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Enabling Synthesis of Triple Reuptake Inhibitor (+)-BMS-820836, a potential Therapeutic Agent for the Treatment of Depression.

Paul C. Lobben[*,†], Rasidul Amin[⊥], Bang-Chi Chen[§], Wenge Cui[//], Min Hu[//], Matthew Isherwood[//], Shuang Liu[//], Kassoum Nacro[//], Brandon Miles[⊥], Bingidimi Mobele[⊥], Richard E. Olson[‡], Bei Wang[§], Yuh-Lin Yang[//], and Rulin Zhao[§]

† Chemical Development, Bristol-Myers Squibb, One Squibb Drive, New Brunswick, NJ 08903, USA

‡ Neuroscience Discovery Chemistry, Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT 06492, USA

§ Discovery Chemistry, Bristol-Myers Squibb Research and Development, Princeton, NJ 08543, USA

//Medicinal Chemistry Department, Albany Molecular Research, Inc., 26 Corporate Circle, Albany, NY 12203, USA

⊥Chemical Development Department Albany Molecular Research, Inc. 21 Corporate Circle Albany, NY 12203, USA

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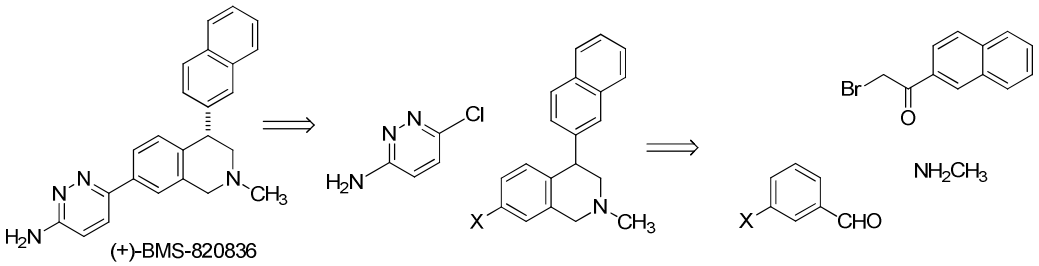


ABSTRACT

Herein, we describe the enabling synthesis of (+)-BMS-820836, a 4,7-disubstitued tetrahydroisoquinoline which was developed as a treatment for a range of neurological diseases, including depression and neurophatic pain. In order to advance the drug candidate into the Phase 1 clinical trials, an efficient and scalable synthesis was required. Three areas of improvement included the development of a regioselective Friedel-Crafts cyclization, a classical resolution for the purification of the desired enantiomer, and a robust Suzuki-Miyaura coupling. These improvements ultimately resulted in the isolation of (+)-BMS-820836 as a free flowing white solid in 99 area% purity and 3% overall yield after 14 steps.

Key words: Suzuki-Miyaura coupling, Friedel-Crafts cyclization

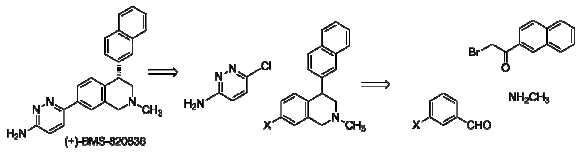
INTRODUCTION

Major depressive disorders are a condition of high prevalence and very high burden on the global health care system and is the fourth leading cause of disease burden according to the World Health Organization.[1] The prevalence of the disease in the United States is estimated at over 6% in a twelve month period and 16% over a lifetime.[2] The symptoms associated with major depression fall into two categories, that of a depressed mood and that of a loss of pleasure (anhedonia).[3] Major depression is typically associated with a hetereogenous dysregulation of the monoaminergic systems. Selective serotonin reuptake inhibitors (SSRIs) and dual serotonin/norepinephrine reuptake inhibitors (SNRIs), are proven therapies for depression. The response rate of current antidepressants is reported to be on the order of 65%, while remission from the disorder is only about 30%.[4] The onset of action for current

therapeutic agents is not rapid, and may take up to four weeks to evoke a response. A compound that shortens the response rate, improves remission, and diminishes the onset of action would represent a considerable improvement over current therapies. With these goals in mind, Bristol-Myers Squibb, in collaboration with Albany Molecular Research, Inc. (AMRI) developed triple reuptake inhibitors (TRIs) as potential antidepressants.[5]

The aim of the triple reuptake inhibitor (TRI) program was to add dopamine inhibition to the already well established mechanisms of SERT and NET inhibition. Dopamine is known to be involved in centrally mediated reward responses and the inhibition of dopamine reuptake transporters (DAT) elevates synaptic dopamine levels.[5a,5b] As part of these efforts, (+)-BMS-820836 was identified as a potent TRI. Further clinical development of (+)-BMS-820836 required an efficient and scalable synthesis of this novel tetrahydroisoquinoline (THIQ) from readily available starting materials shown in Figure 1.

Figure 1. Retrosynthesis for the preparation of BMS-820836

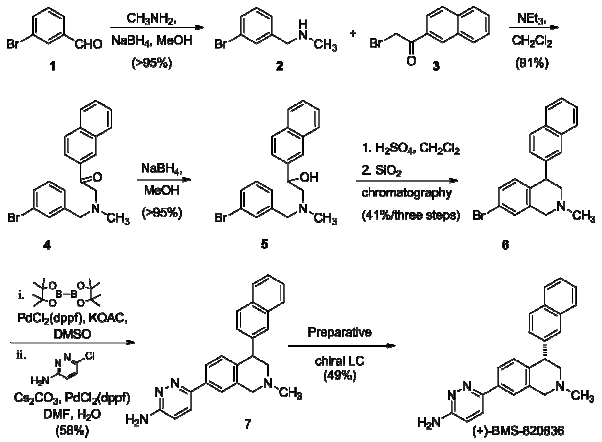


The THIQ motif can be found in natural products and is of general synthetic interest.[6] The first synthesis of (+)-BMS-820836 developed by the Discovery Chemistry group used *m*-bromobenzaldehyde (**1**), methylamine, 2-bromo-2'-acetonaphthone (**3**) and 3-chloro-6-aminopyridazine as starting materials (Scheme 1). The synthesis was expedient, affording (+)-BMS-820836 in seven steps albeit requiring two chromatography operations in order to isolate the final product with the necessary purity. Steps 1-3 were nearly quantitative in yield, yet each intermediate was isolated as an oil and with only moderate purity. The acid-mediated Friedel-Crafts cyclization of **5** gave an unselective 1:1

ratio of the undesired C-5 and desired C-7 THIQ **6**.[7] These isomers were separated with difficulty by silica gel chromatography. Finally, following Suzuki-Miyaura coupling the desired (+)-BMS-820836 was obtained by preparative chiral HPLC on a CHIRACEL OD column in 28% yield over the two steps.

The synthesis represented in Scheme 1 was straightforward and was utilized for the preparation of (+)-BMS-820836 on a multi-gram scale. However, there were several challenges to this route. First, intermediates **2**, **4,** and **5** were only able to be isolated as oils. Second, the poor regioselectivity observed in the Friedel-Crafts cyclization required chromatographic purification of the desired C-7 THIQ **6**. Ultimately chiral chromatography was required to isolate (+)-BMS-820836 as a single enantiomer. We had concerns regarding the modest yield and reproducibility of the Suzuki-Miyaura reaction. Finally we expected that a metal mediation strategy would be required to minimize residual palladium in the drug substance used for Phase 1 clinical trials.[8]

Scheme 1. Discovery Synthesis of BMS-820836



RESULTS AND DISCUSSION

Herein, we report on the development of a route to (+)-BMS-820836 that provided fit-for-purpose solutions to the challenges outlined above.[9] Our goal was to advance the clinical program quickly. To

accomplish this we desired a more efficient synthesis that avoided chromatography and provided greater throughput. An expedient fit-for-purpose synthesis would support early toxicological studies and rapid initiation of Phase 1 clinical studies. We anticipated that improving the regioselectivity of the Friedel-Crafts alkylation and defining conditions to isolate and purify the desired C-7 regioisomer and enantiomer without using chromatography would be key objectives for meeting the aggressive timelines of the Phase I program.

The synthesis of the THIQ core started with the reductive amination of *m*-anisaldehyde and methyl amine (Scheme 2). $NaBH_4$, 0.6 equivalents (optimized) was added, in portions to maintain the internal temperature < 10 °C, to a cold, clear solution of *m*-anisaldehyde and methyl amine in methanol. The resulting secondary amine **9** was isolated as an oil, in good yield and with acceptable purity for downstream processing.[10] Alkylation of crude **9** with bromoketone **3** was accomplished with triethylamine in DCM at <5 °C (Table 1, entry 1). Other solvents provided lower yields and lower purity. Due to its limited stability, compound **10** was immediately reduced with $NaBH_4$ in MeOH at low temperature. The resulting alcohol **11** was extracted into DCM. After an aqueous work-up the desired product was isolated as an oil in nearly quantitative yield and adequate purity for use in the Friedel-Crafts alkylation reaction. The use of methoxy-derivative **10** improved the regioselectivity of the Friedel-Crafts acylation 2.4 fold over the *para*-bromo derivative under standard conditions, favoring the desired C-7 isomer.[11] The best conditions for cyclization required 10 equivalents of CH_3SO_3H in CH_2Cl_2 at -10 ^oC.[12] After an aqueous work-up, **12**, as a mixture of 2.4:1 regioisomers, was isolated as an oil in 71% yield.

Table 1. **Solvent selection for alkylation of 9 with bromo-2-acetonaphthanone (3).**

Entry	Solvent	Crude Yield	Purity
1	DCM	97%	81%
2	EtOAc	83%	86%
3	IPAC	73%	77%
4	MTBE	84%	80%
5	MeOH	72%	58%
6	EtOH	85%	70%
7	THF	52%	73%
8	ACN	47%	52%

Our strategy was to isolate the desired C-7 isomer **12** from the crude mixture of regioisomers via salt formation and thereby circumvent the need for chromatography. To this end, treatment of the crude mixture with one equivalent of oxalic acid in ethanol resulted in the formation of a crystalline oxalate salt. Analysis of the product revealed a significant enrichment in the desired C-7 isomer **12** with a favorable 90:10 ratio. A single reslurry in hot ethanol improved the ratio to 98:2. Subsequent salt break with aqueous NaOH afforded racemic **12** with 97 area% purity and in 50% yield from intermediate **10**.

Table 2. DTTA resolution of racemic 12 in acetone

Entry	Solvent	DTTA Equiv.	Yield	e.e.
1	EtOH	1.00	28%	86%
2	EtOH	0.85	22%	80%
3	EtOH	0.50	12%	86%
4	Acetone	1.00	10%	82%
5	Acetone	0.75	36%	90%
6	Acetone	0.55	8%	88%

After completing the chromatography-free synthesis of the racemic C-7 THIQ 12 core we focused our attention on the isolation of the desired enantiomer. In order to avoid the chiral chromatography, we explored the feasibility of a classical resolution of the enantiomers of **12**. Gratifyingly, from a focused screen of three non-racemic acids, dibenzoyl-D-tartaric acid, (*1S*)-(+)-10-camphor sulfonic acid, and di-*p*-toluoyl-*D*-tartaric acid (*D*-DTTA), the latter acid provided a suitable solid product (Table 2).[13, 6e] Careful selection of the solvent, concentration, and acid stoichiometery led to the identification of conditions under which the desired C-7 enantiomer **13** could be isolated in an acceptable yields (26-35%) and with 94-98% ee. The optimized procedure required two sequential resolutions using D-DTTA in acetone. On a kilogram scale, a slow addition of an acetone solution of D-DTTA (0.75 equiv) over no less than four hours at 55 °C afforded **13** in 90% ee and 40% yield (Table 3). A second iteration with D-DTTA (0.90 equiv) yielded **13** in ≥99% e.e. and 94% yield. Efforts to racemize and recycle the undesired enantiomer proved unsuccessful.[14]

Table 3. Resolution of racemic 12 using DTTA in acetone

	first iteration			second iteration		
Entry	**DTTA**	**yield**	**e.e.**	**DTTA**	**yield**	**e.e.**
1	0.75 mol%	35%	94%	0.90 mol%	71%	99%
2	0.75 mol%	26%	98%	0.90 mol%	90%	99%
3	0.75 mol%	26%	96%	0.90 mol%	88%	99%
4	0.80 mol%	40%	92%	0.90 mol%	94%	99%

Demethylation of **13** under standard conditions was accomplished with aqueous HBr in acetic acid at 105 °C. No erosion of e.e. was observed under the reaction conditions. The hydrobromide salt **14** was crystallized directly from the reaction mixture following the slow addition of water and seeds. After cooling to room temperature, **14** was isolated by filtration in 96% yield and >97 area% purity as an off-white solid. The ability to isolate and use the hydrobromide salt directly avoided a complicated quench and tedious isolation of the free base. It also provided a stable, crystalline intermediate that could be fully characterized and stored under ambient conditions.

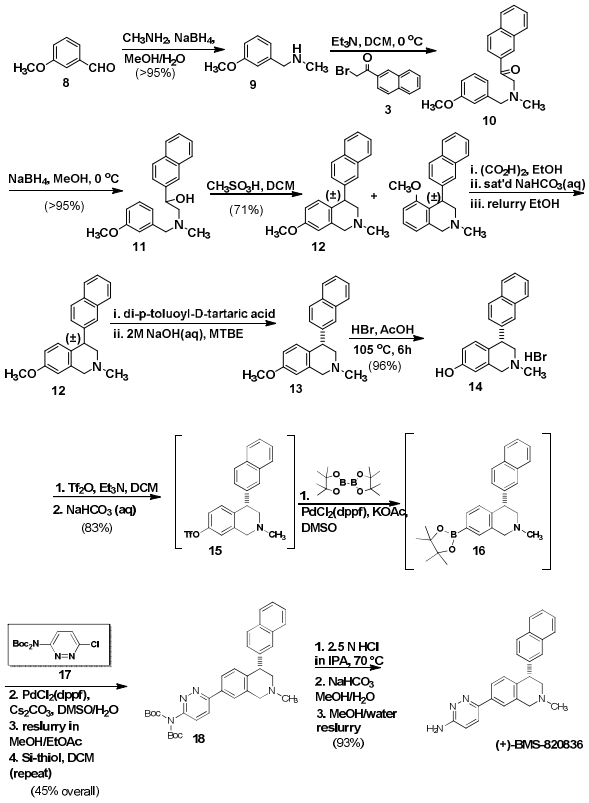
In order to install a synthetic handle for the Suzuki-Miyaura cross-coupling reaction, the phenol intermediate **14** was first converted into the aryl triflate **15**. The use of Et_3N as the base and the careful control of the reaction temperature at -55 °C were identified as the two key parameters for optimal performance.[15] Following an extractive work-up, the crude triflate **15** was obtained in nearly

quantitative yield and was used directly in the subsequent Miyaura borylation. $Pd(dppf)Cl_2$ as the catalyst and potassium acetate as the base provided the pinacol boronate derivative **16**.[16]

Improving the robustness of the Suzuki-Miyaura reaction was an objective. In the first synthesis of (+)-BMS-820836 the cross-coupling reaction was carried out as the last step of the synthesis by using 6-chloropyridazin-3-amine as the electrophilic partner (Scheme 1). This approach required a relatively high catalyst loading of 8mol% and resulted in an unpredictable conversion and afforded a variable yield. In addition, this approach placed importance on impurity control, including residual metals, in the final isolation and was thus deemed undesirable.[17] The extremely low solubility of the API in common organic solvents was another factor that was considered when designing an alternative end-game. The use of bis-Boc protected analog of pyridazine **17**[18] greatly increased the solubility of penultimate intermediate **18** and provided an easy handle to prepare the API by a simple acid-catalyzed deprotection. These synthetic modifications resulted in predictable performance and consistent quality with minimal batch-to-batch variability.

The Suzuki-Miyaura cross-coupling between **16** and **17** worked well under optimized conditions. Fully sparging the reaction mixture and reagents streams with nitrogen reduced the quantity of catalyst needed by 60% and afforded a more predictable impurity profile. Upon reaction completion the cross-coupling product **18** was produced as a brown solid in 70% yield but was contaminated with 1% palladium and 0.1% iron.

Scheme 2. Enabling Synthesis of (+)-BMS-820836



In order to minimize metal contamination in the isolated API, the aqueous work-up and the use of solid supports were evaluated. Optimization of the aqueous work-up reduced the palladium five-fold to 0.2% and the iron three fold to 500 ppm. A screen of commercially available solid supports and absorbents such as charcoal, silica and commercial resins, identified Si-Thiol available from SiliCycle®. Accordingly, two successive treatments with Si-thiol afforded **18** as a white to off-white solid with 70% recovery and with 3 ppm residual palladium.

Deprotection of both Boc groups of penultimate **18** was accomplished using anhydrous HCl in isopropanol. Control of the batch temperature, the equivalents of HCl, and the reaction time minimized the most significant process-related impurity resulting from *trans*-carbamoylation of the

tert-butyl group with the isopropanol. Subsequent salt break with aqueous $NaHCO_3$ afforded (+)-BMS-820836 as a white solid in 93% yield and >99 area% purity.

CONCLUSION

An enabling synthesis of (+)-BMS-820836 that improved the efficiency and throughput over the original discovery route has been developed. The API was isolated as a free flowing white solid in >99 area% purity and 3% overall yield and fourteen steps; seven steps longer than the discovery route. The resulting high quality API supported the aggressive timelines of both the enabling toxicology studies and the clinical development plan. The highlights of the synthesis include the improved regioselectivity of the Friedel-Crafts acylation using the methoxy substituent to afford a 2.4 fold improvement in the regioselectivity. Subsequently, two additional steps were necessary to generate the tosylate from the methoxy substituent in advance of the Suzuki-Miyaura coupling. The use of oxalic acid and di-*p*-toluoyl-D-tartaric acid added four steps to the synthesis, including two requisite salt breaks. This improvement facilitated the isolation of the non-racemic tetrahydroisoquinoline core as a crystalline salt and avoided purification by column chromatography. The optimized Suzuki-Miyaura coupling provided the protected drug substance in a consistent yield of 45-50%, with purity of 99 area% and less than 5 ppm palladium. An added metal remediation step using Si-Thiol achieved <5 ppm palladium in the final API. Deprotection and subsequent salt break afforded the free-base of (+)-BMS-820836 as a white solid in >99 area% purity.

EXPERIMENTAL SECTION

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Proton nuclear magnetic resonance spectra were obtained on a Bruker AV-300 spectrometer at 300

MHz or a Bruker AVANCE 500 spectrometer at 500 MHz, using tetramethylsilane as an internal standard for proton spectra. The mass spectra were obtained on a Finnigan LCQ-DUO spectrometer using electrospray ionization in the positive mode. Reactions were monitored by reverse-phase HPLC or thin layer chromatography (TLC). Unless otherwise noted, yields are uncorrected for purity or potency.

Preparation of 9. To a solution of *m*-anisaldehyde (2.6 kg, 19 mol) in MeOH (18.2 L) that was cooled to 5–10 °C was added a solution of 40 wt% methylamine in water (1.65 L, 19.1 mol) at a rate to maintain an internal temperature of 5–10 °C. After the reaction mixture was stirred for 30 minutes, $NaBH_4$ (450 g, 12 mol) was added in five portions to maintain a batch temperature of <10 °C. After the addition was complete, the reaction mixture was warmed to 20 °C and was stirred until the reaction was deemed complete, as determined by TLC. Water (5.2 L) was added to the reaction mixture a rate to maintain an internal temperature of <25 °C. After agitating the reaction mixture for no less than three hours, the volatile components were distilled under reduced pressure at 30–40 °C until a volume of approximately 7 L. Isopropyl acetate (IPAc, 26 L) and a 20 wt% brine solution (26 L) were successively added and the biphasic mixture was stirred for no less than 15 minutes. The layers were separated and the aqueous layer was extracted once with IPAc (26 L). The combined organic layers were concentrated by rotary evaporation to provide **8** (2.9 kg, 19 mol, >95% yield) as an oil in 80 area% purity as determined by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (t, *J* = 8.0 Hz, 1H), 6.88–6.90 (m, 2H), 6.79 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 2H), 2.48 (s, 3H), 1.41 (br s, 1H).

Preparation of 10. A solution of the **3** (4.4 kg, 18 mol) in DCM (19.8 L) was cooled to 0 °C prior to the drop-wise addition of **8** (2.8 kg, 19 mol) as a solution in DCM (12.6 L) at a rate to maintain an internal temperature of <5 °C. The reaction mixture was stirred for 30 min. prior to the addition of Et_3N (2.5 L,

18 mol.) at a rate to maintain an internal temperature of <10 °C. The reaction mixture was then warmed to 25 °C and was stirred until the reaction was deemed complete, as determined by HPLC analysis. The reaction mixture was washed with water (19.8 L) and the phases were separated and the organic layer was concentrated under reduced pressure to afforded **10** (6.2 kg, 19 mol, >95% yield) as a dark oil. ^{1}H NMR (500 MHz, *d*-DMSO) δ 8.64 (s, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.97-8.03 (m, 3H), 7.65 (dt, *J* = 15.0, 6.9 Hz, 2H), 7.24 (t, *J* = 7.8 Hz, 1H), 6.88–6.93 (m, 2H), 6.82 (dd, *J* = 8.1, 2.4 Hz, 1H), 3.99 (s, 2H), 3.68 (s, 3H), 3.66 (s, 2H), 2.27 (s, 3H).

Preparation of 11. A solution of **10** (5.0 kg, 16 mol) in MeOH (34.8 L) was cooled to –5 °C. $NaBH_4$ (0.54 kg, 14 mol) was added in portions over 4 h in order to maintain an internal temperature of <0 °C. The reaction mixture was warmed to 15 °C and was stirred for 30 min until the reaction was complete, as determined by TLC. Water (15 L) was added and the resulting mixture was stirred for 3 h. The volatile components were removed under reduced pressure to a volume of approximately 20 L. The mixture was partitioned with DCM (25 L) and the phases were separated. The isolated organic layer was concentrated to a constant weight under reduced pressure to afford **11** (5.0 kg, 16 mol, >95% yield) as a dark oil in with 61 area% purity as determined by HPLC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76–7.93 (m, 4H), 7.41–7.53 (m, 3H), 7.23–7.31 (m, 1H), 6.86–6.97 (m, 2H), 6.85 (dd, *J* = 6.0, 2.5 Hz, 1H), 4.96 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.85 (s, 3H), 3.78 (d, *J* = 13.1 Hz, 1H), 3.58 (d, *J* = 13.1 Hz, 1H), 2.69-2.73 (m, 2H), 2.39 (s, 3H).

Preparation of 12. A solution of **11** (625 g, 1.94 mol) in DCM (6.3 L) was cooled to –10 °C prior to the slow dropwise addition of CH_3SO_3H (1.26 L, 19.4 mol) at a rate in order to maintain an internal temperature of <5 °C. *Caution: the addition is strongly exothermic*. The reaction mixture was warmed to room temperature and was stirred for 14 h until the reaction was complete, as determined by TLC. The reaction mixture was cooled to –10 °C and a solution of 50 wt% NaOH (1.5 L) was added followed

by water (750 mL). The layers were separated and the isolated organic layer was concentrated under reduced pressure to give **12** (0.55kg, 93% yield) as a brown oil.

To a solution of **12**, as a 2.4:1 mixture of regioisomers [547 g, 1.80 mol) in absolute EtOH (2 L) at room temperature was slowly added a solution of oxalic acid (162 g, 1.80 mol) in absolute EtOH (0.6 L) in a single portion. *Caution: the addition is exothermic.* The reaction mixture was held with agitation until a precipitate formed. After two additional hours the slurry was filtered to provide **12** as a light yellow solid and a 9:1 mixture of regioisomers. The resulting filter cake was combined with absolute EtOH (6.5 L) and the resulting slurry was heated at 75 °C for 3 h. The slurry was cooled to 25 °C and filtered. The dried solids were partitioned between saturated $NaHCO_3$ (3 L) and EtOAc (3.5 L). The organic layer was isolated and dried over $MgSO_4$. After filtration, the organic layer was concentrated under reduced pressure to afford **12** (355 g, 1.18mol and 91% yield, corrected) as a white solid and 98 area% purity and a 96:4 mixture of isomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72–7.82 (m, 3H), 7.68 (s, 1H), 7.39–7.48 (m, 2H), 7.27 (dd, *J* = 8.4, 1.7 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.64 (s, 1H), 6.63 (d, *J* = 8.1 Hz, 1H), 4.39 (dd, *J* = 8.4, 5.8 Hz, 1H), 3.78 (s, 3H), 3.77 (d, *J* = 14.9 Hz, 1H), 3.61 (d, *J* = 14.9 Hz, 1H), 3.08 (ddd, *J* = 11.5, 4.3, 1.2 Hz, 1H), 2.64 (dd, *J* = 11.5, 8.9 Hz, 1H), 2.44 (s, 3H).

Preparation of 13. A solution of racemic **12** (1.2 kg, 4.0 mol) as a 96:4 mixture of regioisomers) in acetone (48 L) was heated to 55 °C. A portion (7.2 L) of a solution of di-*p*-toluoyl-D-tartaric acid (1.2 kg, 2.8 mol) in acetone (12 L) was added over 2 h imparted a cloudy reaction mixture. Seed crystals of **13** (0.1 wt%) were then added. The reaction mixture was stirred for an additional 30 min. The remaining resolving agent (4.8 L) was slowly added over 3 h. The reaction mixture was cooled to –5 to 5 °C over 5 h and was held for 14 h. The slurry was filtered and the filter cake was conditioned for 6 h under a nitrogen atmosphere. The dried filter cake was partitioned between 2 M aqueous NaOH (3.6 L) and MTBE (12 L). The biphasic mixture was vigorously stirred for 45 min. The phases were separated and

the organic layer was concentrated to afford **13** (0.48 kg, 1.6 mol, 80% yield) as an off-white with 82% e.e.

The isolated solid obtained underwent a second iteration of the resolution process with only two minor changes: 1) the stoichiometry of the resolving agent DTTA was increased from 0.80 equiv to 0.85 equiv and 2) the acetone was increased from 40 vol to 50 vol in the initial solution. As a result **13** (0.37 g, 1.2 mol, 97% yield, corrected) was isolated as an off-white and with 99 area% purity and with >99% e.e. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72–7.82 (m, 3H), 7.68 (s, 1H), 7.39–7.49 (m, 2H), 7.24 (dd, *J* = 8.5, 1.7 Hz, 1H), 6.76 (d, *J* = 9.4 Hz, 1H), 5.59–6.67 (m, 2H), 4.39 (dd, *J* = 8.9, 5.9 Hz, 1H), 3.82 (d, *J* = 15.0 Hz, 1H), 3.76 (s, 3H), 3.67 (d, *J* = 15.0 Hz), 3.11 (ddd, *J* = 11.5, 5.7, 1.1 Hz, 1H), 2.66 (dd, *J* = 11.6, 9.3 Hz, 1H), 2.45 (s, 3H).

Preparation of 14. A mixture of **13** (1.0 kg, 3.3 mol) in AcOH (2.5 L) was mechanically stirred and was heated at 55–60 °C until the the reaction mixture was homogeneous. HBr, 48 wt%, in water (5.0 L, 44 mol) was added and the resulting heterogeneous solution was heated to 105 °C to achieve a homogeneous solution. After 18 hours, the reaction was deemed complete by ^{1}H NMR analysis. The solution was cooled to 95 °C over 15 min. Water (0.9 L) was added over 15 min and seeds of **14** (0.5 wt%) were added. Additional water (3.1 L) was added over 2 h. The resulting slurry was cooled to 25 °C over 2.5 h and filtered. The filter cake was conditioned under nitrogen overnight. The isolated solids were combined with water (4.0 L). The resulting slurry was stirred at ambient temperature for 45 min, was cooled to 5 °C, and was filtered. The isolated solids were conditioned under N_2 overnight, and then were dried *in vacuo* to a constant weight to afford **14** (1.0 kg, 2.7 mol, 85% yield) as a white solid in >99 area% purity, as determined by HPLC. ^{1}H NMR (500 MHz, *d*-DMSO) δ 10.31 (s, 0.85H), 10.11 (br s, 0.15H), 9.60 (s, 1H), 7.61–7.94 (m, 4H), 7.47–7.59 (m, 2H), 7.30 (d, *J* = 7.5 Hz, 1H), 6.69 (s, 1H), 6.50–6.71 (m, 2H), 4.31–4.77 (m, 1H), 4.54 (br s, 2H), 3.84 (br s, 1H), 3.62 (t, *J* = 11.2 Hz, 1H), 2.98 (s, 3H).

Preparation of 15. To a solution of **14** (1.0 kg, 2.7 mol) in DCM (12.4 L) at room temperature was slowly added Et_3N (0.90 L, 6.5 mol) (slightly exothermic). After stirring for 20 min, the reaction mixture was cooled to –55 °C followed by the slow drop-wise addition of Tf_2O (0.56 L, 3.3 mol) over 2.5 h. The internal temperature was maintained below –50 °C. At this point, the reaction was deemed completed, as determined by HPLC analysis. The reaction mixture was warmed to –10 °C and was quenched with 10% aqueous $NaHCO_3$ (6.2 L). The resulting biphasic mixture was warmed to 20 °C and was stirred for 30 min. The layers were separated, and the organic phase was washed with water (6.2 L) and concentrated under reduced pressure to provide **15** (1.2 kg, 2.8 mol, >95% yield) as a dark red oil in 74 area% purity, as determined by HPLC analysis. ^{1}H NMR (500 MHz, *d*-DMSO) δ 7.89–7.97 (m, 3H), 7.76 (s, 1H), 7.40–7.49 (m, 2H), 7.28–7.34 (m, 2H), 7.18 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 1H), 4.43 (t, *J* = 6.2 Hz, 1H), 3.66–3.74 (dd, *J* = 20.8, 15.8 Hz, 2H), 2.99 (dd, *J* = 11.6, 5.6 Hz, 1H), 2.71 (dd, *J* = 11.5, 5.2 Hz, 1H), 2.35 (s, 3H).

Preparation of 18. To a solution of **15** (1.18 kg, 2.80 mol) and DMSO (16.5 L) was added successively bis-pinacolato diboron (0.85 kg, 3.3 mol) and KOAc (0.82 kg, 8.4 mol). The heterogeneous mixture was sparged with nitrogen for 1.5 h. $PdCl_2$(dppf) (60 g, 74 mmol) was added and the reaction mixture was stirred at 85 °C under nitrogen. After an additional 2.5 h the reaction was complete with <5% of **15**, as determined by HPC analysis. A nitrogen-sparged solution of Cs_2CO_3 (2.7 kg, 8.4 mol) in water (4.2 L) was added in one portion. A nitrogen-sparrged slurry of **17** (1.15 kg, 3.49 mol) in DMSO (6.5 L) was then added in a single portion. Caution: exothermic. A second and final charge of $PdCl_2$(dppf) (60 g, 74 mmol) was added. The reaction mixture was stirred at 85 °C for 12 h. The reaction was complete, as determined by HPLC analysis Water (5.0 L) was added and after stirring for 1 h, the mixture was filtered to afford a brown solid which was conditioned under N_2 overnight.

The dried filter cake was dissolved in DCM (18 L) and the organic layer was washed successively with a 10% aqueous LiCl solution (18 L) and a 10% aqueous NH_4OH solution (18 L). The DCM layer was concentrated under reduced pressure. The resulting brown solid was combined with MeOH (6 L); the resulting slurry was stirred at 55 °C for 1 h, cooled to 25 °C and diluted with EtOAc (12 L). The slurry was stirred for an additional hour and filtered. The filter cake was conditioned under N_2 overnight to give **18** (0.75 kg, 1.3 mol) as a gray solid. ICP analysis indicated the palladium content was 2300 ppm. The isolated solid was dissolved in DCM (3.75 L) and was treated with Si-Thiol (1.50 kg, 2 wt% equiv., SiliCycle). The reaction mixture was stirred at 30–35 °C for 4.5 h, cooled to room temperature and filtered. The resin was rinsed with DCM (7.5 L). The combined dark brown organic layers were filtered through a 1.2-micron filter and concentrated under reduced pressure to afford an off-white solid. ICP analysis indicated the palladium content was 160 ppm. A second iteration of the metal-remediation process was performed to also give an off-white solid. ICP analysis indicated the palladium content was 3 ppm. The isolated solid was combined with EtOAc (4.2 L) and the resulting slurry was stirred at ambient temperature for 1 h and filtered. The filter cake was rinsed with EtOAc (500 mL). The filter cake was conditioned under N_2 for two days to afford **18** (0.72 g, 1.3 mol, 47% yield) as a white solid with >99 area% purity, as determined by HPLC analysis. ^{1}H NMR (500 MHz, *d*-DMSO) δ 8.31 (d, *J* = 9.1 Hz, 1H), 8.02 (d, *J* = 1.3 Hz, 1H), 7.83–7.92 (m, 5H), 7.79 (s, 1H), 7.46–7.51 (m, 2H), 7.39 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 4.49 (t, *J* = 6.3 Hz, 1H), 3.78 (dd, *J* = 15.4, 21.9 Hz, 2H), 3.02 (dd, *J* = 11.5, 6.6 Hz, 1H), 2.73 (dd, *J* = 11.4, 7.1 Hz, 1H), 2.39 (s, 3H), 1.41 (s, 18H).

Preparation of 17. A mixture of the 6-chloro-pyridazine-3-aminr (0.50 kg, 3.9 mol) and DMAP (3.77 g, 30.9 mmol) in DMF (3.5 L) was heated to 55 °C and was stirred for 20 min to achieve a homogeneous solution. A solution of Boc_2O (1.9 kg, 8.6 mol) in DMF (0.5 L) was charged in a single portion. *Caution: the addition is endothermic*. The reaction mixture was stirred at 55 °C for 5 h; at which time the

reaction was deemed complete, as determined by HPLC analysis. The reaction was cooled to room temperature. Water (4.4 L) was slowly added; the resulting slurry was stirred for 10 min and then filtered. Note: Exothermic addition and gas evolution.

The brown solid was conditioned overnight under nitrogen. The dried solids were combined with 2-propanol (3.5 L). The mixture was heated at 65 °C to obtain a homogeneous solution. Water (3.5 L) was added over 30 min and the reaction mixture was cooled to room temperature to afford a slurry. The solids were isolated and dried to give **17** as a light brown solid (0.81 kg, 2.4 mol, 63% yield) in 99.7 area% purity by HPLC. ^{1}H NMR (300 MHz, *d*-DMSO) δ 8.00 (dd, *J* = 9.0, 15.0 Hz, 2H), 1.40 (s, 18H).

Preparation of BMS-820836-2HCl. A mixture of **18** (0.75 kg, 1.3 mol) in isopropyl alcohol (3.75 L) was stirred at room temperature as 5–6 N HCl in isopropyl alcohol (3.75 L, 18.8 mol) was added over 5 min (slightly exothermic). The mixture was then heated to 70 °C and held for 18 h, during which time the mixture became a homogeneous yellow solution, and then a white slurry forms. The reaction was deemed complete by HPLC analysis. The mixture was cooled to 25 °C and EtOAc (8 L) was added. After stirring for 1 h, the reaction mixture was filtered to provide BMS-820836-2HCl as a white solid (0.56 kg, 1.3 mol, >95% yield) with >99 area% purity by HPLC. ^{1}H NMR (500 MHz, *d*-DMSO) δ 12.05 (br s, 1H), 8.83 (br s, 2H), 8.38 (d, *J* = 9.7 Hz, 1H), 7.90–7.98 (m, 5H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.69 (d, *J* = 9.7 Hz, 1H), 7.55 (m, 2H), 7.33 (s, 1H), 6.93 (d, *J* = 5.3 Hz, 1H), 4.88–4.98 (m, 1H), 4.68 (br s, 2H), 3.85–3.93 (m, 1H), 3.70–3.81 (m, 1H), 3.55 (br s, 1H), 2.97 (s, 3H).

Preparation of (+)-BMS-820836. To a solution of **BMS-820836-2HCl** (0.55 kg, 1.3 mol) in 50% MeOH (aq) (16.5 L) at room temperature was slowly added a 10% aqueous $NaHCO_3$ (4.4 L) After reaching the cloud point with approximately 0.4 L added, seed crystals of BMS-820836-03 (10.5 g, 2 wt%) were added and the thin slurry was stirred for an additional 1 h. During this time the reaction mixture became very thick. The remaining aqueous $NaHCO_3$ solution (4 L) was added over 40 min and the

reaction mixture was stirred for 2 h and then filtered. After conditioning on the filter under N_2 for 1 h, the wet filter cake was re-suspended in 20% MeOH(aq) (5.5 L), was stirred for 2 h, and then was filtered. The filter cake was conditioned under N_2 for 48 h and then dried *in vacuo* at 35 °C for 48 h to afford **BMS-820836** as a white solid (0.45 kg, 1.2 mol, 98% yield) with >99 area% purity as determined by HPLC. ^{1}H NMR (500 MHz, *d*-DMSO) δ 7.82–7.94 (m, 3H), 7.74–7.82 (m, 3H), 7.66 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.44–7.51 (m, 2H), 7.37 (dd, *J* = 8.4, 1.4 Hz, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.86 (d, *J* = 9.2 Hz, 1H), 6.48 (s, 2H), 4.43 (t, *J* = 6.2 Hz, 1H), 3.72 (dd, *J* = 22.3, 15.1 Hz, 2H), 2.98 (dd, *J* = 11.3, 5.5 Hz, 1H), 2.69 (dd, *J* = 11.4, 7.2 Hz, 1H), 2.36 (s, 3H).

AUTHOR INFORMATION

Corresponding Author

*E-mail: paul.lobben@bms.com.

Notes

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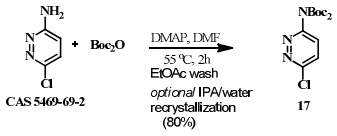

Compound 17 was prepared via the slow addition of Boc_2O to a solution of the 6-chloropyridazin-3-amine and DMAP in DMF while maintaining batch temperature at 55 °C. After an inverse quench and filtration, the product is obtained as a light grey solid in 80% yield (90-97% purity).