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A Concise Synthesis of a Novel Insulin-Like Growth Factor I Receptor (IGF-IR) Inhibitor†

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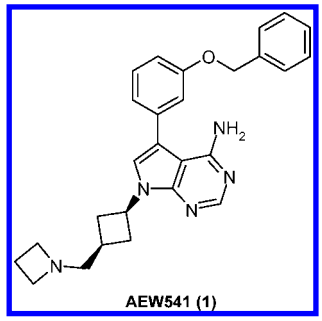
Abstract:

An efficient synthesis of a potent insulin-like growth factor I receptor (IGF-IR) inhibitor AEW541 (1) is described. The key step in the synthesis is the *cis*-selective reductive amination of cyclobutanone, which sets up the desired 1,3-stereochemistry of the cyclobutane ring. The amino group thus generated is used as a handle to build the pyrrolopyrimidine ring. The final step resulting in 1 is accomplished by alkylation of in situ generated mesylate with azetidine.

Introduction

The insulin-like growth factor I receptor (IGF-IR) is a transmembrane tyrosine kinase receptor expressed in a wide variety of cell types. Binding of its cognate ligands, IGF-I and IGF-II, to the extracellular domain of the receptor triggers the activation of its intracellular tyrosine kinase domain and receptor autophosphorylation. A series of downstream signaling events are then initiated via phosphorylation of cellular substrates, which lead to cell proliferation, growth, and survival. Up-regulated levels of both the receptor and its ligands have been observed in a variety of human tumors, particularly in association with pathological events such as invasion and metastasis.[1] Moreover, IGF-IR has been demonstrated experimentally to be required for anchorage-independent growth and oncogenic transformation. A research effort within Novartis resulted in the discovery of AEW541 (**1**) which potently inhibits (IC_{50} 0.15 μM) the recombinant as well as the native IGF-IR kinase.



AEW541 (1)

The Discovery synthesis of AEW541 (**1**) involved 18 chemical steps (Schemes 1–3) and approximately 10 chromatographic purifications and/or high-vacuum distillations. It is a convergent synthesis that was based upon a published procedure.[2] Intermediates **A** and **B** were prepared in gram quantities (Schemes 1 and 2) and combined (Scheme 3). Separation of the *cis/trans* mixture was accomplished by preparative HPLC, and the *cis* isomer was converted to **1**.

It was apparent that a new synthesis was necessary for preparing larger quantities of the drug substance. After a thorough analysis, we decided to proceed using a strategy that would provide a suitably substituted *cis*-1,3-cyclobutane in a selective manner and then use this key building block to construct the remainder of the molecule. This approach would eliminate the highly inefficient and lengthy chromatographic separation of the *cis/trans* isomers, which was a major drawback in the Discovery synthesis (Scheme 3). The approach chosen for the preparation for **1** is pictured retrosynthetically in Scheme 4.

As is evident from Scheme 5, we predicted that reductive amination of an appropriately substituted cyclobutanone would favor the formation of the desired *cis*-3-substituted aminocyclobutane,[3] crucial to the success of this route. Subsequent alkylation of the amino group would provide the precursor required for the construction of the pyrrolopyrimidine ring. Finally, the azetidine function would be introduced by an alkylation method similar to that used in the Discovery synthesis. The entire new route is illustrated in Scheme 5.

cis-Selective Reductive Amination

For the reductive amination of cyclobutanone **2**,[4] sodium triacetoxyborohydride was chosen as the reducing agent on the basis of its availability, ease of handling, and stability. In addition, recent studies had indicated that this was the reagent of choice for this type of transformation.[5] The results of our initial investigation are summarized in Table 1. The reaction involved adding a solution of **2** and **3** in EtOAc to a slurry of sodium triacetoxyborohydride at 45–50 °C in ethyl acetate. After 4 h, the crude product was isolated in 94% yield as a mixture of the *cis/trans* isomers in a ratio of 4.5:1 (Table 1, entry 1).

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† Dedicated to Prof. Dr. Dieter Seebach on the occasion of his 70th birthday.

(1) (a) For reviews, see: Yu, H.; Rohan, T. *J. Natl. Cancer Inst.* **2000**, *92*, 1472–1489. (b) Khandwala, H. M.; McCutcheon, I. E.; Flyvbjerg, A.; Friend, K. E. *Endocrine Rev.* **2000**, *21*, 215–244. (c) Firstenberger, G.; Sonn, H-G. *Lancet Oncol.* **2002**, *3*, 298–302.

(2) Widler, L.; Green, J.; Missbach, M.; Šuša, M.; Altmann, E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 849–852.

(3) Subsequent to the completion of our work, a report appeared delineating a similar approach to a 1,3-*cis* cyclobutane ring; see: Helal, C. J.; Kang, Z.; Lucas, J.; Bohall, B. R. *Org. Lett.* **2004**, *6*, 1853–1856.

(4) The synthesis of this compound will be reported separately.

(5) Abdel-Magid, A. F.; Carson, K.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.

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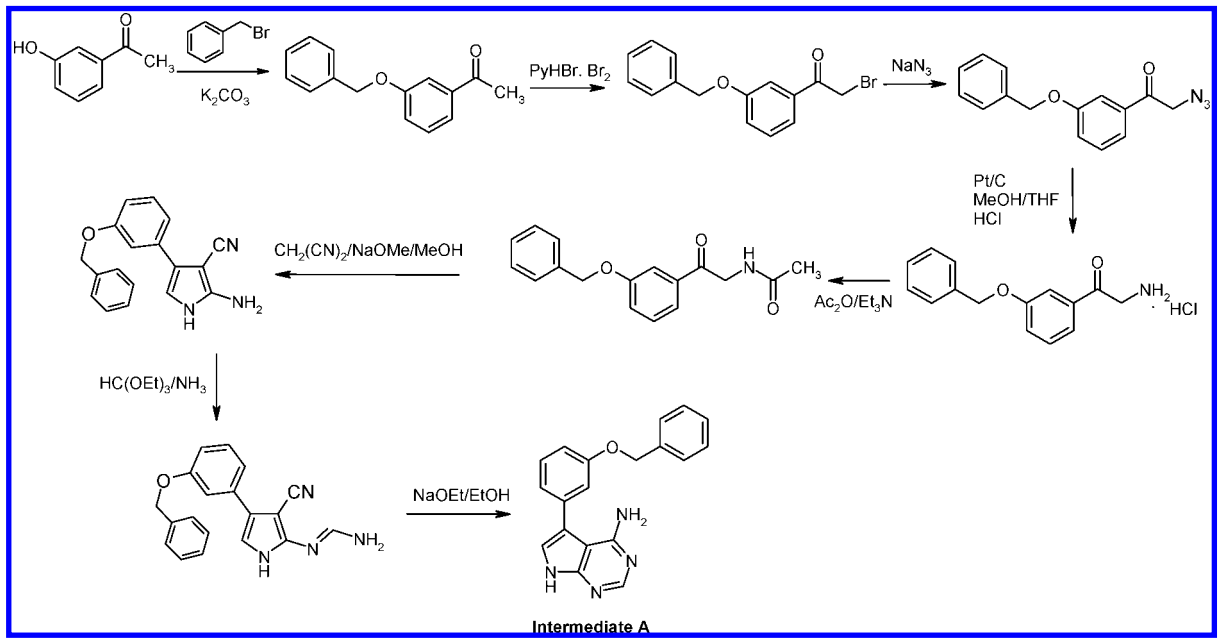
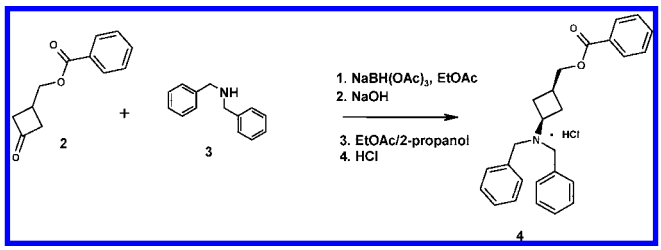
Scheme 1. **Discovery synthesis of intermediate A**



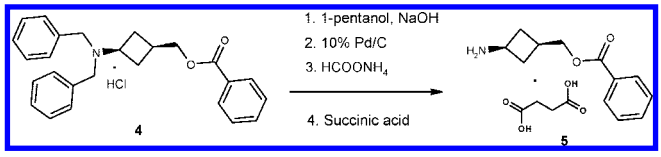
The reaction was also repeated at lower temperatures in an attempt to improve the selectivity. When the reaction was carried out at 20–25 °C (Table 1, entry 2) a *cis/trans* ratio of 5.4:1 was obtained in 84% yield. Acetonitrile and toluene were also tried as alternate solvents; however, the *cis/trans* ratios remained the same.

To separate the *cis/trans* isomers in the crude product by nonchromatographic methods, a large number of salts were prepared and examined. The best of these turned out to be the hydrochloride salt **4**, which was crystallized from an *i*-PrOH/EtOAc/H_2O solvent mixture to provide the *cis* isomer in ~98% isomeric purity in an overall yield of ~60% (Table 1, entry 3). This procedure was scaled up successfully even at higher concentrations (Table 1, entries 4–6).



Hydrogenolysis

Several sets of conditions were studied for debenzylation of **4**. Hydrogenolysis of **4** with 10% Pd/C in ethyl acetate and acetic acid as solvent at 40–45 °C afforded a slow reaction (Table 2, entries 1 and 2).[6] Instead of attempting to optimize these conditions, we decided to investigate the transfer-hydrogenation method using ammonium formate and 10% Pd/C catalyst.[7] The results are summarized in Table 2.



Initially, the reaction was carried out with 2.05 equiv of ammonium formate in ethanol at 40–45 °C. However, this reaction was very slow, requiring the addition of a total of 5 equiv of ammonium formate. Under these conditions, a considerable amount of mono-benzyl product (73%) was formed even after heating to 70–75 °C (Table 2, entry 3). A major improvement was achieved when a mixture of the free base of **4**, *n*-pentanol, and a 10% loading (by weight) of 10% Pd/C was heated to 47 °C and then treated with 5 equiv of ammonium formate in water (Table 2, entry 4). After 4.5 h, the two-phase reaction was 84% complete, and after 12 h, it was 100% complete. The amount of the mono-benzyl intermediate was reduced to less than 1%. With regard to the isolation of **5**, we found that the HCl salt was soluble in *n*-pentanol. Therefore, to maximize the isolated yield the preparation of other salts was investigated. The succinate salt was chosen based on its ease of formation and poor solubility in *n*-pentanol.

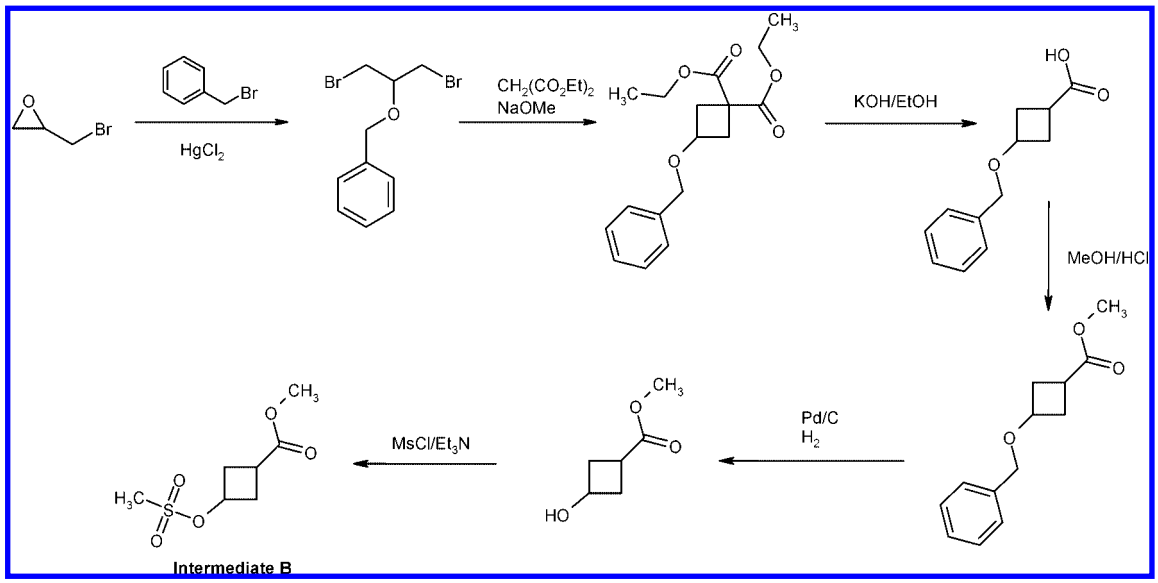
With the isolation procedure in hand, the reaction was carried out using a 5% loading of 10% Pd/C (Table 2, entry 5). The reaction required heating at 40–45 °C for 24 h, and the product was isolated in 65% yield as the succinate salt. In the following experiment (Table 2, entry 6), the recovery was increased by adding heptane to the solution. Product **5** was isolated in 89% yield and 99% purity. This procedure was repeated on 121 g of **4** with a 10% loading of catalyst (Table 2, entry 7). After 10 h, the reaction was complete. Work-up and salt formation resulted in an 83% yield of **5** with 99% HPLC purity.

Selective N-Monoalkylation

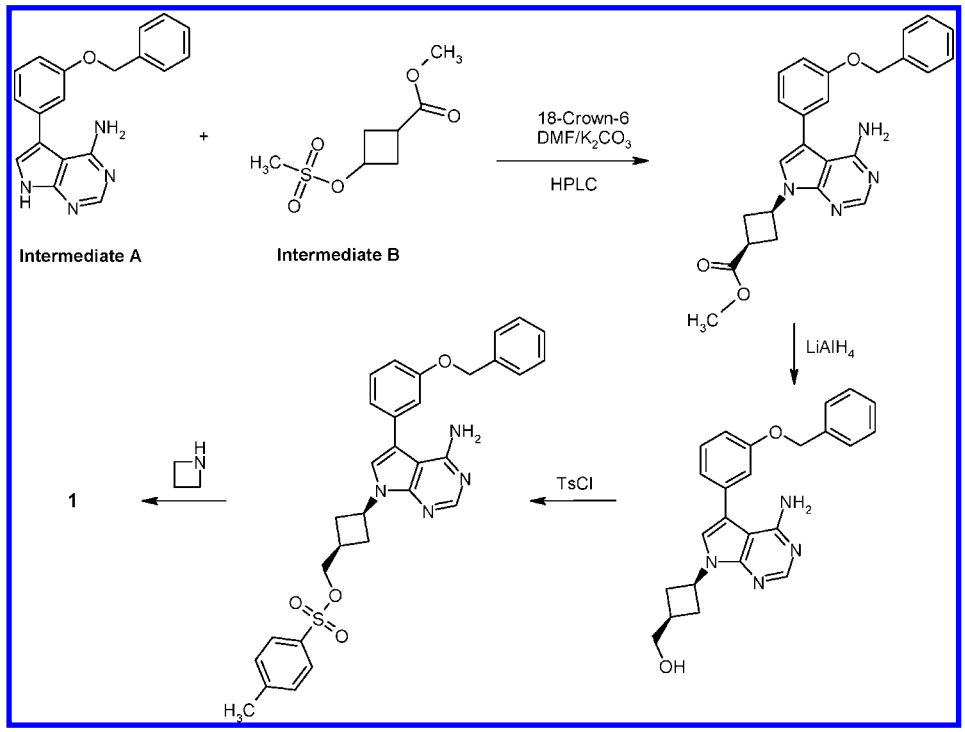
We had envisioned carrying out the alkylation step on the amino alcohol **13**, which was easily obtained from **5** by basic hydrolysis. Following a literature procedure,[2] amino alcohol **13** was treated with α-bromoketone **6** in ethanol containing 2 equiv

(6) The cleavage of benzylamines with H_2/Pd/C is often very slow; see: Hartung, W. H.; Simonoff, R. *Org. React.* **1953**, *VII*, 253.
(7) Prasad, K.; Jiang, X.; Slade, J. S.; Clemens, J.; Repič, O.; Blacklock, T. J. *Adv. Synth. Catal.* **2005**, *347*, 1769–1773.

Scheme 2. **Discovery synthesis of intermediate B**



Scheme 3. **Final steps in the Discovery synthesis of 1**



of diisopropylethylamine at room temperature. HPLC analysis of the reaction mixture showed a ratio of 1:2.9 of mono **14** and dialkyl **15** products (Scheme 6).

In addition, we observed that the desired product **14** was unstable in solution, as the HPLC peak corresponding to it diminished with time. The nature of the decomposition products was not investigated further, although on the basis of its mass spectral data one of the major components appeared to be a dimer.

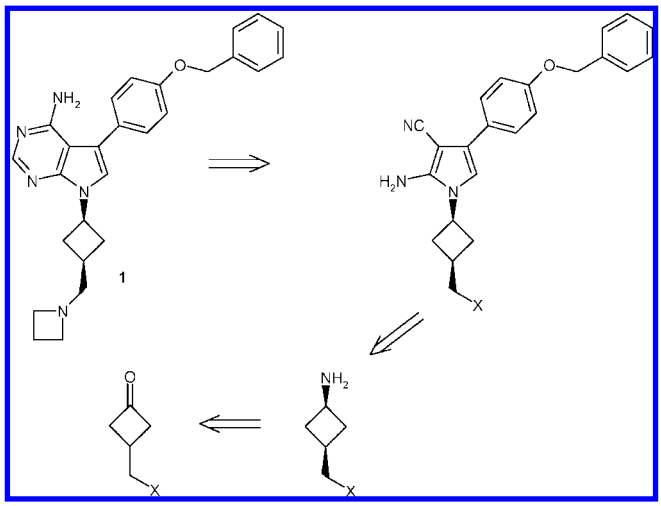
To avoid isolation of this unstable compound and to convert **14** directly into the pyrrole **8**, the reaction mixture was added to a solution of sodium salt of malononitrile at elevated temperature. The desired product **8** was obtained in 30% yield after chromatography (Scheme 7).

With the idea of combining the two steps, an attempt was made to optimize the reaction conditions for this alkylation (**13** + **6** → **14**). These results are summarized in Table 3.

With regard to the solvent effects, reaction in methanol, ethanol, and THF all afforded poor **14:15** ratios even with the use of 2 equiv of the amine (Table 3, entries 2–4). In pyridine, *N*-methylmorpholine, and triethylamine, reaction between **6** and the amine solvents was observed (Table 3, entry 7). Better product ratios were obtained when the reaction was carried out in polar aprotic solvents DMF and NMP (Table 3, entries 8–16).

We found that potassium carbonate was superior to triethylamine and potassium phosphate as a base in DMF (Table 3,

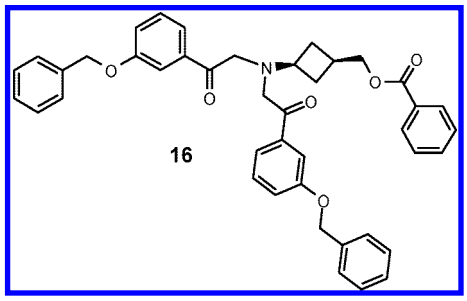
Scheme 4. **Retrosynthetic analysis for the preparation of 1**



entries 8, 10, and 12). However, potassium phosphate was equivalent to potassium carbonate in NMP (Table 3, entries 11 and 13).

As previously mentioned, compound **14** was unstable and provided only poor yields of the pyrrole **8** regardless of the conditions followed for its formation. However, we observed that the free base of the benzoate **5** reacted in a similar fashion with **6** and, more importantly, provided a stable HCl salt of the desired product **7** (Scheme 7). Thus, isolation of the free base **13** was not necessary. The reaction was optimized, and the results are presented in Table 4.

The major drawback of this reaction was that 2 equiv of the expensive **5** was needed; the excess amine was used as base to quench the resulting HBr. Fortunately, the excess **5** could be recovered in 97% purity and recycled. In addition to acetonitrile, a number of other solvents including ethyl acetate (Table 4, entry 2), MTBE (Table 4, entry 3), and propionitrile (Table 4, entry 5) were used but did not offer any advantage over acetonitrile. In some cases, a considerable amount of the dialkylated amine side product **16** was formed. Lowering the reaction temperature to −40 °C (Table 4, entry 6) helped to suppress the formation of this compound. Use of an external base (Table 4, entry 7) instead of excess **5** resulted in a low yield of **7**, and the product was contaminated by the salt of the external base.



The final optimized conditions, (Table 4, entry 8) afforded compound **7** in 57% yield, and 97.7% purity (HPLC).

Construction of the Pyrrole Ring

The preparation of 2-amino-3-cyanopyrroles is well precedented in the literature.[12] A solution of malononitrile in methanol was added to **7** followed by the slow addition of aqueous KOH. After heating the reaction mixture for 1 h at reflux, it was cooled, and water was slowly added to precipitate product **8** in 85% yield with a purity of 98% (Scheme 9).

Synthesis of the Pyrrolo[2,3-*d*]Pyrimidine Ring System

The initial effort to synthesize **9** was based on a literature precedent used by the Discovery group (Scheme 10).[2] Starting from compound **8**, four steps and chromatographic purifications were required to prepare the pyrrolopyrimidine **9**. Thus, **8** was heated in triethyl orthoformate (as solvent) in the presence of catalytic acetic anhydride at 80 °C for 2 h. After the reaction was complete, the excess orthoformate (bp 146 °C) was distilled off under vacuum to give crude **17**. This compound was treated with ammonia/methanol at 21 °C for 16 h to afford amidine **18** in 46% yield after the excess ammonia/methanol was removed under vacuum, and the residue was purified by chromatography. Amidine **18** was dissolved in ethanol in the presence of sodium ethoxide and heated at 80 °C for 1 h to form pyrrolopyrimidine **19**. After removal of solvent, the residue was hydrolyzed with HCl to give crude **9**. After chromatography, **9** was obtained as a brown solid in ∼65% yield. The overall yield of **9** from **8** was only 30%.

We found that the desired pyrrolo[2,3-*d*]pyrimidine ring system could be obtained more efficiently by heating **8** in formamide (as solvent) in the presence of formic acid at 100 °C.[13] The reaction was complete in 2–4 h (Scheme 11). However, under these conditions, formate **20** was formed in addition to many side products.

To improve the efficiency of the reaction, the formamide/formic acid was replaced by formamidine acetate, which had been employed previously in our group in a similar situation.[14] This proved to be a better choice. When **8** was treated with 3.5 equiv of formamidine acetate in ethylene glycol (4 mL/g of **8**) at 135 °C for 3–5 h, **9** was formed as the major product (89–94%; Scheme 12). An intermediate was observed, which we believed to be amidine **21**, as evidenced by LC–MS. This intermediate was observed only in small amounts in the beginning of the reaction as it was quickly converted to **9**.

The reaction mixture was dark, probably due to some polymerization of the formamidine. A Celite filtration during the aqueous workup and a silica gel filtration of the ethyl acetate solution of the product were needed to remove most of the dark impurities. The product was obtained in ∼74% yield.

Treatment of **8** with formamidine hydrochloride also produced **9**. However, formamidine hydrochloride is about 15 times more expensive than formamidine acetate. The reaction with formamidine hydrochloride provided no advantage over formamidine acetate with respect to impurity formation and ease of workup.

(12) (a) Gewald, K. *Z. Chem.* **1961**, *1*, 349. (b) Abdalla, G. M.; Sowell, J. W., Sr. *J. Heterocycl. Chem.* **1987**, *24*, 297–301. (c) Chen, T.-C.; Meade, E. A.; Hinkley, J. M.; Townsend, L. B. *Org. Lett.* **2004**, *6*, 2857–2859.

(13) (a) Pichler, H.; Folkers, G.; Roth, H. J.; Eger, K. *Liebigs Ann. Chem.* **1986**, 1485–1505. (b) Dave, C. G.; Shah, P. R.; Upadhyaya, S. P. *Ind. J. Chem.* **1988**, *27B*, 778–780.

(14) Prasad, K.; Lee, G. T.; Chaudhary, A.; Girgis, M. J.; Streemke, J. W.; Repič, O. *Org. Process Res. Dev.* **2003**, *7*, 723–732.

Scheme 5. **New synthesis of 1**

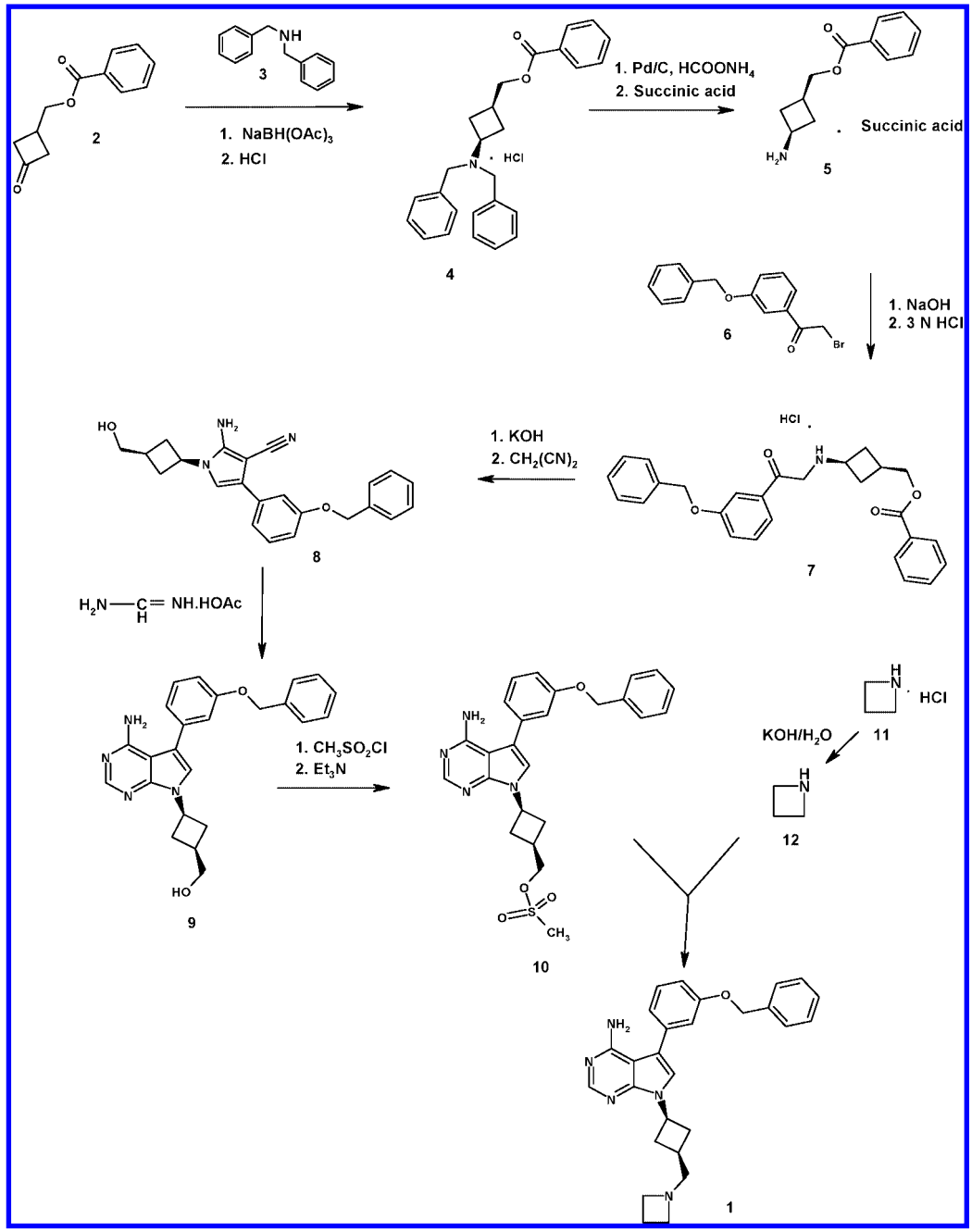


Table 1. **Reductive amination of 2**

entry	reaction conditions	*cis/trans* (%)	yield (%)
1	1.05 equiv **2**, 1.4 equiv $NaBH(OAc)_3$, added **2/3** solution to borohydride in EtOAc, 5 h, 45 °C	82/18	94 (crude)
2	same as entry 1, 20 °C, 16 h	77/13	85 (crude)
3	same as entry 2, solvent changed to *i*-PrOH and HCl added to form salt	98/2	61
4	same as entry 3, scaled up 4×	98/2	64
5	same as entry 3, scaled up 8×	98/2	70
6	same as entry 5, double the concentration[a] (to optimize throughput)	98/2	61

[a] The rate of this reaction was twice as fast as a result of the increase in concentration.

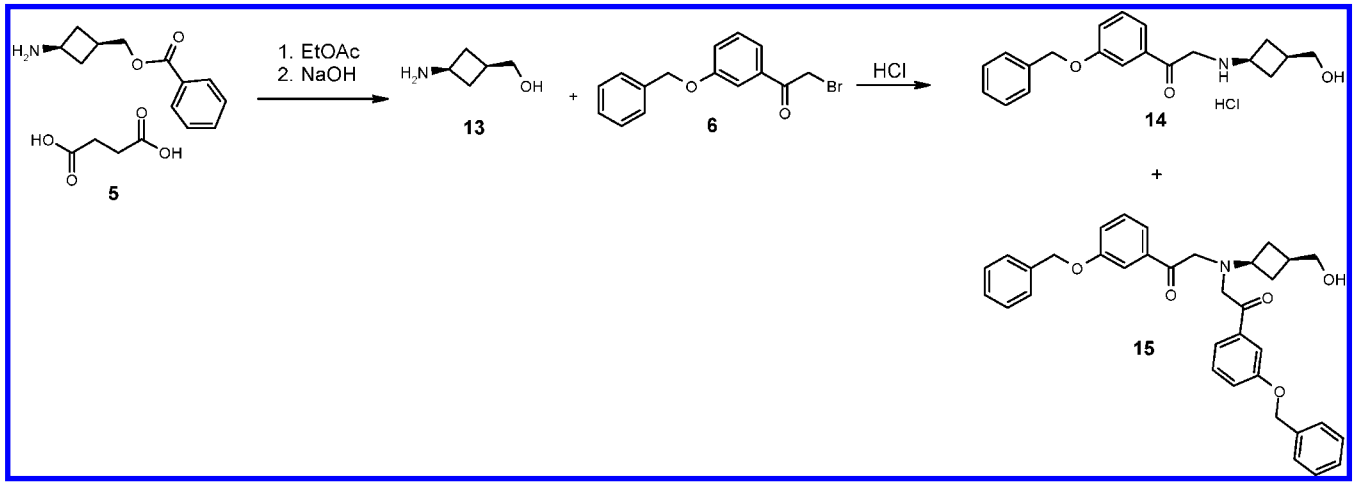
Azetidine Alkylation

The procedure used by Discovery was investigated. It involved the formation of the tosylate of **9** followed by displacement of tosylate group with azetidine **12** to give **1**. The tosylation step was problematic since the tosyl chloride had to be added in several portions, and the reaction was still

Table 2. **Optimization of deprotection conditions**

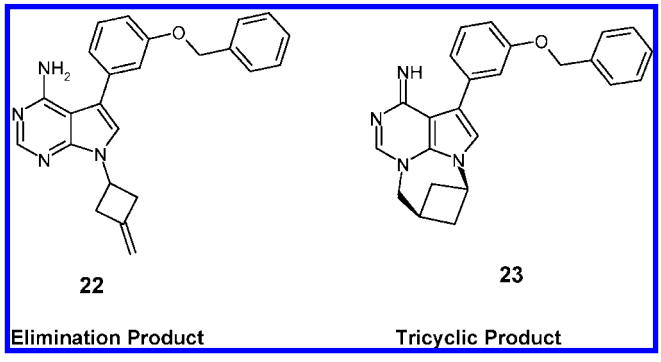
entry	reaction conditions	reaction mixture composition			yield (%)
		5	mono benzyl	**4**	
1	catalytic hydrogenation; EtOAc, 10% by wt of Pd/C (10%), 16 h, 25 °C	41	36	16	
2	catalytic hydrogenation; AcOH, 20% by wt of Pd/C (10%), 48 h, 25 °C		2	97	
3	transfer hydrogenation; EtOH, 20% by wt of Pd/C (10%), 5 equiv $HCOONH_4$, 36 h, 67 °C	15	73	2	
4	transfer hydrogenation; *n*-pentanol, 10% by wt of Pd/C (10%), 5 equiv $HCOONH_4$, 12 h, 47 °C	99	1		
5	transfer hydrogenation; *n*-pentanol, 5% by wt of 10% Pd/C (10%), 5 equiv $HCOONH_4$, 12 h, 47 °C. Aqueous work-up, succinic acid added to crystallize **5**	92	8		65
6	as entry 5, distilled off H_2O at 102 °C, added heptane to increase yield; needed 24 h for complete conversion	99	<1		89
7	as entry 6, 121 g of **4**; used 10% by wt of catalyst, 10 h	99	<1		83

Scheme 6. **Alkylation of amino alcohol 13**



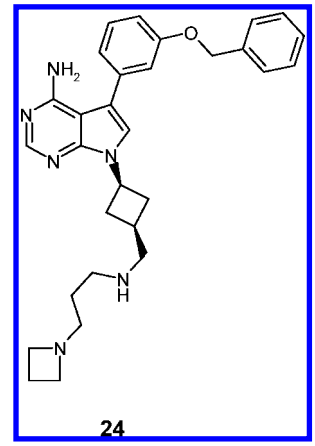
incomplete after 36 h at 0 °C. At higher temperatures, extensive decomposition of tosylate was observed.

In contrast, the formation of the mesylate proceeded cleanly even at 0 to −10 °C in THF (Scheme 13). Initially, the mesylate was isolated prior to the reaction with excess azetidine. However, we found that the mesylate was unstable on standing and decomposed into an elimination product **22** and a tricyclic product **23**. The structures of these by-products were tentatively assigned on the basis of NMR and LC/MS data.



This led to a change in the procedure wherein the mesylate was prepared and used directly without isolation. An excess of the azetidine free base **12** was employed. The reaction was usually complete in 6 h at 60 °C. A significant amount of impurity **24** (5%) was also formed as a result of opening the azetidine ring of **1** with another molecule of azetidine. The structure of this impurity was confirmed by mass spectroscopy.

Further studies were carried out to determine the effect of



temperature on the formation of this side product. We found that at 40 °C the formation of this impurity was minimal, however, the rate of product formation was also slower. At a reaction temperature of 50 °C, only 1% of the ring-opened product was present, and the reaction was complete in 16 h.

Scheme 7. **Preparation of pyrrole 8**

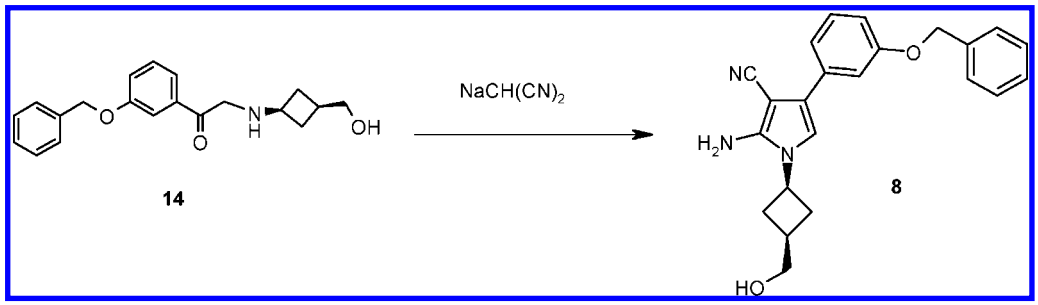


Table 3. **Attempted monoalkylation of 13 with 6**

entry	ratio of 13:6	base (equiv)	solvent	ratio **14**:**15**
1	1:1	(*i*-Pr)$_2$NEt (2)	EtOH	1:2.9
2	2:1	Et$_3$N (2)	MeOH	1.5:1
3	2:1	NaOH (1)	MeOH	
4	2:1	Na$_2$CO$_3$ (2)	MeOH	1.1:1
5	2:1	(*i*-Pr)$_2$NEt (2)	THF	1:1.1
6	1:1	DBU (2)	THF	complex mixture
7	2:1		pyridine, NMM, Et$_3$N	
8	2:1	K$_2$CO$_3$ (2)	DMF	9:1
9	3:1		DMF	4.6:1
10	2:1	Et$_3$N (2)	DMF	3.3:1
11	2:1	K$_3$PO$_4$ (2)	NMP	3.4:1
12	2:1	K$_3$PO$_4$ (2)	DMF	2.9:1
13	2:1	K$_2$CO$_3$ (2)	NMP	2.8:1
14	2:1	K$_2$CO$_3$ (4)	NMP	3:1
15	1.2:1	K$_2$CO$_3$ (4)	DMF	1.7:1
16	1.2:1	K$_2$CO$_3$ (4)	NMP	1:1.9

[a] No product was observed due to the reaction of **6** with sodium hydroxide. [b] Compound **6** was unstable in these solvents.

These conditions were chosen for the final process. It is interesting to note that no elimination product was formed under these conditions.

For the isolation of the **1**, the product was extracted into aqueous citric acid and the pH adjusted to 10, at which point the compound crystallized from solution. The compound could be further purified by recrystallization from ethyl acetate or isopropyl acetate. Isopropyl acetate was chosen for better recovery. In the laboratory, the yields were 59–63%, and the purity of the **1** was 99%.

Azetidine Preparation

Azetidine free base **12** was obtained from the HCl salt **11** according to a literature procedure.[15] This was accomplished by the slow addition of a concentrated solution of the HCl salt in water to a concentrated solution of KOH in water at 95–100 °C, at which point the low boiling azetidine distilled out of the mixture. During this flash distillation, water formed an azeotrope with azetidine, and as a result the distillate contained varying amounts of water (up to 11%). On the basis of our previous experience, we found that the reaction could tolerate up to 10% water in the azetidine without having a deleterious effect on the yield or quality of **1**. Subsequently, this procedure was modified. The new process used more KOH and less water than employed previously. In addition, the reaction temperature was kept below 85 °C to minimize the co-distillation of water with azetidine. The yield for this step was 84%, and the azetidine was found to contain 2.2% of water by Karl Fischer analysis.

(15) Causey, D. H.; Mays, R. P.; Shamblee, D. A.; Lo, Y. S. *Synth. Commun.* **1988**, *18*, 205–211.

Conclusion

We have synthesized **1** in six linear steps starting from readily available starting materials. The synthesis is efficient and has been scaled up to prepare 20 kg of **1**. An efficient method for selective *cis* reductive amination of 3-substituted cyclobutanone was described. Construction of the pyrrolopyrimidine ring system from the corresponding suitably substituted pyrrole was simplified. The instability of the pure mesylate of **9** was overcome by using the mesylate in situ for azetidine alkylation.

Experimental Section

General. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AVANCE DPX-300 spectrometer (^{1}H NMR at 300 MHz). Analytical high performance liquid chromatography (HPLC) was carried out using a Waters Alliance 2690 Separations Module, a Waters 996 Photodiode Array Detector (MaxPlot), and a 4.6 mm × 25 cm Waters C18 Symmetry column. Reactions were carried out under an atmosphere of nitrogen. Residual water content was determined by Karl Fischer titration. Unless reported otherwise, all reaction temperatures refer to the measured temperature of reaction mixtures not to the cooling or heating bath temperatures.

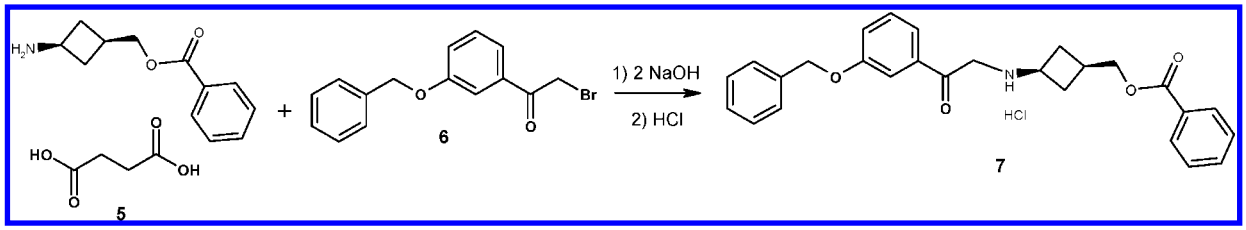
***cis*-3-Bis(phenylmethyl)aminocyclobutanemethyl Benzoate Hydrochloride 4.** Charge a 500-mL, 4-necked, round-bottomed flask with 24.8 g (0.121 mol) of **2**, 22.5 g (0.115

Table 4. **Monoalkylation of 5**

entry	reaction conditions	product 7 (% HPLC purity)	yield[a] (%)
1	2 equiv **5,** 1 equiv **6**, acetonitrile, 20–25 °C, 1 h; added EtOAc/HCl	98	28
2	2 equiv **5**, 1 equiv **6**, EtOAc, –15 to –10 °C, 1 h; added EtOAc/HCl	93	47
3	2 equiv **5**, 1 equiv **6**, MTBE, –15 to –10 °C, 1 h; added EtOAc/HCl	rate of reaction was slow; large amount of dialkylated material was observed	
4	scaled 2×; added 37% HCl	89.8; 8% dialkyl	60
5	2 equiv **5**, 1 equiv **6**, propionitrile, −15 to –10 °C, 1 h; added 37% HCl	79; 18% dialkyl	47
6	2 equiv **5**, 1 equiv **6**, acetonitrile, −40 to −35 °C, 3 h; added 6 N HCl	96; 3% **5**	55
7	1.3 equiv **5**, 1 equiv **6**, acetonitrile, 3 equiv Hunig's base, −40 to −35 °C, 3 h; added 6 N HCl	95 (material was mainly HCl salt of Hunig's base)	
8	2 equiv **5**, 1 equiv **6**, acetonitrile, −16 to −10 °C, stirred 1 h; added 3 N HCl	97.7	57

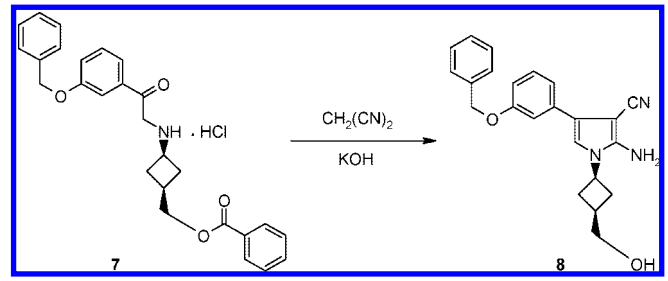
[a] Based on **6**.

Scheme 8. **Alkylation of 5**



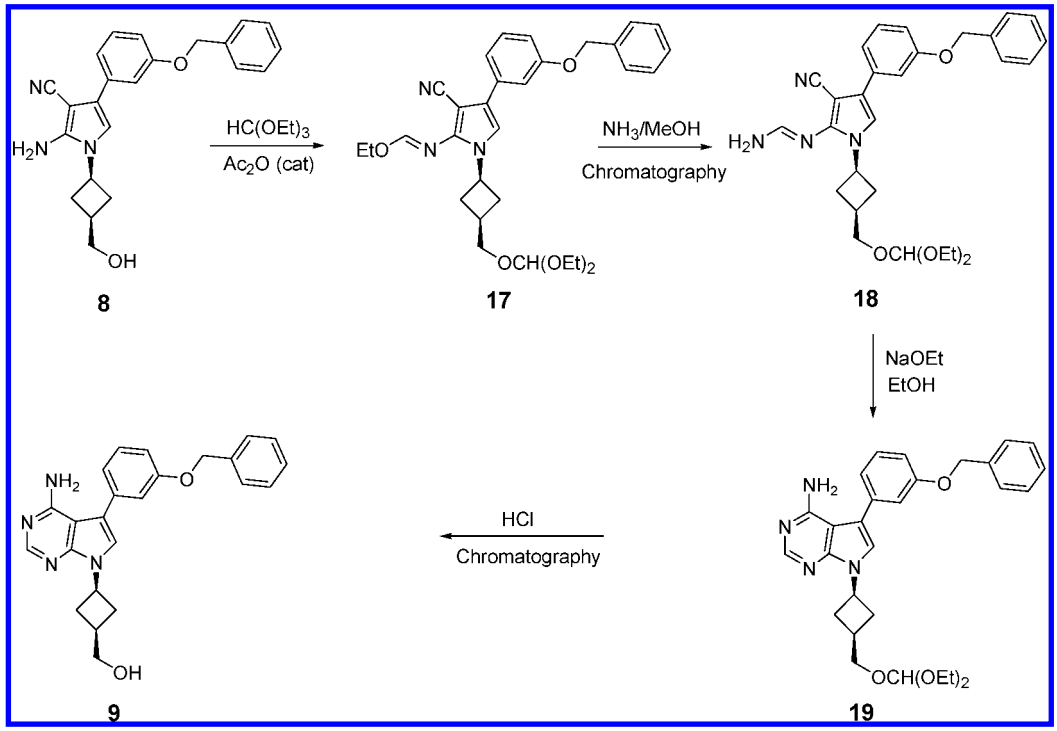
mol) of **3**,and 101.5 g (112.5 mL) of ethyl acetate. Stir the homogeneous reaction mixture for 1 h at 20–25 °C. Charge a 2-L, 4-necked, round-bottomed flask with 34.1 g (0.161 mol) of sodium triacetoxyborohydride and 203.0 g (225 mL) of ethyl acetate. Stir for 15 min at room temperature. Add the (**2** + **3**) solution over 30–40 min. Stir the heterogeneous reaction mixture at 20–25 °C for 16 h. Add 426.4 g (410 mL) of 2 N NaOH over 15 min. Stir for 1 h at 20–25 °C. Caution: H_2 evolution. Remove the lower aqueous layer and wash the ethyl acetate solution of **4** with 2 × 300 g of water. Mark a 1-L round-bottomed flask at 130 mL. Charge the flask with the ethyl acetate solution of **4** and concentrate to a volume of 130–150 mL, using atmospheric distillation conditions. Cool the residual solution to 65 °C and add 94.2 g (120 mL) of 2-propanol. Hold the solution at 65–70 °C. Add 12.0 g (0.121 mol) of hydrochloric acid (37 wt %) over 5–10 min. Cool from 65 °C to 43–45 °C. At 45 °C seed the reaction mixture with 20 mg of **4**. Cool from 43–45 °C to 32–33 °C over 0.5 h. Stir at 32–33 °C for at least 90 min. Cool to 20–25 °C over 0.5 h. Hold 1 h at 20–25 °C. Isolate the solid by filtration and wash the cake with 78.5 g (100 mL) of 2-propanol. Dry the cake on the funnel for 30 min, then dry in a vacuum oven at 60–65 °C (35–50 mm Hg) for at least 16 h, to yield **4** as a white solid, 29.9 g (62% yield), 98.9% *cis* isomer; 1.1% *trans* isomer by HPLC analysis; mp 165 °C; ^{1}H NMR ($CDCl_3$) δ 8.0 (d, J = 9.0 Hz, 2H), 7.55 (m, 13H), 4.35 (d, J = 9.0 Hz, 2H), 4.07 (m, 4H), 3.31 (m, 1H), 2.86 (m, 2H), 2.20 (m, 3H); ^{13}C NMR (DMSO, d_6) δ 165.61, 133.31, 131.43, 130.17, 129.92, 129.51, 129.28, 129.24, 128.70, 128.63, 128.52, 67.49, 551.6, 54.38, 29.70, 26.40; MS m/z 386 (M^+). Anal. Calcd for $C_{26}H_{28}ClNO_2$: C, 74.00; H, 6.69; N, 3.32; Cl, 8.40. Found: C, 74.08; H, 6.65; N, 3.31; Cl, 8.62.

Scheme 9. **Preparation of pyrrole 8**

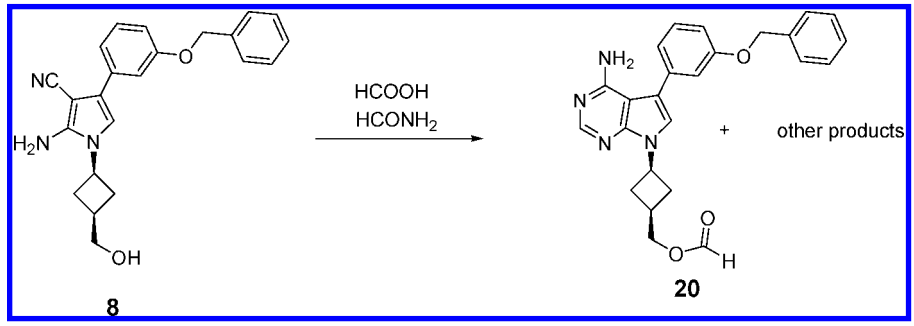


***cis*-3-Aminocyclobutanemethyl Benzoate Butanedioate (1:1 Salt) 5.** Charge a 1-L round-bottomed flask with 121.0 g (0.286 mol) of **4** and 405.5 g (500 mL) of 1-pentanol. Stir the heterogeneous reaction mixture at 20-25 °C. Add 312.0 g (300 mL) of 1 N NaOH. Stir the two-phase reaction mixture for 15 min at 20-25 °C. Heat to 45-50 °C and stir for 5 min. Remove the lower aqueous layer and cool the organic layer to 20-25 °C. Charge a 2-L, 4-necked, round-bottomed flask with 24.2 g of 10% Pd/C and add the 1-pentanol solution of the **4** free-base. Charge a 250-mL round-bottomed flask with 90.2 g (1.43 mol) of ammonium formate and 150.0 g (150 mL) of water. Stir for 15 min. Heat the reaction mixture containing the free-base of **4** and 10% Pd/C to 45–50 °C then add the aqueous ammonium formate solution over 30-40 min. Stir the heterogeneous reaction mixture at 45–50 °C for 16 h (possible H_2 evolution). When analysis determines completeness of reaction, cool to 20–25 °C. Filter and wash the cake with 81.1 g (100 mL) of 1-pentanol and 50.0 g (50 mL) of water. Separate the lower aqueous layer from the filtrate. Wash the organic layer with 2 × 100 mL of water. Heat to 45–50 °C and stir for 5 min. Remove the lower aqueous layer. Heat to an internal temperature of 102 °C and collect ~100 mL of distillate using

Scheme 10. **Discovery approach to 9**



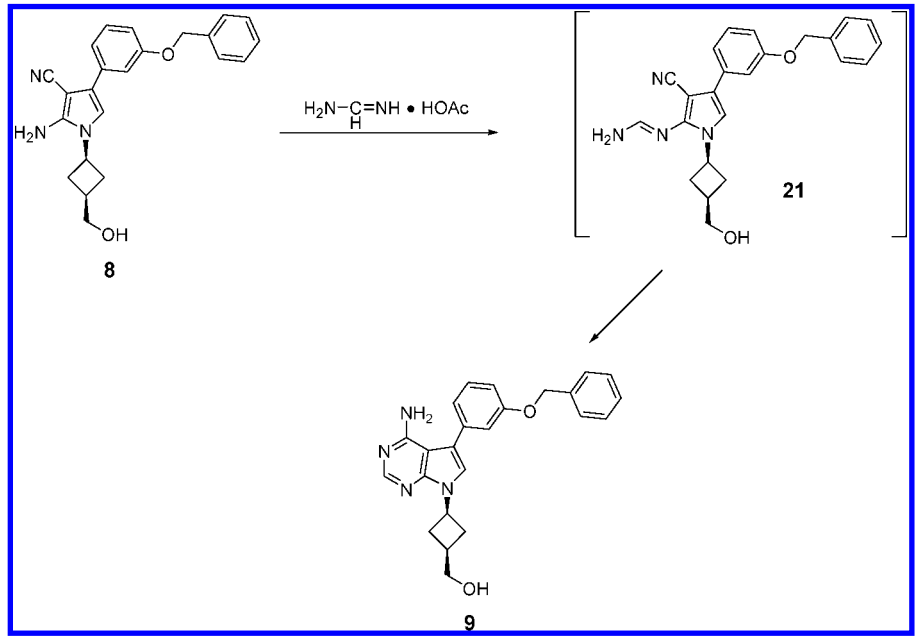
Scheme 11. **Alternate preparation of the pyrrolo[2,3-*d*]pyrimidine ring system**



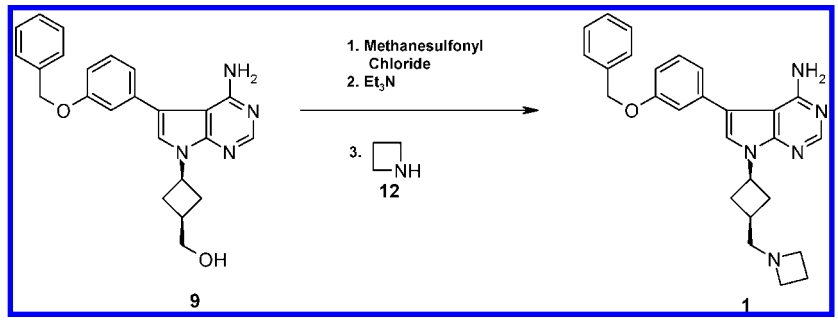
atmospheric distillation conditions. Cool to an internal temperature 30 °C. Add 33.8 g (0.29 mol) of succinic acid. Heat the organic layer to 95–100 °C to obtain a homogeneous reaction mixture. Cool from 95–100 to 20–25 °C over 2 h. Stir at 20–25 °C for at least 90 min. Add 171.0 g (250 mL) of heptane over 30 min and stir for 1.5 h at 20–25 °C. Isolate the solid by filtration and wash the cake with 112.1 g (150 mL) of 1:1 mixture of heptane and 1-pentanol. Dry the cake on the funnel for 30 min and then dry in a vacuum oven at 55–60 °C (35–50 mm Hg) for at least 16 h to yield 77.5 g of **5** as a white solid (80% yield); mp 165–170 °C; ^{1}H NMR (DMSO, d_6) δ 9.96 (br s, 4H), 8.00 (m, 2H), 7.68 (m, 1H), 7.54 (m, 2H), 4.25 (d, 2H), 3.55 (m, 1H), 2.45 (m, 3H), 2.33 (s, 4H), 1.92 (m, 2H); ^{13}C NMR (DMSO, d_6) δ 175.08, 165.72, 133.34, 129.63, 129.20, 128.72, 67.39, 41.32, 31.44, 30.70, 27.13; MS *m/z* 206 (M^+). Anal. Calcd for $C_{16}H_{24}NO_6$: C, 59.44; H, 7.48; N, 4.33. Found: C, 59.46; H, 7.21; N, 4.29.

2-[*cis*-3-[(Benzoyloxy)methyl]cyclobutyl]amino]-1-[3-(phenylmethoxy)phenylethanone Hydrochloride 7. Charge a 1-L round-bottomed flask with 101.7 g (0.31 mol) of **5**, 451.0 g (500 mL) of ethyl acetate and 200 g (200 mL) of water. Stir the heterogeneous reaction mixture at 22 ± 5 °C. Add 54.6 g (0.68 mol) of 50% NaOH and rinse with 20 mL of water. Stir the two-phase reaction mixture for 10 min. Remove the lower aqueous layer and wash the upper organic layer with 200 mL of water. Concentrate the organic phase to a volume of 180–220 mL using a maximum internal temperature of 40–45 °C at 100−150 mm Hg vacuum. Add 314.4 g (400 mL) of acetonitrile and concentrate the mixture to a volume of 180–220 mL using a maximum internal temperature of 40–45 °C and 80–150 mm Hg vacuum. Add 314.4 g (400 mL) of acetonitrile and concentrate the mixture to a volume of 180–220 mL using a maximum internal temperature of 40–45 °C and 80–150 mm Hg vacuum. Charge a 2-L, 4-necked, round-bottomed flask with the free-base solution of **5** and 216.2 g (275 mL) of acetonitrile. Stir the reaction mixture for 10 min at 20–25 °C to obtain a solution. Cool to –16 to –10 °C. Charge a 250-mL round-bottomed flask with 47.3 g (0.155 mol) of **6** and 149.3 g (190 mL) of acetonitrile and stir for 15 min to obtain a solution. Add the acetonitrile solution of **6** to the flask containing the solution of **5** over 30–40 min. The temperature is kept at –16 to –10 °C by controlling the rate of addition. Stir the homogeneous reaction mixture at –16 to –10 °C for 30–40 min. Add 77 mL (0.23 mol) of 3 N hydrochloric acid over 10 min and stir for 1 h at –16 to –10 °C. Isolate the solid by filtration and wash the cake with 235.8 g (300 mL) of

Scheme 12. **Formamidine approach to 9**



Scheme 13. **Azetidine alkylation**



acetonitrile. Dry the cake on the funnel for 30 min, then dry in an oven at 20–25 °C (35–50 mm Hg) for at least 16 h, to yield an 40.3 g of **7** as an off-white solid (56% yield based on **6**); mp 203 °C (dec), 97% HPLC purity (area normalization); ^{1}H NMR (DMSO, d_6) δ 9.50 (br s, 2H), 7.98 (m, 2H), 7.45 (m, 12H), 5.22 (s, 2H), 4.70 (s, 2H), 4.31 (m, 2H), 3.76 (m, 1H), 2.33 (m, 4H); ^{13}C NMR (DMSO, d_6) δ 192.12, 165.72, 158.55, 136.57, 134.94, 133.35, 130.22, 129.62, 129.24, 128.73, 128.46, 127.97, 127.78, 121.16, 120.81, 114.02, 69.57, 67.37, 50.09, 47.75, 28.78, 26.78; HRMS calcd for $C_{27}H_{28}NO_4$ (M + 1) 430.1940, found 430.1930.

2-Amino-1-[*cis*-3-(hydroxymethyl)cyclobutyl]-4-[3-(phenylmethoxy)phenyl]-1*H*-pyrrole-3-carbonitrile 8. Charge a nitrogen-flushed 2-L, 4-necked round-bottomed flask with 46.6 g of compound **7**. Add a solution of 13.2 g of malononitrile in 369 g (466 mL) of methanol. Stir the mixture at 22 ± 3 °C. Add a solution of 16.8 g of potassium hydroxide in 84 mL of water over a period of 5 min. Heat the reaction mixture to reflux (72 ± 3 °C) over 20 min and maintain this temperature for 30 min. Cool the reaction to 32 ± 3 °C over 15 min. Add 932 mL of water over 30 min and stir the resulting suspension at this temperature for an additional 30 min. Filter the solids through a polypropylene filter pad and wash the solids twice with (2 × 100 g) of deionized water (22 ± 3 °C). Dry the solids at 45 °C and 180 mbar for 18 h to afford **8** as a dark orange crystalline solid (94% yield); mp 128 °C, 96% HPLC purity (area normalization); ^{1}H NMR (DMSO, d_6) δ 7.37–7.51 (m, 4H), 7.34 (m, 1H), 7.17–7.29 (m, 3H), 6.89 (s, 1H), 6.85 (dd, J = 8.2 Hz, 2.5 Hz, 1H), 5.91 (s, 2H), 5.11 (s, 2H), 4.60 (s, 1H), 4.43 (quintet, J = 8.4 Hz, 1H), 3.44 (s, 2H), 2.40 (m, 2H), 1.98-2.18 (m, 3H); ^{13}C NMR (DMSO, d_6) δ 158.6,148.4, 137.1, 135.4, 129.6, 128.5, 127.9, 127.8, 120.8, 118.6, 117.6, 112.1, 111.6, 109.5, 69.2, 68.7, 64.1, 44.7, 32.2, 29.9; HRMS calcd for $C_{23}H_{24}N_3O_2$ (M + 1) 374.1869, found 374.1852. Anal. Calcd for $C_{23}H_{23}N_3O_2$: C, 73.98; H, 6.21; N, 11.25. Found: C, 73.48; H, 6.69; N, 11.09.

3-[4-Amino-5-[3-(phenylmethoxy)phenyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]-*cis*-cyclobutanemethanol 9. Charge a 1-L, 4-necked round-bottomed flask with 74.0 g of **8**, 72.2 g of formamidine acetate, and 296 mL of ethylene glycol. Heat the mixture to 120 ±>3 °C over ~2 h and maintain this temperature for 3 h. A small quantity of ammonia evolves at above 80 °C as indicated by wet pH paper, and the suspension turns to a dark solution when the temperature reaches ~100 °C. Heat to 135 ± 3 °C over ~0.5 h and maintain this temperature for 4 h. Charge a 5-L, 4-necked round-bottomed flask with 1.6 L of ethyl acetate. Add the reaction mixture with stirring. Rinse with 25 mL (27.8 g) of ethylene glycol followed by 190 mL of ethyl acetate. Charge 590 g of deionized water over a period of 20 min and stir for 10 min. Stop stirring. Let the mixture settle for ~15 min. Separate the bottom layer (aqueous phase). Restart the stirring and add 30 g of Hyflo Super Gel. After 5–10

min of stirring, filter the suspension using a Buchner funnel. Wash the filter cake with 190 mL of ethyl acetate. Add the filtrate back to the 5-L flask. Add 590 mL of deionized water with stirring. Separate the bottom layer. Wash the organic phase with 2 × 590 mL of deionized water and 590 mL of saturated sodium chloride solution. To an 4.4 cm (i.d.) glass column, charge 20 g of sand to fill in the conical bottom. Charge 52 g of Silica Gel 60 to make a 5.5-cm bed. Cover the bed with cotton. Stir the reaction mixture and add 37 g of anhydrous magnesium sulfate. Stir for 5 min. Pour the batch onto the silica gel bed. Set the nitrogen pressure at 10–65 mm Hg so that the filtration time is about 2.5 h (10–14 mL/min). Wash the silica with 2 × 190-mL portions of ethyl acetate under the same pressure. Briefly blow the cake dry with nitrogen. Transfer the solution in three portions into a 2-L, 4-necked round-bottomed flask. Distill the combined solution at 20–35 °C (20–57 °C bath temperature) at ∼0.2 bar over ∼2 h until the volume is ∼330 mL. Use 200 mL of tetrahydrofuran to dissolve the precipitated product when needed and add to the solution for distillation. Cool the batch to 22 ± 3 °C. Charge 260 mL of *n*-heptane over ∼2 h. Stir the mixture for a minimum of 4 h at this temperature. Filter through a 600-mL Buchner funnel. Wash the cake with 2 × 50 mL (2 × 34 g) of *n*-heptane. Discard the mother liquor and washes. Air-dry the product on the filtration funnel for ∼1 h. Dry the product in a vacuum oven at ∼50 °C/12 mm Hg for 16 h to afford 79.4 g (68%) of **9** as a greenish solid; mp 140 °C, HPLC purity 98.7% (area normalization); ^{1}H NMR ($CDCl_3$) δ 8.33 (s, 1H), 7.48–7.35 (m, 6), 7.12 (s, 1H), 7.10–7.08 (m, 2H), 7.02–7.00 (m, 1H), 5.16 (s, 2H), 5.14–5.08 (m, 3H), 3.76 (d, J = 4.4 Hz, 1H), 2.98 (br s, 1H), 2.70-2.56 (m, 4H), 2.54–2.45 (m, 1H), 1.86 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 159.1, 157.0, 151.5, 150.2, 136.8, 136.3, 130.2, 128.7, 128.1, 127.4, 121.4, 121.1, 116.2, 115.0, 113.9, 101.4, 69.9, 65.2, 45.8, 32.2, 29.9. Anal. Calcd for $C_{24}H_{24}N_4O_2$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.69; H, 6.13; N, 13.87.

7-[*cis*-3-(1-Azetidinylmethyl)cyclobutyl]-5-[3-(phenylmethoxy)phenyl]-7*H*-pyrrolo[2,3-*d*]-pyrimidin-4-amine 1. Flush a 2-L, 4-necked round-bottomed flask with nitrogen and add 50 g (0.125 mol) of compound **9** and 500 mL of dry tetrahydrofuran. Stir the mixture at a batch temperature of −20 to −30 °C and add 21.8 mL of triethylamine. Add 10.6 mL of methanesulfonyl chloride while maintaining the temperature at or below −20 °C. Stir for an additional 30 min and filter to remove the triethylamine hydrochloride. Wash the filter cake with 100 mL of dry tetrahydrofuran and combine the wash with the filtrate. Add the combined filtrates to a 2-L, 4-necked round-bottomed flask. Begin a very slight nitrogen sweep so as not to displace azetidine from the reaction mixture. Add 54.5 mL (0.75 mol) of azetidine **12** over 1 to 2 min and heat to 50 °C. Maintain this temperature for at least 12 h and then cool to 15 °C. Add 640 mL of 10% aqueous citric acid solution over 1–2 min to pH ∼5.5. There will be an exotherm (15–29 °C). Concentrate at 100 mbar (jacket T = 50 °C) to remove tetrahydrofuran. Extract the concentrate with 2 × 250 mL of ethyl acetate. Concentrate at 100 mbar (jacket T = 50 °C) to remove traces of ethyl acetate. Flush the flask with nitrogen and return the solution (volume, ∼450 mL). Stir at 30 °C and add 90 mL of absolute ethanol. The pH is ∼5.4. Adjust the pH by the dropwise addition of 6 N sodium hydroxide solution to the point where the solution turns cloudy, usually near pH = 8 (volume of added base, ∼85 mL). Add seed crystals of pure **1** and stir for 30 min or until crystallization is observed. Increase the stirring rate and continue basification to pH = 10.0 (total volume of base, ∼108 mL). Filter the solids then wash with 100 mL of water. Dry the solids in a vacuum oven at 45 °C and 50 mbar to afford crude **1** (51.03 g, 93% yield) as a tan-colored solid.

Recrystallization. Charge 75.0 g of crude **1** and 1125 mL of isopropyl acetate to a 3-L, 4-necked round-bottomed flask. Heat to reflux (90 °C) and hold for 1 h. Cool to 70 °C and filter the solution through Filter Cel. Wash the filter cake with 100 mL of isopropyl acetate and combine the filtrates. Concentrate the combined filtrates to a volume of ∼500 mL on a rotary evaporator. Transfer the concentrate (which may contain some precipitated solid) to a clean 2-L, 4-necked round-bottomed flask and add fresh isopropyl acetate (250 mL or as much as needed to reach a volume of 750 mL). Heat the solution at reflux and hold for 15 min. Cool the solution to 22 °C over 0.5 h and stir for a minimum of 3 h. Filter the resulting solids and wash twice with a total of 300 mL of isopropyl acetate. Dry the solids at 45 °C and 50 mbar for 18 h to afford 44 g of **1** as an off-white solid (59% overall); mp 145 °C; HPLC purity 98.7% (area normalization); ^{1}H NMR ($CDCl_3$) δ 8.17 (s, 1H), 7.14–7.39 (m, 6H), 6.93–7.06 (m, 6H), 6.86 (m, 1H), 5.37 (br s, 2H), 5.05 (m, 1H), 5.00 (s, 2H), 3.08 (t, J = 7.0 Hz, 4H), 2.57 (m, 2H), 2.41 (d, J = 6.2 Hz, 2H), 1.83-2.17 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 159.2, 157.2, 152.0, 150.6, 136.9, 136.5, 130.3, 128.8, 128.1, 127.5, 121.4, 120.0, 116.5, 115.1, 113.9, 101.1, 70.0, 65.8, 55.9, 45.3, 36.0, 27.4, 18.2; HRMS calcd for $C_{27}H_{29}N_5O$ (M + 1) 374.1869, found 374.1852.

Azetidine 12. Charge a 1-L Erlenmeyer flask with 374.2 g (4.0 mol) of compound (**11**) and 280 g (280 mL) of water. Stir at 20 ± 3 °C until the solid is dissolved and a solution results. Charge a 2-L, 4-necked round-bottomed flask with 230 g (230 mL) of water. Stir and carefully add in portions 459.4 g (6.96 mol) of potassium hydroxide. After the exotherm from KOH addition subsides, warm the solution to 95 °C. Hold the temperature at 95 ± 5 °C. Charge the solution of azetidine HCl (**11**) in water to the hot KOH / water solution. Control the rate of addition so that the product steadily but slowly distills. Collect the product (**12**) in a cooled receiver. Complete the addition in 3 h. Stir the reaction mixture at 95 ± 5 °C until the product stops distilling. Store the product **12** cold. Yield: 203.7 g (89%), bp 61–62 °C.

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