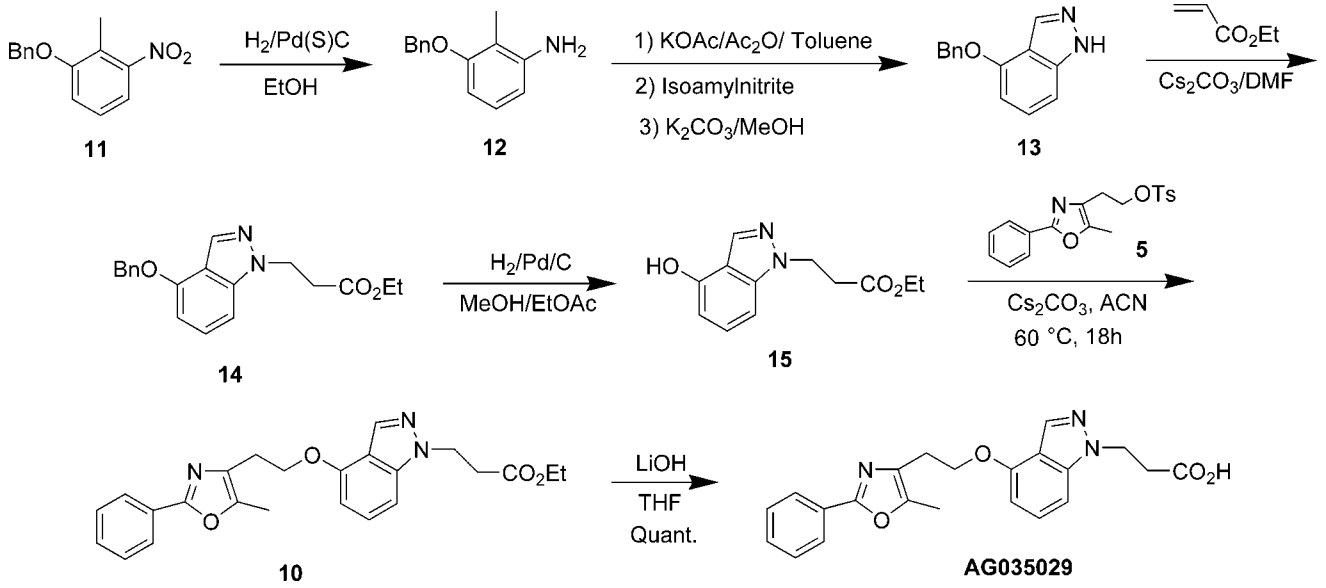
Scheme 1. **Modified medicinal chemistry route to AG035029**



Scheme 2. **Synthesis of AG035029 via a convergent route**



nitro group was reduced to give the aniline (**12**) by catalytic hydrogenation using sulfur poisoned Pd/C as catalyst, which, after Jacobsen indazole synthesis, afforded **13**. Conjugate addition of the indazole at N1 to ethyl acrylate followed by debenzylation yielded phenol **15**. The phenol was then treated with the tosylate **5** to form the ether bond in **10**. Hydrolysis of **10** yielded **AG035029** in an overall yield comparable to that from the linear route, without any optimization work having been performed to this point. Since this route is convergent, it has an advantage over the linear route in terms of efficiency and cost. It was decided to pursue optimization of the convergent route.

During the pilot run, some weak links in the synthesis were identified. For instance, the reduction of the nitro group in **11** was not totally selective, with some debenzylation being observed. Also, extensive double addition occurred during the Michael reaction, as shown in Scheme 3 (**13** to **16**). Further, the byproduct **16** was very difficult to remove, even with chromatography. To address these and other process-related issues, each step in the convergent route was

Scheme 3. **Alkylation of indazole 13**

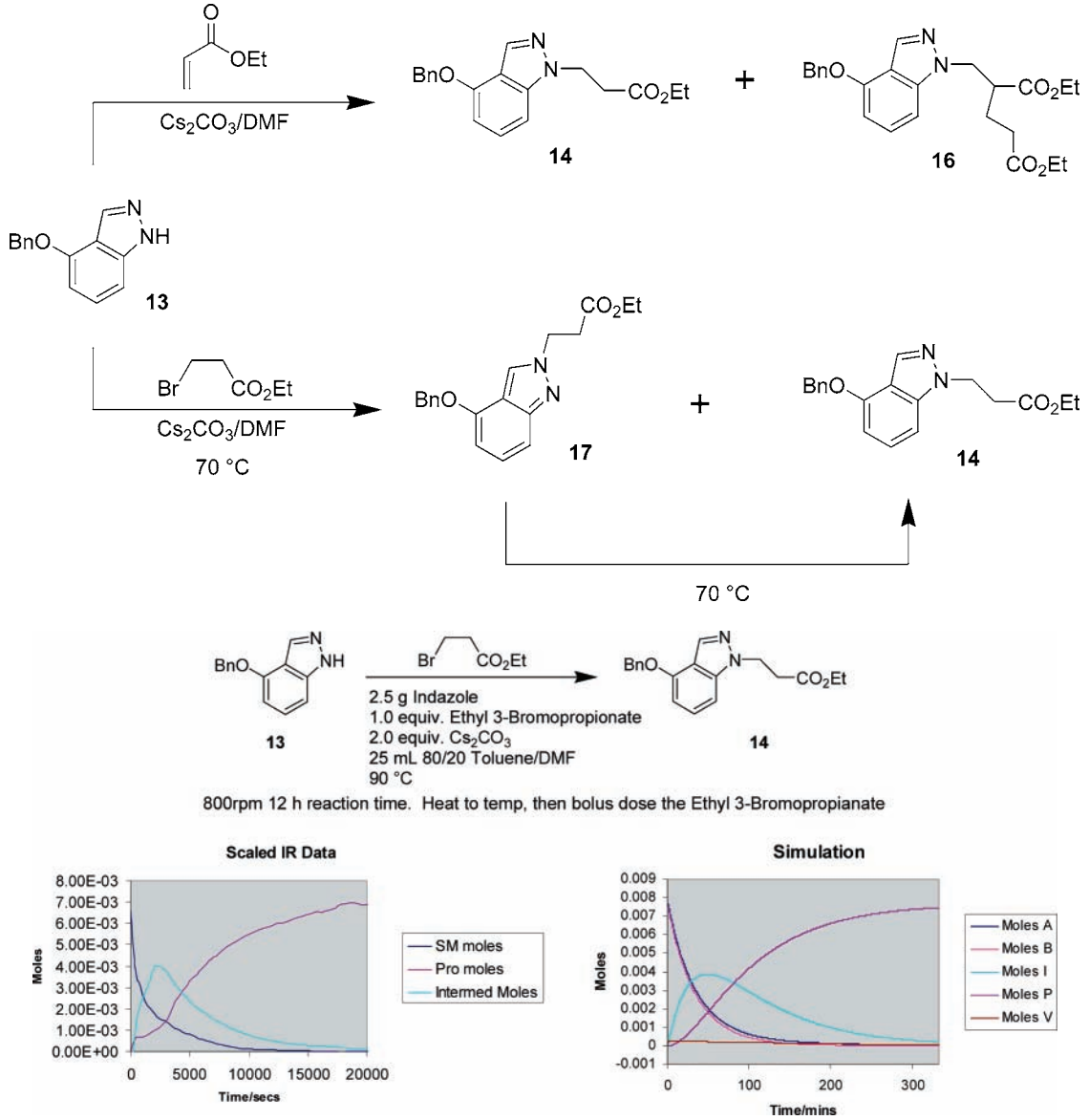


Figure 2. **IR indicates involvement of an intermediate.**

studied individually. Screening of different catalysts on a High-Pressure ChemScan automated reactor system promptly identified 3% Pt/C as the catalyst of choice. In the presence of this catalyst, no debenzylation was observed while the reduction of the nitro group was complete in 18 h. Jacobson indazole synthesis was found to require no more than 2 equiv of *iso*-amyl nitrite and afforded intermediate **13** consistently in greater than 80% overall yield from **11**. This reaction was followed closely by HPLC to ensure each intermediate in the process was completely formed before the next reagent was added.

The bottleneck of the convergent route appeared to be the introduction of the N1− side chain. Initially, compound **14** was prepared from **13** via Michael addition to ethyl acrylate. Unfortunately, the desired product was always obtained in an admixture with **16**, apparently from double Michael addition (Scheme 3). This byproduct could be present at levels approaching 25% and was more pronounced when the reaction was scaled-up. In addition, the byproduct was extremely hard to remove through crystallization or chromatography and could not be purged during down stream chemistry. Use of lower temperatures (e.g., −15 °C) appeared to reduce the level of **16** for small batch sizes (1 g), but upon scale-up this effect was diminished. To overcome the problem, an alkylation was envisaged in lieu of the Michael reaction (Scheme 3). Alkylation of indazole **13** with ethyl 3-bromopropionate gratifyingly did not furnish the undesired double Michael product **16**; however a mixture of isomers **14** and **17** was now obtained.

Furthermore this was a capricious process; sometimes the desired 1-alkylated product **14** was obtained exclusively, whilst on other occasions up to 20% of the undesired 2-isomer **17** was obtained despite apparently identical reaction conditions. The reaction was clearly not fully understood and hence was out of control. Experience has shown that such processes are prime candidates for study with ReactIR, which immediately revealed the participation

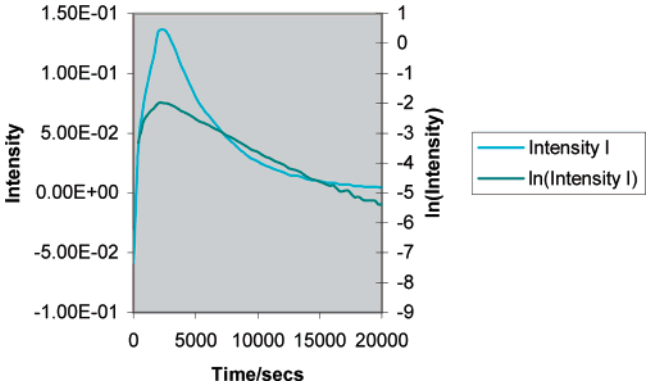


Figure 3. **Product derived through first-order decay of an intermediate species.**

of an intermediate species (absorbing at 1549 cm^{-1}), ruling out a simple S_N2-like mechanism (Figure 2).

The IR data also illustrated that product was formed in-line with the rate of decay of the intermediate and not the rate of decay of the starting indazole. Furthermore, this was a first-order process as deemed from the linearity of the ln-(intensity) versus time plot (Figure 3).

The reaction was also studied using neat toluene as solvent in place of 80:20 toluene/DMF, and under these conditions ReactIR did not indicate involvement of an intermediate species. Rather the reaction proceeded with slight induction at 80 °C, which had completely disappeared by 90 °C furnishing *n*th order kinetics, typical for an S_N2 type process (Figure 4). Most importantly the selectivity was always poor in the absence of DMF. These results appear to suggest that different mechanisms operate in pure toluene and 80:20 toluene/DMF.

This data suggested that the intermediate was responsible for the selective alkylation and that DMF was intimately involved its formation. The following mechanism was proposed, proceeding through the intermediacy of a Vilsmeier-like species (at too low a concentration to observe spectroscopically) which could react to form the observed intermediate **I** (Figure 5). The simulated profile is compared to the scaled IR data in Figure 2.

In a subsequent experiment the reagents were charged at room temperature and the mixture was slowly heated to 90 °C. ReactIR revealed that the indazole started to get consumed at approximately 30 °C and was completely consumed by 40 °C, furnishing the intermediate species. Decay of the intermediate to product was apparent once the reactor temperature exceeded 60 °C (Figure 6).

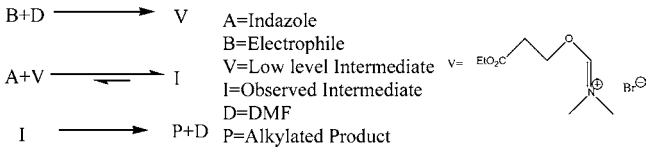


Figure 5. **Proposed mechanism.**

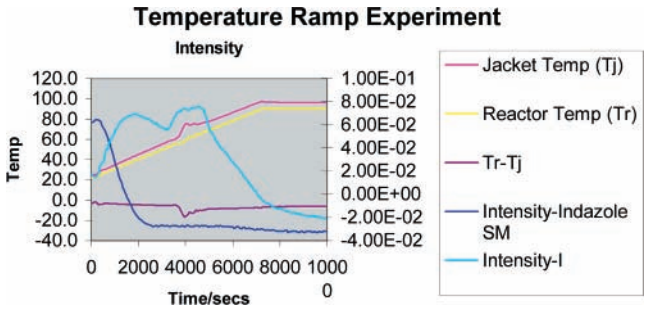


Figure 6. **Temperature ramp experiment.**

The key to success for the process was clear; the reaction mixture needed an isothermal hold at 40 °C to allow for

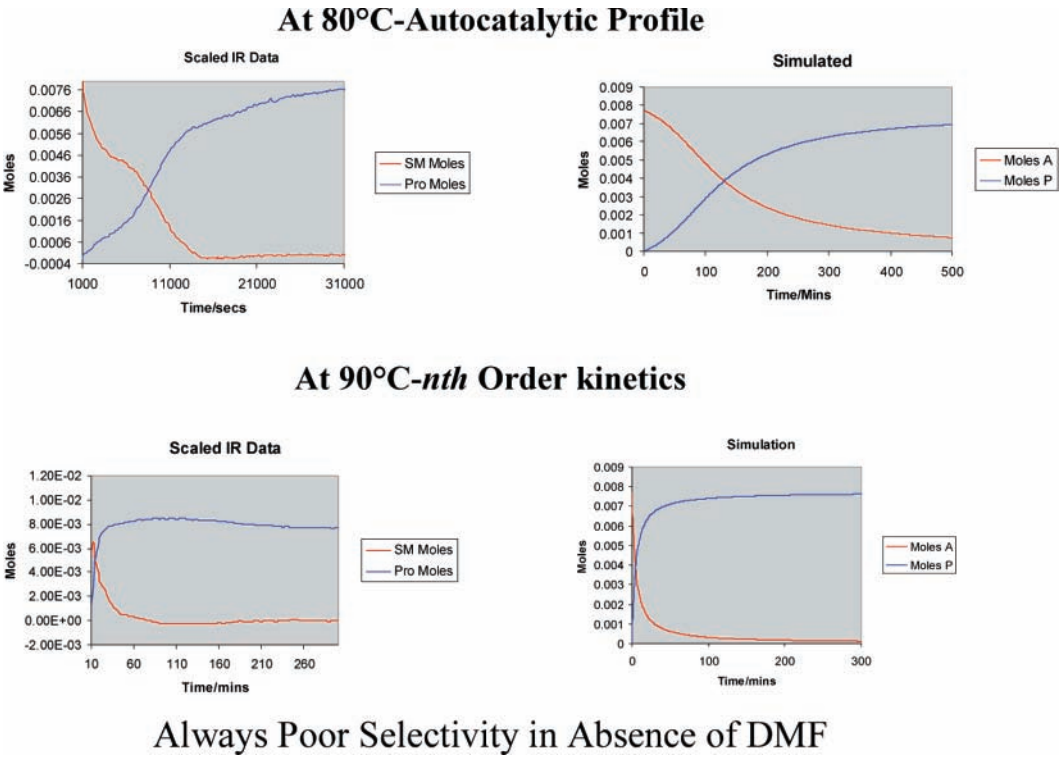


Figure 4. **Reaction profile in absence of DMF.**

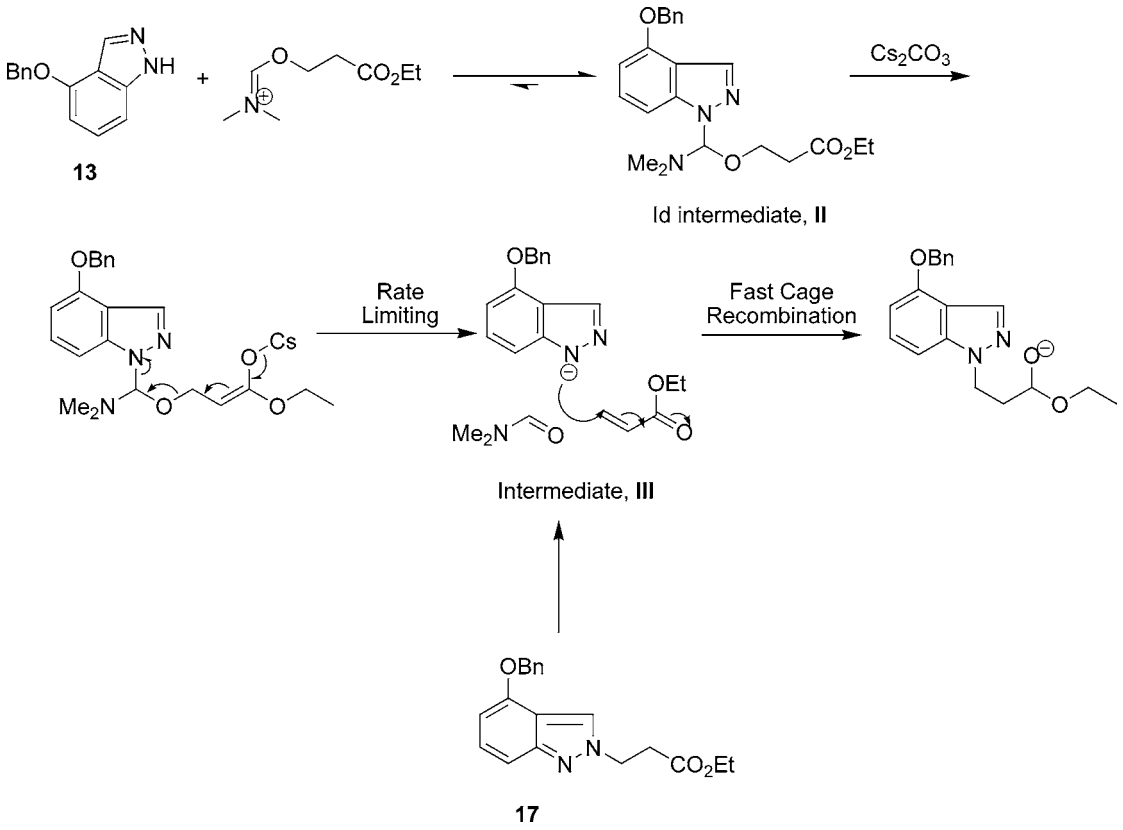


Figure 7. **S_Ni mechanism.**

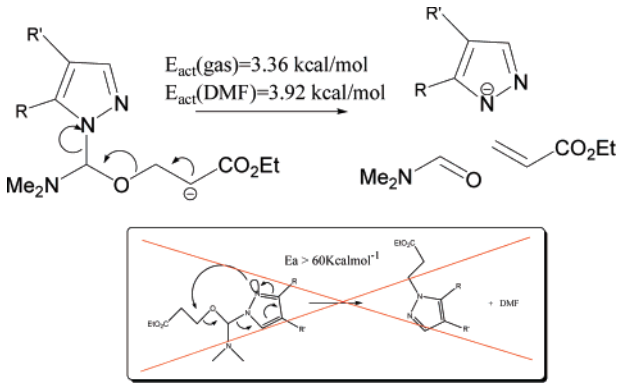


Figure 8. **Computational measurements support S_Ni.**

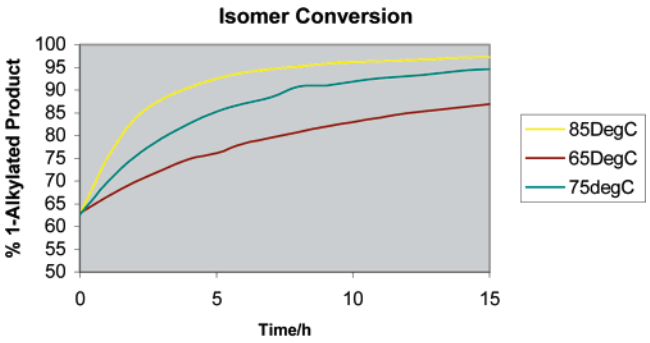


Figure 9. **Isomer conversion.**

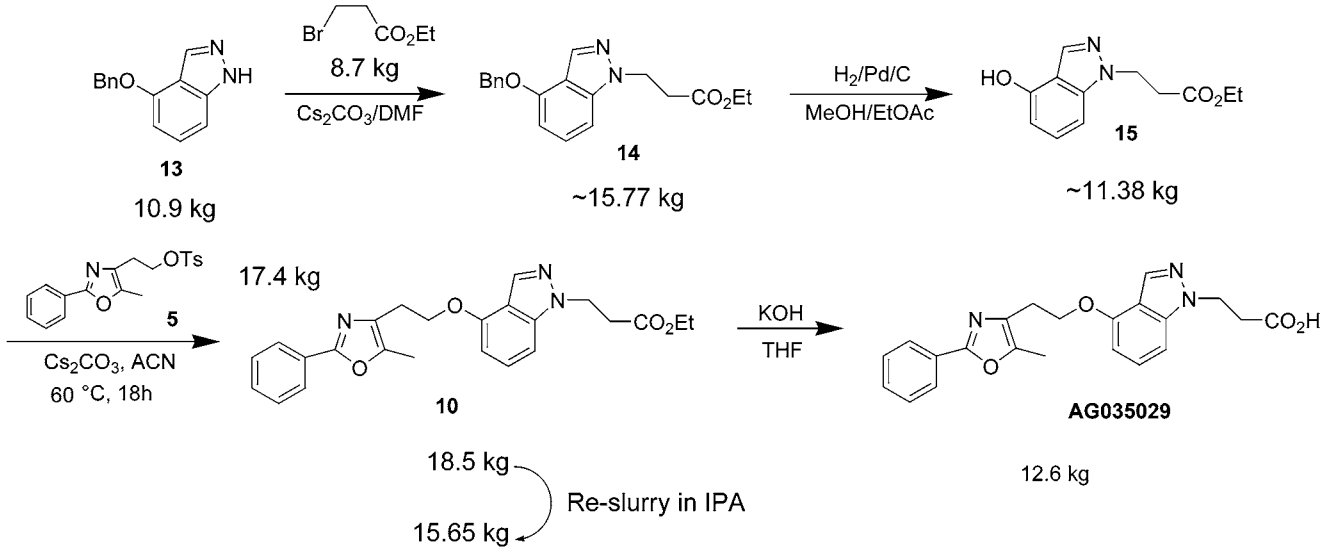
complete formation of the intermediate species, followed by heating to 90 °C to allow for collapse of the intermediate to product. The process was now highly reproducible in the laboratory and was successfully up-scaled to >20 kg at the Pfizer pilot facility. Based upon these kinetic measurements, an S_Ni mechanism is proposed (Figure 7) and is supported by computational calculations (see figures in ref 4),[4] consistent with a similar process proposed by Hamel.[5]

Computational measurements also allowed an alternate mechanism proceeding through a five-membered transition state to be ruled out (Figure 8).

Earlier in the study it was observed that even for cases when product was obtained with poor selectivity, isomerization to the thermodynamic 1-alkylated product **14** could be achieved with prolonged heating. The isomerization was studied in an 80:20 toluene/DMF mixture at three different temperatures over a 16 h period, analyzed by HPLC at hourly intervals. The isomerization progress is plotted in Figure 9.

The half-life for the interconversion was 12.5, 3.7, and 3.4 h at 65, 75, and 85 °C, respectively. Presumably isomerization occurs via a dissociative mechanism to ethyl acrylate; however a fast cage-like recombination to product is envisaged since the double-Michael byproduct **16** was not observed. In this respect the isomerization is completely analogous to the proposed S_Ni mechanism in Figure 7. The difference lies in the readily reversible formation of the intermediate **III**, allowing the thermodynamic equilibration to occur at much lower temperatures. In this latter case, heating is required solely to overcome the energy barrier to the rate-limiting (and entropically favored) Grobe-like fragmentation of **17**. Once dissociated, rapid recombination to furnish desired N1-alylated product (**14**) is inevitable.[6] Under the optimized conditions, the alkylation yielded the desired **14** cleanly. After the workup, the intermediate (**14**) was

Scheme 4. **Improved convergent route**



present in MTBE solution that could be used in the next step without further purification.

Formation of 10 via Tandem Telescoping. The next step was the debenzylation of compound **14** to set the stage for the ether formation. Screening of a variety of commercial catalysts revealed that Degussa's $Pd(OH)_2/C$ was the best choice when MTBE is the solvent. It rapidly catalyzed the debenzylation, yet the over reduction of the indazole ring system was limited. Debenzylation by transfer hydrogenation (Pd/C, $HCOONH_4$, ethanol, rt) afforded the desired phenol **15** cleanly, with only a trace of over-reduction. The drawback of transfer hydrogenation was the operational inconvenience: a solvent exchange was required to make the ethanolic solution and the residue salt in the ethanolic solution after the reaction sublimized during the solvent exchange in the next step, a manageable inconvenience yet extremely annoying. When the pros and cons of the two options were weighed, it was felt the use of molecular hydrogen was a better choice, especially when considering the small amount of the over-reduction byproduct could be easily removed in the next step. Thus, the MTBE solution of compound **15** was converted to an acetonitrile solution by solvent exchange, which was allowed to react with tosylate **5** in the presence of Cs_sCO_3 at 60 °C to give the penultimate intermediate (**10**). The product was easily isolated by addition of water as an antisolvent to precipitate it out of the solution. Normally the product was >97% pure that could be used directly in the next step. Reslurring the intermediate in *i*-PrOH at room temperature could upgrade any lot to >97% in greater than 90% recovery without fail. The overall yield for the three steps from intermediate **13** was >70%.

End Game. Hydrolysis of the penultimate intermediate (**10**) in THF afforded the crude API in the anionic form. Partitioning the crude reaction mixture in water and MTBE allowed most of the impurities to go to the organic layer and upgrade the API in the aqueous layer to >98% pure. Unfortunately, acidification of the aqueous layer often times afforded the API as a thick oil instead of a solid. On the other hand, the sequence of extracting the API as a free acid into DCM, speck-free filtration, followed by solvent exchange into *iso*-propyl alcohol always gave highly crystalline material. The API is freely soluble in IPA at reflux and crystallizes out of the solution during cooling. This added crystallization also upgraded the API to >99% purity, with no qualified impurities of >0.3% observed, and no unqualified impurities of >0.1% were present. The material that was produced this way affords form **A** API as a freely moving powder. As a bonus, the particle size of the API had a distribution of $D_{50} = 10$ micron and $D_{90} = 36$ micron, which served the formulation of Phase I drug product and Phase II drug product well.

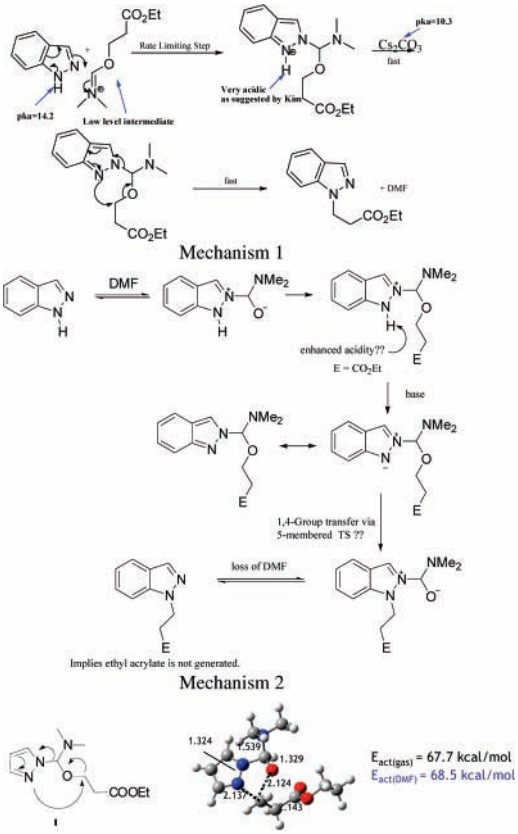
This process had been employed to produce three lots of API, 1.5 kg of non-GMP, 1.5 kg of GMP, and 12.6 kg of GMP, without incidents. In the third campaign, the GMP starting materials (**13** and **5**) were manufactured outside Pfizer using the process provided by Pfizer (vide supra). The downstream chemistry was carried out in-house, which is summarized in Scheme 4. In this campaign, an overall yield of 66% from **13** was achieved. The material passed the spec without incident.

Polymorphs. A second form (form B) was found during the polymorph screening. Although form B has a lower melting point (164 °C; form A has mp of 173 °C), solubility studies indicated that the new form does have lower solubility, indicating it is the more stable form.[7a] This enantiotropic system was studied in considerable detail, and a transition temperature of 95 °C was determined.[7b] Efforts were made to convert form A to form B in a controlled manner, our experiments indicated that spontaneous nucleation always generates form A, and form B could be produced only when induced. Studies of the *meta*-stable zone for form B in DME/heptane using HEL Automate and Lasentec FBRM established a cooling/seeding regiment that consistently gave form B. The robustness of the process has been demonstrated on a 500 g scale. Planning of conversion on a 10 kg scale is underway and will be reported in due course.

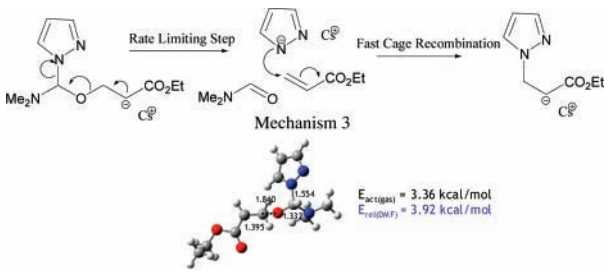
Conclusion

An efficient and safe process for the preparation of drug candidate **AG035029** was developed which provided many significant advantages over the original process used by Discovery chemists. The process development employed new technologies extensively, which made it possible for us to develop a scalable process expeditiously. The process was scaled-up in the kilo lab and pilot plant on a multikilogram scale without incident.

(4) Note: Three mechanistic possibilities were proposed to describe the formation of the key intermediate observed in the kinetic studies. Density functional theory calculations (B3LYP/6-31G(d)) were carried out on simpler model systems to explore these mechanisms. The first two mechanisms proposed a rearrangement of the substituent from N2 to N1 of **I** via a five-membered ring transition state as shown in Figure 10. The computed activation energy barrier (E_{act}) for this rearrangement was extremely high (~68 kcal/mol). This can be attributed to the overwhelming strain involved in the five-membered ring transition state to achieve the N2 to N1 rearrangement. Transition structure geometry and activation energy barrier for the proposed N2 to N1 rearrangement via five-membered ring transition state.



The third mechanism proposed the disproportionation of **II** (see Figure 7) via a Grobe type fragmentation as shown followed by a fast cage recombination to form the intermediate. The computed activation energy barrier (E_{act}) for this fragmentation is 3.9 kcal/mol in $\epsilon = 37.2$, the dielectric constant for DMF (3.4 kcal/mol in the gas phase, $\epsilon = 1$). This implies that this proposed mechanism is indeed feasible and consistent with the observed experimental data. Transition structure geometry and activation energy barrier for the proposed Grobe fragmentation in the rate-limiting step of the reaction.



Experimental Section

General. All melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER-SPECTROSPIN 300 UltraShield instrument operating at 300 and 75.5 MHz, respectively, using $CDCl_3$ or d_6-DMSO as the solvent. Electron ionization low-resolution spectra were determined at an ionizing voltage of 70 eV. Electron spray low-resolution spectra were determined at an ionizing voltage of 70 eV. Column chromatography was carried out on Universal silica gel (32−63 μm) using the indicated solvents as eluents. HRMS data were determined on a Micromass Q-TOF-2 mass spectrometer. All the starting materials and solvents were used as received without further purification.

3-Benzyloxy-2-methyl-phenylamine (**12**). A 2.5 L Parr flask was charged with 3% Pt/C (62% water, 3.30 g, 3 wt %) and then charged with a solution of **11** (110.0 g, 0.453 mol) in ethanol (1.6 L). The reaction was pressurized with hydrogen gas at 50 psi. After 30 min, the pressure dropped to 5 psi and was refreshed to 50 psi. After 1 h (from the commence of the reaction), the pressure dropped to 3 psi and was refreshed to 50 psi. After 3 h (from the commence of the reaction), the pressure dropped to 40 psi and was refreshed to 50 psi. The reaction was monitored by HPLC for the disappearance of **11** and the formation of **12**. At 18 h, the reaction was complete. The reaction mixture was filtered through a pad of Celite 521. The pad was rinsed with EtOH (200 mL). The combined filtrates were concentrated leaving an amber oil (94.82 g, 98%). NOTE: Oil crystallizes upon sitting. The material showed satisfactory purity and was used directly in the next step without further purification. Mp 42−44 °C. ^{1}H NMR (300 MHz, DMSO): δ 1.95 (s, 3H), 4.81 (s, 2H), 5.00 (s, 2H), 6.26 (d, J = 8.1 Hz, 1H), 6.28 (d, J = 8.1 Hz, 1H), 6.80 (dd, J = 8.1, 8.1 Hz, 1H), 7.25−7.47 (m, 5H). ^{13}C NMR (75.5 MHz, DMSO): δ 9.3, 69.2, 100.5, 108.0, 108.8, 126.0, 127.2, 127.5, 128.4, 137.9, 147.6, 156.7. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.81; H, 7.15; N, 6.60.

4-Benzyloxy-1*H*-indazole (**13**). A 5 L three-neck flask, equipped with a mechanical stirrer, temperature probe, and condenser was charged with 3-benzyl-2-methyl-phenylamine (80.0 g, 0.375 mol) and 3.2 L of toluene, followed by KOAc (40.5 g, 0.412 mol) and Ac_2O (141.6 mL, 1.50 mol). After stirring for 1 h, the mixture became very thick. The reaction was monitored by HPLC for the disappearance of starting material; after 2.5 h, all the starting material was consumed. To the thick suspension was charged isoamylnitrite (100.8

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mL, 0.750 mol). The resulting mixture was heated to 80 °C and stirred for 18 h, at which time HPLC of an aliquot indicated the reaction was complete. Heating was stopped allowing the reaction mixture to cool to 40 °C, and then 4.15 M NaOH (904 mL, 3.75 mol) was charged followed by TBA-OH (1 M in MeOH, 37.5 mL, 37.5 mmol). The resulting mixture was stirred slowly (150 rpm) for 4 h, at which time HPLC of an aliquot suggested the hydrolysis was complete. The mixture was allowed to cool to room temperature, and then the layers were separated. The organic layer was washed with water (3 × 1600 mL). The resulting organic layer was concentrated to a wet solid. The residue was dissolved into DCM (800 mL) and then charged with heptane (800 mL). The resulting mixture was concentrated to half the volume (≈ 800 mL) at 40 °C under a vacuum (450 mbar). The resulting mixture was allowed to cool to 20 °C and then was filtered. The filtered solids were washed with heptane (400 mL) and dried to afford 67.44 g (80% yield) of the title compound as a light yellow solid. Mp 118−123 °C. ^{1}H NMR (300 MHz, DMSO): δ 5.27 (s, 2H), 6.62 (d, J = 7.5 Hz, 1H), 7.10 (d, J = 8.7 Hz, 1H), 7.23 (dd, J = 8.1, 8.1 Hz, 1H), 7.29−7.46 (m, 3H), 7.48−7.55 (m, 2H), 8.06 (s, 1H), 13.05 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO) δ 69.2, 100.8, 102.9, 114.8, 127.1, 127.5, 127.8, 128.4, 130.9, 137.0, 141.7, 151.9. Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.02; H, 5.30; N, 12.41.

3-(4-Benzyloxy-indazol-1-yl)-propionic Acid Ethyl Ester (**14**). A 1 L three-neck flask, equipped with a mechanical stirrer, temperature probe, chart recorder, and condenser was charged with **13** (95.0 g, 0.424 mol), DMF (475 mL), cesium carbonate (275.5 g, 0.847 mol), and ethyl bromopropionate (55.0 mL, 0.424 mol) in that order. The reaction was heated to 40 °C while vigorous stirring was maintained. (NOTE: The reaction appears to be autocatalytic and may continue to heat past 40 °C. In this case, the reaction continued to heat to 59 °C before it came back down to 40 °C in 1 h.) The reaction was monitored by HPLC for the disappearance of **13**, and after 3 h all the starting material was consumed. The reaction was then heated to 90 °C and maintained at this temperature for 1.25 h. After cooling to 40 °C, the reaction vessel was charged with MTBE (950 mL) followed by water (950 mL) while stirring to dissolve all the salts. The layers were then separated, and the organic layer was set aside. The aqueous layer was then washed with MTBE (2 × 500 mL). The organic layers were combined and concentrated to about half the original volume, leaving 1 L of solution. The production should satisfactory purity and was used in the next step without further purification. ^{1}H NMR (300 MHz, DMSO): δ 1.06 (t, J = 7.2 Hz, 3H), 2.89 (t, J = 6.6 Hz, 2H), 3.97 (q, J = 7.2 Hz, 2H), 4.58 (t, J = 6.6 Hz, 2H), 5.26 (s, 2H), 6.65 (d, J = 7.2 Hz, 1H), 7.17−7.44 (m, 5H), 7.46−7.54 (m, 2H), 8.05 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO): δ 13.9, 34.0, 44.0, 60.1, 69.3, 101.1, 102.6, 115.4, 127.4, 127.6, 127.9, 128.5, 130.5, 136.9, 141.2, 151.9, 170.7. Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.29; H, 6.29; N, 8.66.

3-(4-Hydroxy-indazol-1-yl)-propionic Acid Ethyl Ester (**15**). A 2.5 L Parr flask was charged with 20% $Pd(OH)_2$ (8.5 g, 10 wt %%) under argon and then charged with an MTBE (1500 mL) solution of **14**. The reaction was pressurized with hydrogen gas to 47 psi. The pressure was refreshed after 10 min to 47 psi. The reaction was shaken for 12 h total. The reaction was monitored by HPLC for the disappearance of **14** and the formation of **15**. After agitation overnight, all of **14** was consumed. The reaction mixture was filtered through a pad of Celite 521. The pad was rinsed with MTBE (170 mL). The combined filtrates were carried on to the next step. An analytical sample was prepared by concentrating the solution to afford an oil, which solidified on standing. Slurring the solid in MTBE/heptane gave an off-white solid after filtration and drying. Mp 103−105 °C. ^{1}H NMR (300 MHz, DMSO): δ 1.08 (t, J = 7.0 Hz, 3H), 2.88 (t, J = 6.6 Hz, 2H), 3.99 (q, J = 7.1 Hz, 2H), 4.55 (t, J = 6.4 Hz, 2H), 6.42 (d, J = 7.5 Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H), 7.16 (dd, J = 8.3, 7.3 Hz, 1H), 8.03 (s, 1H), 10.07 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO): δ 13.8, 33.9, 43.9, 60.0, 100.2, 103.6, 115.1, 127.4, 130.7, 141.4, 151.0, 170.7. Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.54; H, 5.94; N, 11.91.

Toluene-4-sulfonic Acid 2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethyl Ester (**5**). A 3 L four-neck flask equipped with a mechanical stirrer, temperature probe, and nitrogen bubbler was charged 1.0 L of anhydrous DCM, followed by 2-(5-methyl-2-phenyl-oxazol-4-yl)-ethanol (**4**, 101.15 g, 0.50 mol). The flask was then immersed in a bucket of ice−water, after stirring for half an hour, the internal temperature dropped to 3 °C. The flask was then charged with TsO_2O (179.5 g, 0.55 mol) followed by (i-Pr)$_2$NEt (131 mL, 0.75 mol); the temp surged from 3 °C to 6 °C in this process. The reaction mixture was allowed to stir at ambient temperature for 18 h, at which time HPLC of an aliquot indicated the reaction was complete. The reaction mixture was poured into a 4 L separation funnel, and 1 L of water was added. After partitioning, the aqueous phase was washed once with 1 L of DCM. The combined organic layers were washed three times with 1 L of water. The organic phase was concentrated on rotary evaporator at 26 °C bath temperature. The material crystallized at the end of the concentration. The solid was further dried in a high vacuum for 8 h to afford 170.5 g of the title compound. Mp 93−95 °C. ^{1}H NMR (300 MHz, DMSO): δ 2.11 (s, 3H), 2.25 (s, 3H), 2.76 (t, J = 6.0 Hz, 2H), 4.24 (t, J = 5.9 Hz, 2H), 7.25 (d, J = 7.9 Hz, 2H), 7.43−7.53 (m, 3H), 7.62 (d, J = 8.3 Hz, 2H), 7.74−7.83 (m, 2H). ^{13}C NMR (75.5 MHz, DMSO): δ 9.6, 20.7, 25.0, 69.2, 125.4, 127.0, 127.4, 129.0, 129.8, 130.0, 131.3, 132.0, 144.7, 145.2, 158.3. Anal. Calcd for $C_{19}H_{19}NO_4S$: C, 63.85; H, 5.36; N, 3.92. Found: C, 63.93; H, 5.45; N, 3.93.

3-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-indazol-1-yl}-propionic Acid Ethyl Ester (**10**). A 3 L four-neck flask, equipped with a mechanical stirrer, temperature probe, and condenser was charged with 1.50 L of a homogeneous solution of **15** (∼105 g, 0.449 mol based on **13**) in MTBE in portions. The flask was marked for the volumes of 0.60, 1.1, and 1.5 L, respectively. The total volume was reduced to 0.60 L by distilling the MTBE out at atmospheric pressure, under the protection of nitrogen. Heating was then stopped,

and the contents in the flask were allowed to cool until boiling ceased. The flask was charged with the balance 0.70 L of the MTBE solution of **15**. The total volume was reduced to 0.60 L by distilling the MTBE out at atmospheric pressure, under the protection of nitrogen. Heating was once again stopped, and the contents in the flask were allowed to cool until boiling ceased. The flask was charged with 1.5 L of acetonitrile. The total volume was reduced to 0.60 L by distilling the solvent out at atmospheric pressure, under the protection of nitrogen. Heating was stopped, and the contents in the flask were allowed to cool to room temperature. A sample was taken and checked with NMR. No sign of the presence of MTBE was observed.

The flask was then charged with acetonitrile until a total volume of 1.1 L was reached, followed by cesium carbonate (219.3 g) and **5** in that order. The reaction mixture was heated to 65 °C and stirred for a total of 18 h. The reaction was monitored with HPLC (TFASH) for the disappearance of **15**; after 18 h, the reaction was complete. The reaction was cooled to room temperature and then charged with water (1.25 L). The resulting mixture was stirred for 6 h at room temperature, followed by storing at 4 °C for 18 h, at which time a thick precipitate formed. The mixture was filtered. The cake was washed with 300 mL of water and sucked dry. The cake was transferred to a glass dish and dried at 40 °C/28 in. vacuum for 18 h. The cake weighed 162.0 g. Mp 96−98 °C. ^{1}H NMR (300 MHz, DMSO): δ 1.06 (t, J = 6.9 Hz, 3H), 2.88 (t, J = 6.6 Hz, 2H), 3.02 (t, J = 6.0 Hz, 2H), 3.97 (q, J = 7.2 Hz, 2H), 4.37 (t, J = 6.6 Hz, 2H), 4.57 (t, J = 6.6 Hz, 2H), 6.60 (d, J = 7.2 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 7.27 (dd, J = 8.1, 7.5 Hz, 1H), 7.43−7.53 (m, 3H), 7.87−7.93 (m, 2H), 7.95 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO): δ 9.9, 13.9, 25.6, 34.0, 44.0, 60.1, 66.5, 100.6, 102.5, 115.2, 125.4, 127.1, 127.4, 129.1, 130.1, 130.3, 132.7, 141.1, 145.3, 152.0, 158.4, 170.7. Anal. Calcd for $C_{24}H_{25}N_3O_4$: C, 68.72; H, 6.01; N, 10.02. Found: C, 68.69; H, 5.97; N, 9.95.

AG035029 Form A. A 5 L three-neck flask, equipped with a mechanical stirrer and temperature probe, was charged with compound **10** (93.0 g, 0.221 mol), THF, and a solution of 37.2 g (0.664 mol) of KOH in 0.35 L of water in that order. The progression of the reaction was monitored by HPLC for the disappearance of **10**; after 3 h, the reaction was complete. The reaction was charged with water (1.0 L) followed by MTBE (1.0 L). The resulting mixture was stirred followed by separation of layers. The organic layer was discarded. The aqueous layer was treated with 180.9 g (1.33 mol) of $KHSO_4$, and 1.0 L of DCM was added; the mixture was thoroughly agitated followed by separation of layers. The aqueous layer was discarded. The organic layer was then concentrated to dryness.

A 5 L three-neck flask, equipped with a mechanical stirrer, temperature probe, and condenser, was charged with the crude **AG035029**, MTBE (1.6 L), and EtOH (200 mL), in that order. The reaction mixture was heated to reflux and stirred for a total of 18 h, cooled to room temperature, and then stirred for 18 h; a thick precipitate formed at this point. The mixture was filtered. The cake was washed with 200 mL of MTBE and sucked dry. The cake was transferred to a glass dish and dried at 40 °C/ 28 in. vacuum for 18 h. The cake weighed 72.0 g (83%). Mp 173 °C. ^{1}H NMR (300 MHz, DMSO): δ 2.39 (s, 3H), 2.81 (t, J = 6.8 Hz, 2H), 3.01 (t, J = 6.4 Hz, 2H), 4.35 (t, J = 6.4 Hz, 2H), 4.52 (t, J = 6.4 Hz, 2H), 6.59 (d, J = 7.2 Hz, 1H), 7.16−7.30 (m, 2H), 7.42−7.52 (m, 3H), 7.86−7.93 (m, 2H), 7.94 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO): δ 9.9, 25.6, 33.9, 44.1, 66.6, 100.6, 102.6, 115.2, 125.4, 127.1, 127.4, 129.1, 130.1, 130.2, 132.7, 141.1, 145.3, 152.0, 158.4, 172.2. Anal. Calcd for $C_{22}H_{21}N_3O_4$: C, 67.51; H, 5.41; N, 10.74. Found: C, 67.38; H, 5.26; N, 10.65.

AG035029 Form B. A 3 L four-neck flask, equipped with a mechanical stirrer and temperature probe, was charged with form A **AG035029** (178 g, 0.454 mol), followed by 1.8 L of DME. The mixture was heated to reflux and maintained for 1 h. The mixture became a homogeneous solution. The mixture was cooled to 60 °C, and 1.45 g of form B AG035029 seed were added immediately. The resulting mixture was allowed to stir for 18 h at this temperature. XRD of an aliquot indicated the material was form B. Heating stopped, and the mixture was allowed to cool to room temperature and stir for 24 h. The mixture was filtered, washed with 180 mL of DME, and sucked dry. The cake was dried in the oven at 40 °C/28 in. vacuum for 6 h to afford 143 g of form B **AG035029**. Mp 164 °C. ^{1}H NMR (300 MHz, DMSO): δ 2.39 (s, 3H), 2.81 (t, J = 6.8 Hz, 2H), 3.01 (t, J = 6.4 Hz, 2H), 4.35 (t, J = 6.4 Hz, 2H), 4.52 (t, J = 6.4 Hz, 2H), 6.59 (d, J = 7.2 Hz, 1H), 7.16−7.30 (m, 2H), 7.42−7.52 (m, 3H), 7.86−7.93 (m, 2H), 7.94 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO): δ 9.9, 25.6, 33.9, 44.1, 66.6, 100.6, 102.6, 115.2, 125.4, 127.1, 127.4, 129.1, 130.1, 130.2, 132.7, 141.1, 145.3, 152.0, 158.4, 172.2. Anal. Calcd for $C_{22}H_{21}N_3O_4$: C, 67.51; H, 5.41; N, 10.74. Found: C, 67.38; H, 5.26; N, 10.65.

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