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Effects of Various Bases on Acid-Catalyzed Amination of 2-Chloro-5-ethylpyrimidine: Synthesis of PPARpan Agonist GW693085

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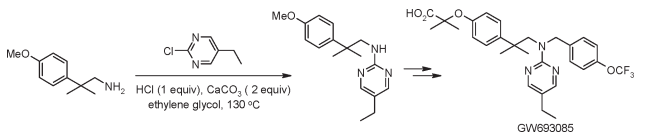
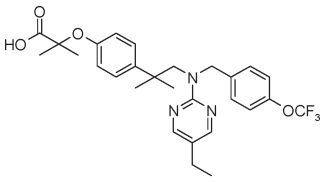


A unique buffering effect of various bases, *i*-Pr_2NEt and $CaCO_3$ in particular, was observed for the acid-catalyzed chloro displacement of 2-chloro-5-ethylpyrimidine with a 2-methyl-2-phenylpropanamine. The use of the carefully chosen bases was essential for the progression of the chloro displacement as well as the stability of the product in the presence of HCl formed. Research work leading to an efficient synthesis of PPARpan agonist GW693085 is described, featuring highly selective sequential *N*- and *O*-alkylations.

Peroxisome proliferator-activated receptors (PPARs) are members of the steroid/thyroid/retinoid nuclear receptor superfamily. The three subtypes (α, γ, and δ) constitute a subfamily, each having a distinct distribution in the body. PPARs have been shown to be important in energy balance through their participation in regulating the proteins involved in carbohydrate and lipoprotein metabolism.[1] Recently, selective PPAR agonists were dosed in combination to show that there could be synergy in lowering glucose and triglycerides.[2] GW693085 (**1**) is a PPARpan agonist, combining the activity of the three known subtypes of the PPAR agonists into a single molecule.[2e]



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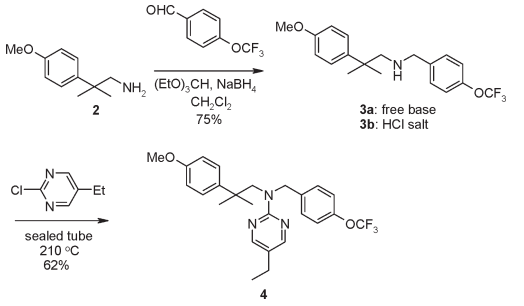
Development of **1** as a drug candidate for type 2 diabetes required a supply of multikilogram quantities for preclinical and clinical investigation. The target compound is a 5-ethyl-2-pyrimidinamine with neopentyl and benzyl substituents on the exocyclic nitrogen. Herein, we report process research leading to a highly efficient and robust synthesis, incorporating excellent selectivity in sequential *N*- and *O*-alkylations. Screening of various types of bases in the amination of 2-chloro-5-ethylpyrimidine revealed the unique buffering effect of calcium carbonate and *i*-Pr_2NEt (Hunig's base) in the acid-catalyzed amination.

SCHEME 1



Initially, the tertiary amino skeleton of **1** was constructed as shown in Scheme 1. 2-Methyl-2-(4-(methoxyphenyl)-1-propanamine (**2**) underwent reductive amination with 4-(trifluoromethoxy)benzaldehyde to provide the secondary amine (**3a**).[3] A high-temperature coupling between free base **3a** and 2-chloro-5-ethylpyrimidine in a sealed tube at 210 °C in the presence of *i*-Pr_2NEt afforded 62% yield of tertiary amine **4**. Other attempts including microwave irradation[4] and some known palladium-catalyzed amination conditions ($Pd_2(dba)_3$, BINAP, NaO-*t*-Bu, toluene)[5] gave no desired product at all. The lack of reactivity was attributed to significant steric hindrance in **3a** due to the *N*-substituents including the neopentyl moiety.

Due to safety and scalability concerns,[6] our efforts shifted to identifying alternative routes. Amine **2** and its highly

(1) For reviews on modulators of PPARs and their mechanism and actions, see: (a) Cho, M. C.; Lee, K.; Paik, S. G.; Yoon, D. Y. *PPAR Res.* **2008**, 679137. (b) Chang, F.; Jaber, L. A.; Berlie, H. D.; O'Connell, M. B. *Ann. Pharmacother.* **2007**, *41*, 973. (c) Rubenstrunk, A.; Hanf, R.; Hum, D. W.; Fruchart, J. C.; Staels, B. *Biochim. Biophys. Acta* **2007**, 1065. (d) Sternbach, D. D. *Ann. Rev. Med. Chem.* **2003**, *38*, 71.

(2) (a) Feldman, P. L.; Lamber, M. H.; Henke, B. R. *Curr. Top. Med. Chem.* **2008**, *8*, 728. (b) Franklin, M. C.; Lewis, M. C.; Wilson, J. G.; Brown, J. G.; Strole, C. A.; Oliver, W. Jr.; Winegar, D. A. *Diabetes* **2002**, *51* (Suppl. 2), 556-P. (c) Lewis, M. C.; Winegar, D. A.; Bodkin, N. L.; Hansen, B. C.; Oliver, W., Jr. *Diabetes* **2002**, *51* (Suppl. 2), 566-P. (d) Lewis, M. C.; Wilson, J. G.; Franklin, M. C.; Brown, J. G.; Strole, C. A.; Oliver, W., Jr.; Winegar, D. A. *Diabetes* **2002**, *51* (Suppl. 2), 567-P. (e) Rodolfo, C.; Henke, B. R.; Lambert, M. H., III; Liu, G. K.; Smith, J. S. PCT Int. Appl., WO/2003074495, **2003**.

(3) Primary amine **2** was prepared from the nitrile precursor 2-(4-methoxyphenyl)-2-methylpropionitrile by reduction with $LiAlH_4$. For a preparation of the nitrile from nucleophilic aromatic substitution (SNAr) of a corresponding fluoroarene and a secondary nitrile, see: Caron, S.; Vazquez, E; Wojcik, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 712.

(4) For a report on nucleophilic substitution reactions of 2-halopyrimidyl and pyrazyl halides under focused microwave irradiation, see: Cherng, Y.-J. *Tetrahedron* **2002**, *581*, 887.

(5) (a) Wolfe, J. P.; Wagaw, S.; Buchwald, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969.

(6) Differential scanning calorimetry (DSC) indicated that 2-chloro-5-ethylpyrimidine decomposes at 210−260 °C and releases 1.1 kJ/g of energy.

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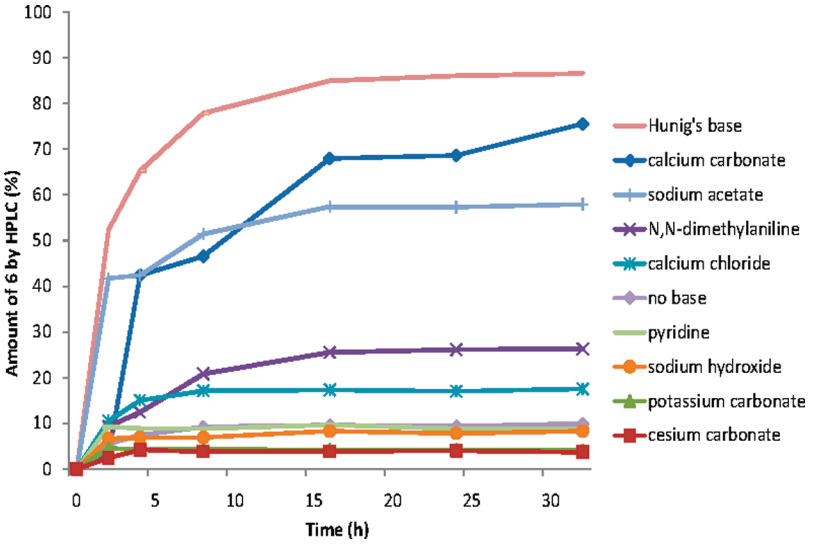
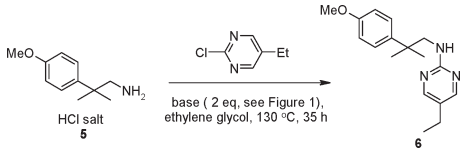


FIGURE 1. Effects of various bases on the reaction of **5** and 2-chloro-5-ethylpyrimidine.

SCHEME 2



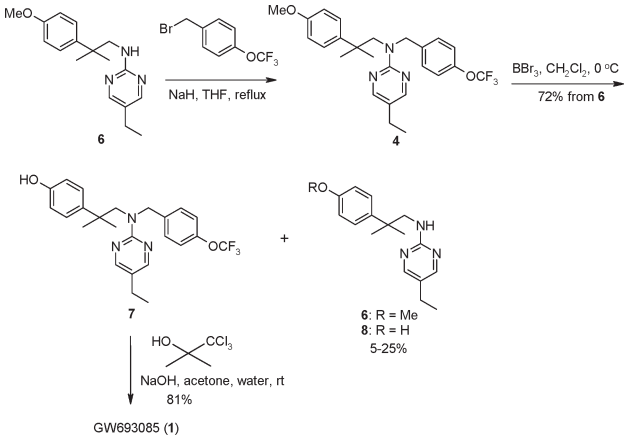
crystalline hydrochloride salt **5** were found to be much more reactive than the secondary amine (**3a**) in reaction with 2-chloro-5-ethylpyrimidine (Scheme 2). The 2-aminopyrimidine product (**6**) was highly crystalline, yet several significant observations were made. The reaction was found to be quite sensitive to the conditions used. Although it is known that amination of 2-chloropyrimidine is acid catalyzed,[7] we found that the reaction of **5** with 2-chloro-5-ethylpyrimidine was accompanied by significant acid-induced decomposition including cleavage of the methyl ether and breakdown of the pyrimidine ring unless the reaction was mediated by a base.

A variety of common bases were screened for the reaction with results shown in Figure 1. The conversion of **5** to **6** was measured by the area under curve (AUC) of product **6** on reversed-phase HPLC. There was only about 10% of product without an added base. Significant amount of decomposition to more polar impurities related to demethylation from **5** and **6** was observed under the high temperature needed for the reaction. On the other hand, strong bases such as NaOH, Cs_2CO_3, K_2CO_3, and pyridine inhibited the reaction with AUC of the product below 10%. Powdered $CaCO_3$ (particle size 8.5−10 μm) and *i*-Pr_2NEt were by far the best basic mediators in the screening with 76% and 87% product, respectively (Figure 1).

We postulate that the heterogeneous nature of the base, in the case with $CaCO_3$, and the low miscibility of the base with ethylene glycol solvent, in the case of Hunig's base, allowed the acid-catalyzed amination of the chloropyrimidine to proceed while still being able to function as a base to neutralize the excess acid generated from the reaction itself.

(7) Gunzenhauser, S.; Balli, H. *Helv. Chim. Acta* **1988**, *71*, 33.

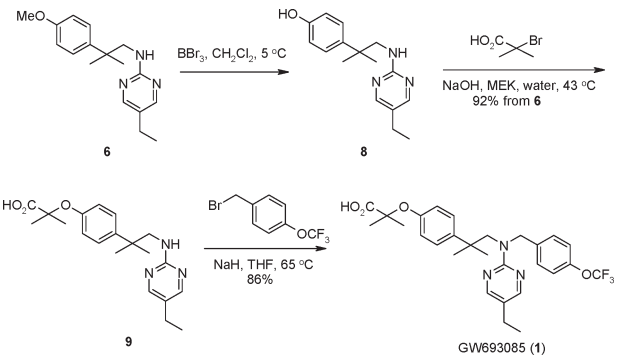
SCHEME 3



The role of the base as an acid scavenger became prominent only as more hydrogen chloride was generated from the chloro displacement. This reduced the levels of byproducts induced by decomposition in the presence of a high concentration of acid. NaOAc and *N*,*N*-dimethylaniline, with 58% and 26% product, respectively, were better than strong bases for the reaction but did not provide enough product for isolation. Unlike the reaction with the heterogeneous and mildly basic $CaCO_3$, reaction in the presence of heterogeneous but slightly acidic $CaCl_2$ produced less than 20% product. The reactions with $CaCO_3$ and *i*-Pr_2NEt base were subsequently optimized to provide 70−80% isolated yield of crystalline product **6** in scaleup. No optimization on the particle size of $CaCO_3$ was carried out.

Our initial approach to convert the 2-aminopyrimidine (**6**) to the drug candidate (**1**) is shown in Scheme 3. Alkylation with (4-trifluoromethoxy)benzyl bromide gave tertiary amine **4**. It was essential to preform the amide anion from **6** with a strong base for the alkylation to occur at the targeted exocylic nitrogen. Although the amide anion could be formed with many strong bases, NaH gave the cleanest alkylation. Use of a variety of weaker bases including tertiary amines (Hunig's base, Et_3N), pyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), K_2CO_3, and $CaCO_3$ in various solvents led

SCHEME 4



to recovered **6** with mild heating. When heated to over 100 °C in the presence of those weak bases, the reaction gave rise to only a trace of desired tertiary amine product **4**, along with a byproduct (30−60% by HPLC) which was identified as structure ***i*** on the basis of analysis with HPLC−MS fragementation.[8] Although cleavage of the methyl ether from **4** appeared straightforward with typical conditions such as BBr_3 in CH_2Cl_2,[9] the reaction was complicated due to competitive loss of the *N*-benzyl moiety from both **4** and **7**, producing side products **6** and **8**. The penultimate phenolic intermediate (**7**) could only be isolated by silica gel chromatography. The isobutyryl moiety was then installed through a Bargellini reaction with chloretone in the presence of NaOH.[10] However, as much as 30% of mesityl oxide byproduct derived from the base-catalyzed acetone condensation was formed during the reaction. An alternative synthetic sequence was desired with a penultimate crystalline intermediate and without the side products from debenzylation.

Further process research led to a new and much more desirable route starting with **6** shown in Scheme 4. The new synthesis benefits from the elimination of the competitive debenzylation, usage of an alternative reagent to introduce the isobutyryl headgroup that avoids the formation of the mesityl oxide, and assurance of a crystalline penultimate intermediate prior to the final formation of the active pharmaceutical ingredient (API).

Demethylation from **6** by BBr_3 afforded phenolic intermediate **8** which was used for the next step with no need for purification. Incorporation of the isobutyryl moiety was accomplished in 92% yield by reaction of 2-bromo-2-methylpropionic acid with **8** in a basified methyl ethyl ketone (MEK) solution. Penultimate intermediate **9** was isolated from methanol as a highly crystalline white solid. Surprisingly, this reaction was completely *O*-selective in the presence of the 2-aminopyrimidine moiety. In contrast, when phenol **8** was used under Bargellini reaction conditions with chloretone,[10] the reaction produced small quantities of *N*-alkylation as well as *N*,*O*-bisalkylation byproducts. This should not be surprising in light of application of Bargellini reactions in synthesis of piperazinones by Lai[11a,b] and Rychnovsky.[11c] They have demonstrated that even a tertiary amino group of α-amino alcohols would preferably react on the nitrogen. Mechanistically, it was not clear if the 2-bromoisobutyric reagent worked through a α-lactone intermediate. Online monitoring with a React-IR did not detect any absorbance that could be attributable to a α-lactone intermediate. Anchimeric assistance or neighboring group participation for the bromo displacement appears to be the most probable explanation for the fast and clean reaction.

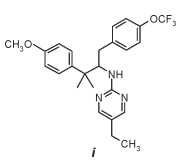
In another example of *N*- vs *O*-selectivity, the 2-alkylaminopyrimidine (**9**) was selectively *N*-alkylated with (4-trifluoromethoxy)benzyl bromide in the presence of NaH to give an 86% yield of crystalline GW693085 (**1**). There was no alkylation on the carboxylic oxygen. In a testimony to the robustness of this alkylation, use of 2 equiv of the alkylating reagent and 4 equiv of the base still produced no benzyl ester. Any excess amount of (4-trifluoromethoxy)benzyl bromide, a strong alkylator and therefore a potential human carcinogen, was quenched by addition of sodium methoxide to the reaction mixture.

In conclusion, an efficient and robust synthesis of PPARpan agonist GW693085 has been developed. Key features include excellent nitrogen/oxygen chemoselectivity in the alkylation of two major intermediates, crystalline intermediates, and the brevity of the synthesis. The use of a heterogeneous base such as $CaCO_3$ in acid-catalyzed alkylamination of 2-chloro-5-ethylpyrimidine was noteworthy. A strong base or a base miscible with the solvent used in the reaction would prevent the chloro displacement. On the other hand, there was significant decomposition of the 2-aminopyridmidine product in the absence of a base as a buffer.

Experimental Section

2-Methyl-2-(4-methyloxyphenyl)-1-propanamine Hydrochloride (5). To a solution of 1.00 kg (6.79 mol) of (4-methoxyphenyl)-acetonitrile in 4.6 L of THF in a 30 L reactor was added 13.9 L (27.8 mol) of lithium diisopropylamide (2 M in heptane/THF/ethylbenzene) with cooling. The addition rate was such that the internal temperature was maintained below 25 °C. After being stirred at 25 °C for 1 h, the mixture was cooled to 5 °C and treated with 1.6 L (16.9 mol) of dimethyl sulfate as a solution in 5.1 L of THF at below 20 °C. The reaction was cooled to 5 °C and quenched with a mixture of 2.4 L (28.2 mol) of concentrated HCl and 1.8 L of water. The layers were separated, and the organic layer was successively washed with 7.4 L of water and 7.4 L of brine. The organic layer was concentrated under vacuum to 3 L. After being heated to 45 °C, the concentrated nitrile intermediate was treated with 6.6 L (6.60 mol) of 1 M $LiAlH_4$ in THF with temperature maintained below 50 °C. After being stirred for 2 h, the reaction was quenched by a mixture of 0.2 L of water and 0.6 L of THF followed by 0.2 L of 15% NaOH and 0.6 L of water. The mixture was stirred for 1 h and filtered. The filtering

(8) The formation of this byproduct could be explained by the initial alkylation by the benzyl bromide through the endocyclic pyrimidine nitrogen. The resultant iminium would undergo a sigmatropic rearrangement to give *i*. See the Supporting Information for LC−MS analysis and the proposed pathway for the formation of *i*.



i

(9) McOmie, J. F. W.; West, D. E. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 412

(10) (a) Bargellini, G. *Gazz. Chim. Ital.* **1906**, *36*, 329. (b) Weizmann, C.; Sulzbacher, M.; Bergmann, E. *J. Am. Chem. Soc.* **1948**, *70*, 1153.

(11) (a) Lai, J. T. *J. Org. Chem.* **1980**, *45*, 754. (b) Lai, J. T. *Synthesis* **1984**, 122. (c) Rychnovsky, S. D.; Beauchamp, T.; Vaidyanathan, R.; Kwan, T. *J. Org. Chem.* **1998**, *63*, 6363.

cake was washed with 3 L of THF. The combined filtrates containing free base **3** were concentrated under vacuum to about 2 L and diluted with 1.9 L of ethanol and 20 L of toluene. The brown solution was then treated with 0.60 L (7.20 mol) of concentrated HCl. After removal of about 1 L of the solvents, the mixture was cooled to 5 °C over 2 h and stirred for 1 h. The mixture was filtered, washed with 2.0 L of toluene, and dried at 65 °C to afford 1.10 kg (94%) of **5** as an off-white crystalline solid: ^{1}H NMR (300 MHz, CD_3OD) δ 1.43 (s, 6H), 3.15 (s, 2H), 3.81 (s, 3H), 6.97 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H). Anal. Calcd for $C_{11}H_{17}NO \cdot HCl$: C, 61.25; H, 8.41; N, 6.49; Cl, 16.43. Found: C, 61.20; H, 8.44; N, 6.39; Cl, 16.66.

5-Ethyl-*N*-[2-methyl-2-[4-(methyloxy)phenyl]propyl]-2-pyrimidinamine (6). To a mixture of 5.64 g (26.1 mmol) of HCl salt **5** and 3.3 mL (27.4 mmol) of 2-chloro-5-ethylpyrimidine in 20 mL of ethylene glycol was added 5.23 g (52.3 mmol) of $CaCO_3$ (particle size 8.5−10 μm). The addition was in three portions over 5 min to facilitate smooth stirring. The heterogeneous mixture was heated at 130 °C for 26 h. The mixture was cooled to ambient temperature and filtered through a short plug of Celite 545. The filtering cake was washed with 40 mL of EtOAc. The combined filtrates were diluted with 40 mL of water, and the aqueous layer was extracted with 2 × 40 mL of EtOAc. The combined organic layers were successively washed with 40 mL of water and 40 mL of brine. The organic layer was concentrated under vacuum to near dryness and diluted with 10 mL of *i*-PrOH. After being stirred with ice cooling for 3 h, the solids were filtered, washed with 6 mL of heptane, and dried at 60 °C to provide 5.61 g (75%) of **6** as a white crystalline solid: mp 77.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, J = 7.0 Hz, 3H), 1.35 (s, 6H), 2.43 (q, J = 7.0 Hz, 2H), 3.59 (d, J = 7.0 Hz, 2H), 3.78 (s, 3H), 4.70 (s, 1H), 6.86 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 8.07 (s, 2H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 161.7, 158.1, 157.5, 138.8, 127.3, 125.2, 114.0, 55.5, 53.3, 38.4, 27.2, 23.0, 15.8. Anal. Calcd for $C_{17}H_{23}N_3O$: C, 71.55; H, 8.12; N, 14.72. Found: C 71.85; H, 8.17; N, 14.52.

4-[2-[(5-Ethyl-2-pyrimidinyl)amino]-1,1-dimethylethyl]phenol (8). To a solution of 50.0 g (175 mmol) of **6** in 500 mL of CH_2Cl_2 was added 49.7 mL (526 mmol) of BBr_3 over 15 min with ice cooling. The resultant white slurry was stirred at 5 °C for 2 h. The reaction was quenched by transferring to 605 mL of 20% aqueous K_2CO_3 solution over 30 min with ice-cooling. The layers were separated, and the aqueous layer was extracted with 300 mL of CH_2Cl_2. The combined organic layers were washed with 300 mL of brine and concentrated under vacuum to provide 62.3 g (quantitative) of **8** as a thick oil. The crude was used for the next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, J = 7.0 Hz, 3H), 1.34 (s, 6H), 2.45 (q, J = 7.0 Hz, 2H), 3.58 (d, J = 7.0 Hz, 2H), 4.93 (s, 1H), 6.66 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 8.11 (s, 2H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 160.8, 157.5, 155.4, 137.0, 127.3, 125.3, 115.6, 53.4, 38.3, 27.3, 22.9, 15.6. An analytical sample as light yellow oil was obtained by chromatography on silica gel (30−70% EtOAc in hexanes). Anal. Calcd for $C_{16}H_{21}N_3O$: C, 70.82; H, 7.80; N, 15.49. Found: C 70.80; H, 7.84; N, 15.41.

2-[[4-[2-[(5-Ethyl-2-pyrimidinyl)amino]-1,1-dimethylethyl]phenyl]-oxy]-2-methylpropanoic Acid (9). A solution of 58.3 g (175 mmol) of crude **8** in 500 mL of 2-butanone was prepared at 43 °C, followed by addition of 51.6 g (1.29 mol) of NaOH (20−40 mesh) and 3.8 mL (211 mmol) of water. The mixture was stirred at 43 °C for 3 h. The heating was removed, and the mixture was treated with 64.6 g (387 mmol) of 2-bromo-2-methylpropionic acid as a solution in 200 mL of MEK over 20 min. After being heated back to 43 °C and stirred for 1.5 h, the reaction mixture was cooled to ambient temperature, quenched with 200 mL of water, and stirred for 15 min. The layers were separated, and the aqueous layer was extracted with 150 mL of MEK. The combined organic layers were acidified (pH 2.5 for aqueous layer) with 27 mL (405 mmol) of 86% H_3PO_4 as a solution in 130 mL of water. The organic layer was washed with 150 mL of brine and concentrated under vacuum to about 125 mL. The resultant white slurry was treated with 40 mL of MeOH, stirred at −10 °C for 4 h, and filtered. The filtering cake was washed with 30 mL of MeOH and dried at 60 °C to provide 46.3 g (79%) of the first crop of **9** as a white crystalline solid. The filtrate was treated with about 50 mL (50 mmol) of 1 N NaOH to raise the pH to 6. After addition of 100 mL of EtOAc, the organic layer was washed with brine, concentrated to 60 mL, and stirred with ice cooling for 5 h. The resultant slurry was filtered, washed with 5 mL of MeOH, and dried at 60 °C to afford 7.88 g (13%) of the second crop of **9** as a white crystalline solid. The overall yield was 54.2 g (92%) of **9**: mp 142.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, J = 7.0 Hz, 3H), 1.37 (s, 6H), 1.52 (s, 3H), 2.41 (q, J = 7.0 Hz, 2H), 3.62 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 8.0 Hz, 2H), 6.97 (br. s, 1H), 7.26 (d, J = 8.0 Hz, 2H), 8.00 (s, 2H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 178.9, 160.0, 153.8, 140.2, 127.1, 124.3, 119.3, 79.3, 53.1, 38.7, 27.2, 25.6, 22.7, 15.4. Anal. Calcd for $C_{20}H_{27}N_3O_3$: C, 67.20; H, 7.61; N, 11.76. Found: C 67.00; H, 7.64; N, 11.70.

2-[[4-[2-[(5-Ethyl-2-pyrimidinyl)[[4-[(trifluoromethyl)oxy]phenyl]-methyl]amino]-1,1-dimethylethyl]phenyl]oxy]-2-methylpropanoic Acid (GW693085, 1). A slurry of 7.16 g (179 mmol) of NaH (60% dispersion in mineral oil) in 40 mL of THF was heated to 40 °C, followed by addition of 20.0 g (56.0 mmol) of **9** as a solution in 160 mL of THF over 20 min. The exotherm from the addition brought the reaction to about 44 °C. After the addition, the yellow slurry was heated to 65 °C and stirred for 50 min. The mixture was then treated with 16.1 mL (101 mmol) of 4-(trifluoromethoxy)benzyl bromide over 10 min. The resultant light yellow mixture was heated to 65 °C and stirred for 40 min. After being cooled to ambient temperature, the mixture was treated with 51.4 mL of 25% NaOMe in MeOH over 10 min and stirred for 40 min to quench the excess alkylating reagent (to undetectable by HPLC at UV 220 nm). The mixture was diluted with 100 mL of water, and the aqueous layer was extracted with 100 mL of EtOAc. The combined organic layers were treated with a mixture of 4.5 mL of 87% H_3PO_4 and 100 mL of water. The organic layer was washed with 100 mL of brine and concentrated under vacuum to about 60 mL. The partially crystallized mixture was diluted with 10 mL of EtOAc and 30 mL of heptane to facilitate the stirring. After being stirred at −5 °C for 2 h, the mixture was filtered, washed with 40 mL of heptane, and dried at 70 °C to give 25.7 g (86%) of **1** as a white crystalline solid: mp 112.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, J = 8.0 Hz, 3H), 1.34 (s, 6H), 1.61 (s, 6H), 2.46 (q, J = 8.0 Hz, 2H), 3.80 (s, 2H), 4.25 (s, 2H), 6.88 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 8.0 Hz, 2H), 7.01 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 8.17 (s, 2H), 10.95 (br. s, 1H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 177.9, 157.2, 153.0, 148.1, 143.7, 137.8, 128.4, 127.3, 124.6, 121.9, 120.7, 80.0, 58.3, 50.2, 40.2, 27.0, 25.4, 22.9, 15.6; HRMS (ESI+) m/z calcd for $C_{28}H_{33}F_3N_3O_4$ (MH^+) 532.2418, found 532.2406. Anal. Calcd for $C_{28}H_{32}F_3N_3O_4$: C, 63.27; H, 6.07; N, 7.91. Found: C, 63.37; H, 6.16; N, 7.92.

Supporting Information Available: Experimental procedures for compounds **3b**, **4**, and **7**, additional procedure for compound **1**, LC−MS analysis, the proposed pathway for the formation of *i*, and NMR spectra for all new compounds (**1**−**9**). This material is available free of charge via the Internet at http://pubs.acs.org.