Organic Process Research & Development

Article

pubs.acs.org/OPRD

Initial Process Development and Scale-Up of the Synthesis of a Triple Reuptake Inhibitor ALB 109780

Qiang Yang,*[,†] Luckner G. Ulysse,[†] Mark D. McLaws,[†] Daniel K. Keefe,[†] Brian P. Haney,[†] Congxiang Zha,[‡] Peter R. Guzzo,[‡] and Shuang Liu[‡]

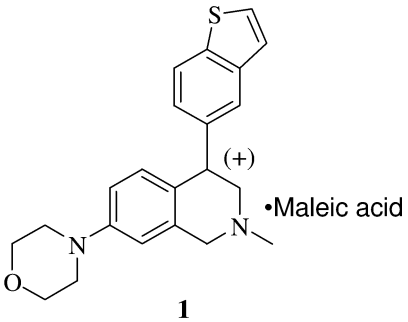
[†]Chemical Development Department, AMRI, 21 Corporate Circle, Albany, New York 12203, United States

[‡]Discovery R&D, AMRI, 30 Corporate Circle, Albany, New York 12203, United States

ABSTRACT: Early process development toward a triple reuptake inhibitor is described. Three different routes were evaluated; one of them was optimized and scaled up to generate 470 g of API as this route minimized the formation of undesired side products. The selected route featured Eaton's reagent-mediated cyclization of a phenyl acetamide, copper-mediated Buchwald–Hartwig coupling to install a morpholine moiety, and palladium-catalyzed α-arylation of a dihydroisoquinolinone to construct the core structure.

INTRODUCTION

Major depressive disorder (MDD) is the leading cause of disability in the U.S. for population ages 15–44.[1] It affects approximately 14.8 million American adults, or about 6.7% of the U.S. population age 18 and older in a given year[2] and represents a huge economic burden on society.[3] Despite the tremendous benefits of serotonin or dual serotonin and norepinephrine reuptake inhibitors (SSRIs and SNRIs, respectively) in treating depression, 30–40% of patients do not adequately respond to treatment with currently available antidepressants.[4,5] In pursuit of novel antidepressant therapies, our Discovery Research and Development colleagues identified **ALB 109780** (**1**) (Figure 1) as a triple reuptake inhibitor (TRI, inhibits the reuptake of serotonin, norephinephrine, and dopamine) that could lead to improved treatment for depression.[6] In order to supply material for toxicological studies we were required to manufacture approximately 500 g of the active pharmaceutical ingredient (API). Herein we report the results of our initial development efforts and scale-up of the synthesis of **ALB 109780**.



1
(ALB 109780)

Figure 1. Structure of ALB 109780.

RESULTS AND DISCUSSION

Evaluation of the Synthesis of 9 via the Original Procedure. The original synthesis of the key intermediate **9** for the synthesis of **1** is depicted in Scheme 1.[7] Acyl chloride formation was originally conducted in 5 equiv of neat thionyl chloride with concentration to dryness and dissolution of the crude product in dichloromethane (DCM), followed by reaction with aqueous methylamine in tetrahydrofuran (THF). The reaction was quenched with water upon completion and extracted with DCM. The organic layer was dried over sodium sulfate and concentrated to dryness to afford the desired amide in >95% HPLC purity. After optimization, compound **2** was suspended in two volumes of toluene and 10 mol % of DMF and treated under dose-controlled condition with 1.2 equiv of thionyl chloride at 40 °C to ensure complete reaction. The resulting solution was cooled to ambient temperature and transferred to an aqueous solution of methylamine at 0–25 °C. The resulting suspension was filtered to afford the desired amide **3** in 88–94% yields and excellent HPLC purity (96.4 to >99%).[8,9]

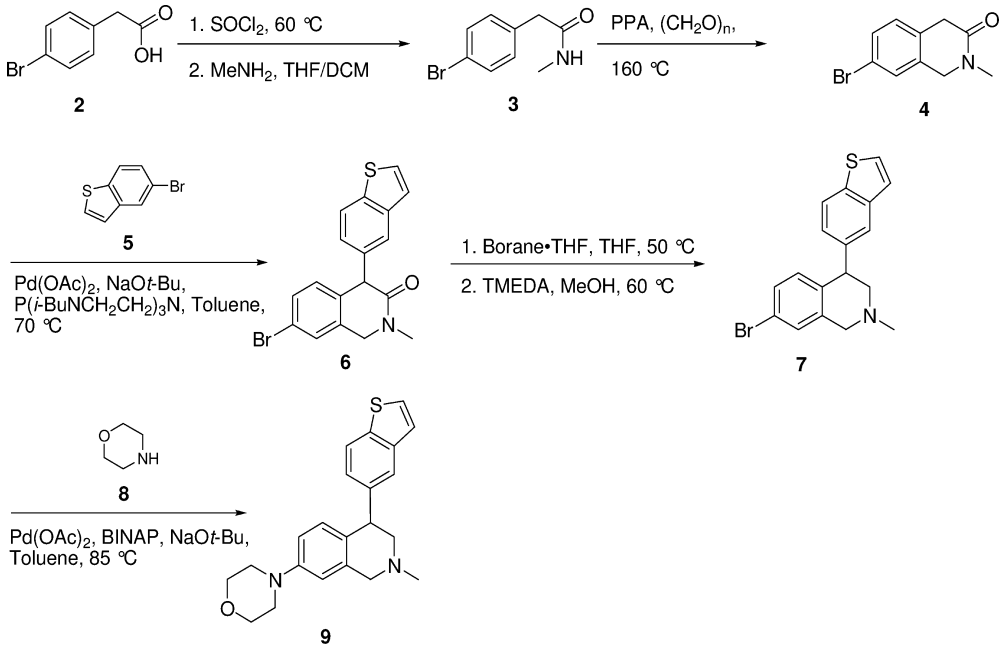
Initially, the synthesis of **4** was conducted in polyphosphoric acid (PPA) at 160 °C with paraformaldehyde. Upon completion, the reaction was quenched with water, extracted with ethyl acetate, dried over magnesium sulfate, and concentrated to dryness to afford an oil. In an effort to identify more process friendly conditions for this transformation, we found that at 80 °C Eaton's reagent (P_2O_5 in methanesulfonic acid) worked similarly to PPA. The desired cyclized product **4** was obtained in excellent yield by neutralization of the reaction to pH 8.0 with sodium hydroxide, followed by extraction of the product with isopropyl acetate (IPAc) and isolation by filtration after the organic layer was concentrated to a thick suspension. Multiple batches of the chemistry from **2** were successfully executed in our kilo laboratories on 2–3-kg scale and afforded the desired product in >90% yield and >92% HPLC purity.[8,9]

With a steady supply of **4** in hand, our focus shifted to the evaluation of the downstream chemistry. However, difficulties were quickly encountered during preliminary development investigations. A des-bromo impurity (**6a**, Figure 2) was observed in

Received: January 6, 2012
Published: February 13, 2012

   dx.doi.org/10.1021/op3000064 | *Org. Process Res. Dev.* 2012, 16, 499–506

Scheme 1. Original synthesis of 9



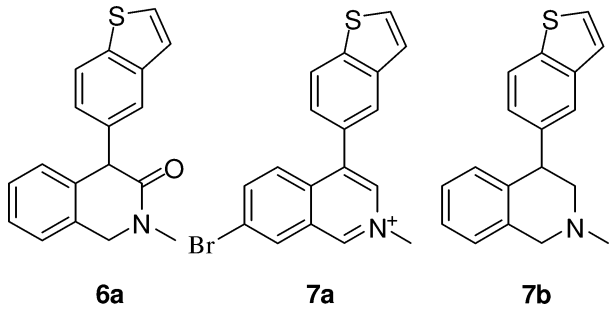
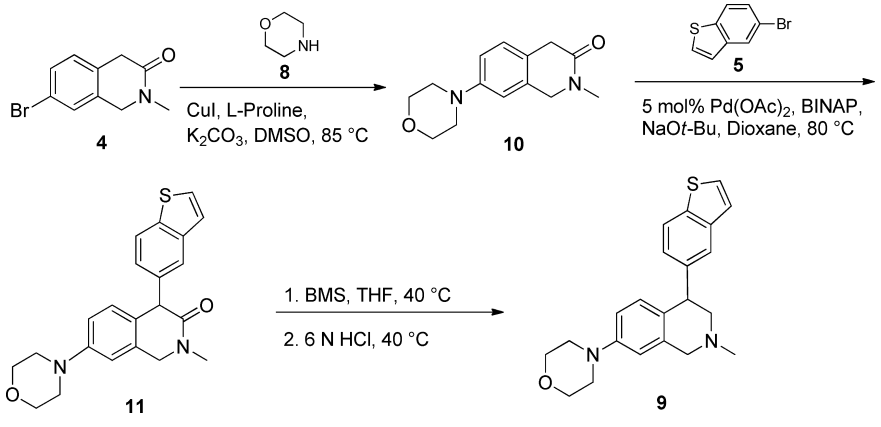


Figure 2. Major impurities via the original synthesis.

the synthesis of **6** in the presence of palladium acetate, 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane, and sodium *tert*-butoxide in toluene at 70 °C.[10] The desired product was obtained in low yields (20−50%) after column purification due to material lost to the formation of this impurity and subsequent extensive column purification. Attempts to optimize reaction conditions such as reaction temperature, catalyst loading, alternative bases, and alternative solvents to suppress the formation of des-bromo impurity **6a** did not afford satisfactory results. A byproduct (**7a**, Figure 2) was found in the synthesis of **7** during the decomplexation using tetramethylethylenediamine (TMEDA). Although this impurity was significantly suppressed when the decomplexation was performed in hydrochloric acid (HCl) solution, extensive column chromatography purification was still necessary to purify the material. Another des-bromo impurity (**7b**, Figure 2) was observed during the coupling of **8** with **7** to form **9**.[11,12] Although a total of approximately 150 g of **1** was obtained through this route to satisfy immediate needs, it was realized that the route outlined in Scheme 1 was not suitable for large-scale production of **9**.

Optimization of the Synthesis of 9 via Second-Generation Procedure. The chemistry outlined in Scheme 2, which involved incorporation of the morpholine moiety before the benzothiophene, was evaluated in an effort to avoid the formation of des-bromo impurity **6a**.[7] Two reaction conditions were investigated for this coupling. A much cleaner reaction profile was obtained when the reaction was performed in the presence of copper(I) iodide, potassium phosphate, and *L*-proline in dimethyl sulfoxide[13] compared to when it was

Scheme 2. Second-generation synthesis of 9



dx.doi.org/10.1021/op3000064 | Org. Process Res. Dev. 2012, 16, 499−506

Table 1. Optimization of reaction conditions for the α-arylation of 10

						IPC by HPLC (% AUC)[a]			
entry	solvent	**5** (equiv)	$Pd(OAc)_2$(mol %)	temp. (°C)	NaO*t*-Bu (eq)	**11**	**10**	impurity **1**	impurity **2**
1	dioxane	1.2	10	80	1.00	74.7	7.6	16.2	1.5
2	dioxane	1.2	5	80	1.50	98.8	0.05	0.8	0.2
3	dioxane	1.2	10	60	1.00	74.9	7.8	11.6	5.7
4	dioxane	1.2	5	60	1.50	86.4	4.3	7.7	1.5
5	dioxane	1.4	7.5	70	1.25	87.5	3.0	8.4	1.1
6	dioxane	1.6	10	80	1.50	94.0	0.3	4.4	1.3
7	dioxane	1.6	5	80	1.00	80.2	6.4	12.9	0.6
8	dioxane	1.6	10	60	1.50	88.2	1.6	4.3	5.9
9	dioxane	1.6	5	60	1.00	69.7	15.3	12.7	2.3
10	toluene	1.2	10	80	1.50	83.8	0.3	5.9	9.9
11	toluene	1.2	5	80	1.00	74.7	7.6	11.4	6.3
12	toluene	1.2	10	60	1.50	83.3	1.2	4.0	11.6
13	toluene	1.2	5	60	1.00	60.4	17.3	16.7	5.6
14	toluene	1.4	7.5	70	1.25	76.7	4.7	8.0	10.7
15	toluene	1.6	10	80	1.00	66.2	12.2	14.1	7.5
16	toluene	1.6	5	80	1.50	91.1	0.05	1.8	7.1
17	toluene	1.6	5	60	1.50	75.5	4.3	13.6	6.6
18	toluene	1.6	10	60	1.00	51.8	18.3	14.4	15.5

[a]Without integrating **5**.

conducted in the presence of palladium acetate, X-phos, and cesium carbonate in *m*-xylene.[14]

Initially several acid and base washes were used to remove inorganic salts and other impurities. The crude product was then purified by silica gel column chromatography. However, it was found that all of the acid and base washes, except for the first quench in brine solution, caused emulsions on scale. In order to avoid the emulsions, the reaction mixture was quenched into brine solution and diluted with ethyl acetate. The organic layer was filtered through a silica gel plug to remove inorganic salts and polar impurities. The filtrates were concentrated to afford the desired product **10** as a light-yellow crystalline solid in 68% yield and 98.5% HPLC purity.

In developing the α-arylation of **10**, a preliminary screening of reaction conditions revealed that the combination of $Pd(OAc)_2$, BINAP, and NaO*t*-Bu was optimal for this reaction.[15−18] The conditions were further investigated to improve the conversion and suppress the formation of impurities (Table 1). In general, dioxane provided better conversion and crude purity than toluene. Increasing the amount of **5** had a detrimental impact on the crude purity of the reaction irrespective of the amount of catalyst used. Better conversion was observed when a higher amount of base was used. The best results were obtained with 1.2 equiv of **5** in dioxane at 80 °C in the presence of 5 mol % of $Pd(OAc)_2$ and 1.5 equiv of NaO*t*-Bu (Table 1, entry 2).

As a matter of general practice, we perform simple reaction calorimetry experiments on known or suspected exothermic processes when such chemistry is to be run at a scale exceeding typical bench-scale equipment. The aim of such calorimetry experiments is to gain some understanding of the thermal profile and heat flow of a process so that proper controls are established to maintain safe operation. On occasion, these studies reveal subtle thermal events often missed on small scale, which can potentially be significant upon scale up. The α-arylation of compound **10** was such a case. Aside from the expected exotherm arising from addition of sodium *tert*-butoxide, no observable exotherm was revealed on small scale upon heating to the reaction temperature. Regardless, reaction calorimetry was performed since coupling reactions of this type can potentially be exothermic, and the process lacked any dosing operation which could be used to halt the chemistry.

The expected exotherm from the sodium *tert*-butoxide addition was rapid and easily controlled by portionwise dosing (Figure 3). The total heat output was mild (−24 kJ/mol, ΔT_{ad} = 7 K), and no significant heat accumulation was observed.

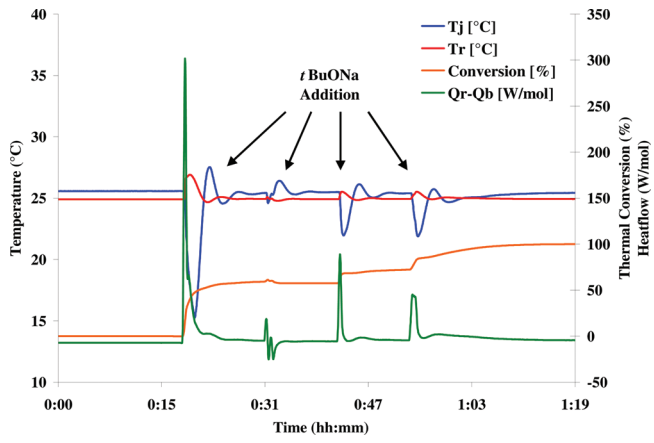


Figure 3. RC1 calorimetry of α-arylation of 10: NaO*t*-Bu addition.

The thermal profile upon heating revealed a significant exothermic event once the system approached approximately 60 °C, at which point the reaction became self-heating (Figure 4). Integration of heat flow indicated that 70% of heat output occurred after the system became self-heating. Total heat output was calculated to be −221 kJ/mol (ΔT_{ad} = 62 K), suggesting that, in the absence of active cooling, the system would quickly exceed the boiling point of the solvent. An experiment in which 5-bromobenzothiophene was dosed at an elevated reaction temperature provided adequate control of this exothermic event; however, such a modification to the process resulted in vastly increased byproduct formation which severely degraded the purity of the isolated product. For the purposes of this campaign, it was decided to run multiple batches on small

dx.doi.org/10.1021/op3000064 | *Org. Process Res. Dev.* 2012, 16, 499−506

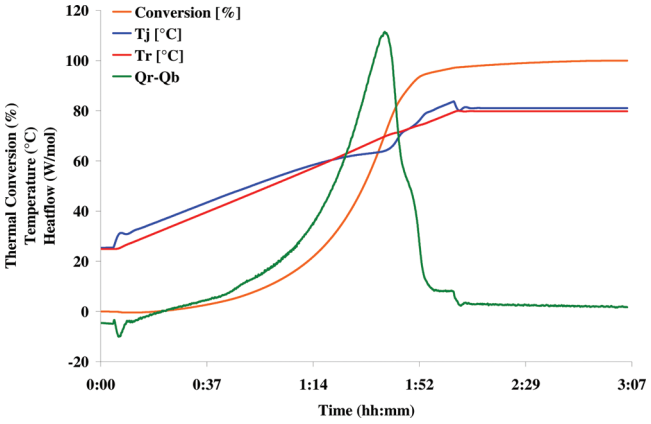


Figure 4. RC1 calorimetry of α-arylation: heat cycle.

scales as cooling capacity and the ability to mitigate risk in the event of a cooling excursion is much better on smaller scale. The reaction mixture was quenched with water upon reaction completion and extracted with DCM. The organic layer was filtered through a silica gel plug using ethyl acetate as eluent to remove residual inorganic impurities. The filtrates were concentrated to render the desired product as a brown solid in >99% HPLC purity.

The reduction of **11** was performed using borane-dimethylsulfide (BMS) under the conditions developed for the reduction of **6**. Reaction calorimetry of the reduction was expected to show heat output during addition of the reductant and upon reaction quench with aqueous hydrochloric acid. The thermal profile of the reduction shown in Figure 5 revealed a

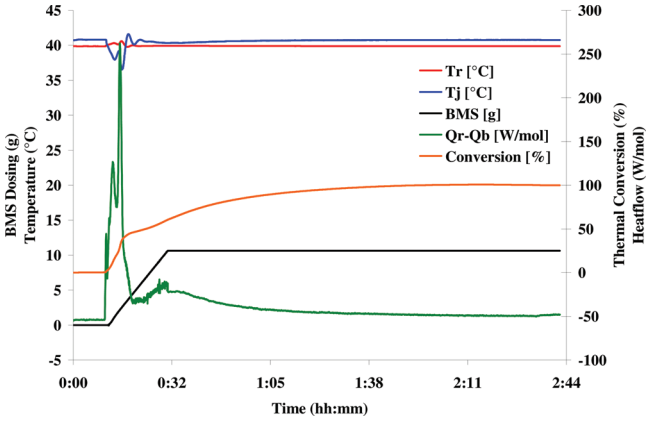


Figure 5. RC1 calorimetry of borane reduction: BMS addition.

pronounced exotherm immediately upon addition of BMS with a peak output of 252 W/mol which quickly subsided once approximately 30% of the BMS had been added. Upon completion of BMS addition, a decaying heat flow was observed which ended within approximately one hour. A total heat output of −140 kJ/mol (ΔT_{ad} = 11 K) was deemed moderate and well within controllable limits. However, the pronounced thermal output early in the BMS addition and decaying heat flow postaddition warranted an extended addition time to prevent buildup of reactive reagents. Thus, BMS was carefully added into a solution of compound **11** in THF at 35 °C under nitrogen atmosphere, and the reaction mixture was stirred at 40 °C until it was complete. The exotherm was readily controlled by maintaining a conservative addition rate.

As discussed in the synthesis of **7**, HCl was used to replace TMEDA for decomplexation upon reaction completion to minimize the formation of an elimination impurity. Thermal assessment of the 6 N HCl addition is shown in Figure 6. The

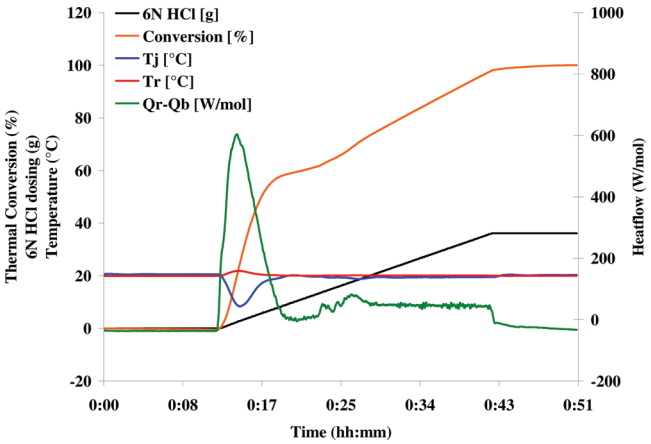


Figure 6. RC1 calorimetry of borane reduction: 6 N HCl addition.

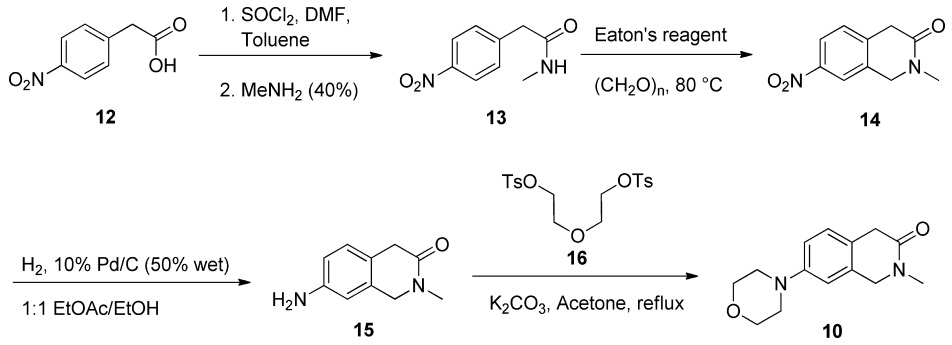
most pronounced heat output was observed early in the quench with a peak output of 602 W/mol after addition of approximately 10% of the quench solution. The strongly exothermic quench subsided moderately after the first 20% of the quench solution was added and remained relatively constant throughout the remaining dosing cycle. No accumulated heat was observed. The thermal profile observed during quench resulted in a net output of −259 kJ/mol (ΔT_{ad} = 12 K). Careful control of the addition rate early in the quench cycle was practiced to ensure proper control of this thermal event.

The reaction mixture was cooled to ambient temperature from 40 °C upon completion of decomplexation. It was basified with sodium hydroxide solution to pH 13 and extracted twice with ethyl acetate. The combined organic layers were passed through silica gel, and the filtrates were solvent swapped to acetonitrile and treated with activated charcoal to scavenge residual palladium. The product **9** was isolated as a yellow solid in 66% yield over the reduction and charcoal treatment. The purity was improved to 95.4% from 87.5% after the treatment.

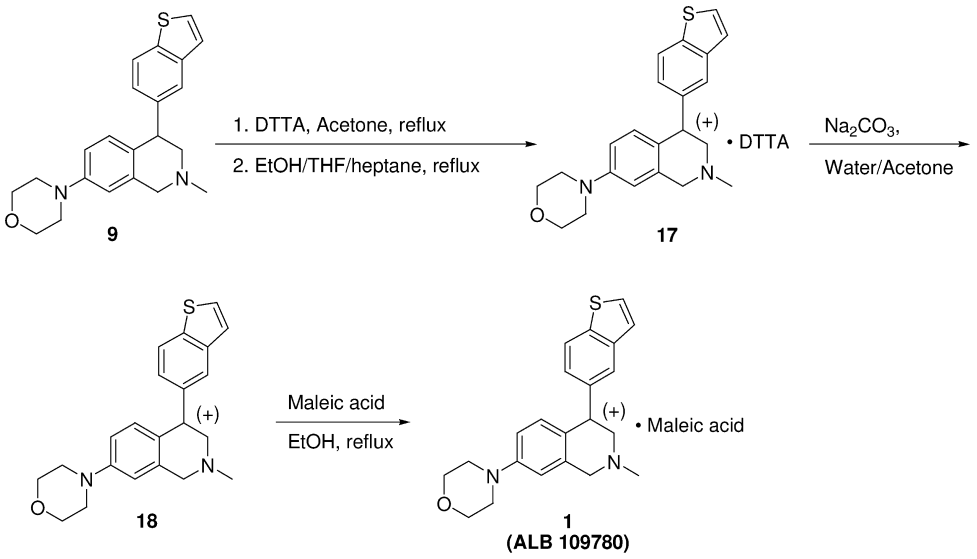
Alternative Synthesis of 10. Concurrently with the above investigations, an alternative strategy to install the morpholine moiety for the synthesis of **10** as depicted in Scheme 3 was also investigated. Hence, 4-nitrophenyl acetic acid **12** was activated as its acid chloride using thionyl chloride in the presence of DMF in toluene and quenched into aqueous methylamine solution to afford the desired product **13** as a pale-yellow solid in quantitative yield and >99% HPLC purity after filtration and drying.[8,9] The obtained amide **13** was reacted with paraformamide under the Eaton's reagent-mediated cyclization conditions to afford **14** as a yellow solid in 98% yield and >99% HPLC purity.[8,9] Hydrogenation of **14** was conducted in the presence of 10% Pd/C in 1:1 EtOAc/EtOH to afford aniline **15** as a white solid in 89% yield after filtration to remove catalyst and concentration of the filtrates.[19] Reaction of **15** with diethylene glycol di(*p*-toluenesulfonate) **16** in the presence of potassium carbonate in acetone at reflux afforded the desired product **10** as a light-yellow solid in 75% yield after column chromatography purification.[20] However, this route was not further pursued due to concerns of diethylene glycol di(*p*-toluenesulfonate) **16** as a potential genotoxin.[21−23]

dx.doi.org/10.1021/op3000064 | *Org. Process Res. Dev.* 2012, 16, 499−506

Scheme 3. Alternative synthesis of 10



Scheme 4. End game: resolution and salt formation



End Game: Resolution and Salt Formation. On lab scale the resolution of **9** using (+)-di-*p*-toluoyl-D-tartaric acid [(+)-DTTA] was conducted by adding a solution of (+)-DTTA in acetone to a solution of racemic **9** in acetone at reflux. The resulting solution was cooled to −5 °C to afford the desired product as a white solid after filtration in 81−88% ee. The chiral purity was further upgraded to 98.8% ee after the isolated product was recrystallized by dissolving in 36 volumes of 10% EtOH/THF at reflux (68 °C) and adding 12 volumes of heptane as antisolvent to facilitate crystallization. However, on scale the resolution of racemic **9** with (+)-DTTA following the above procedure provided only racemic DTTA salt. While the cause for this premature precipitation of the racemic DTTA salt was not clear, small-scale use-tests indicated that the chiral purity could be enhanced to 94% ee by reslurrying the racemic DTTA salt in 20 volumes of 1:9 EtOH/THF at 65 °C, followed by adding 10 volumes of heptane to maximize yield. The large batches of racemic DTTA salt were then processed following the reslurry procedure to afford the desired product **17** as a white solid in 93.3−94.0% ee.

Free-basing of (+)-DTTA salt **17** was conducted by suspending **17** in acetone and treating with sodium carbonate aqueous solution. Originally the mixture was extracted with ethyl acetate and concentrated to dryness to afford the desired product in >95% yield. On scale, **17** was suspended in a mixture of aqueous acetone and treated with 6 equiv of sodium carbonate solution. The resulting suspension was filtered to afford the desired product in quantitative yield and 97.1% HPLC purity. The chiral purity was determined to be 94.3% ee. The free base **18** was heated to reflux in ethanol and treated with a solution of 1.1 equiv of maleic acid. It was cooled to −5 °C and filtered to afford the desired product **1** as a white solid in 91% yield and 98.1% HPLC purity (see Scheme 4). The chiral purity was determined to be >99.9% ee after isolation. Small-scale studies also revealed that the chiral purity could be upgraded to >99% ee during salt formation from starting material with only 86% ee.

■ CONCLUSIONS

Three different routes were evaluated for the synthesis of **1** during initial process development. The route outlined in Schemes 2 and 4 was chosen for further optimization as this route minimized the formation of impurities. Safety studies by RC1 were performed for most of the stages, and a delayed exotherm was observed during the coupling of **5** with **10** to form **11**. This reaction was conducted on small scales to ensure safety as cooling capacity and the ability to mitigate risk in the event of a cooling excursion is much better on smaller scale; however, further development is required before the process can be scaled up safely. The selected route was significantly improved and scaled up to deliver a total of 470 g of **1** for toxicological study. The optimized process represents a solid base for further development of a process suitable for large-scale production.

dx.doi.org/10.1021/op3000064 | *Org. Process Res. Dev.* 2012, 16, 499−506

EXPERIMENTAL SECTION

Reaction progress and chemical purity were evaluated by HPLC analysis using a Waters Sunfire C18 column (150 mm × 4.6 mm) with a mobile phase A (water + 0.05% TFA) and B (acetonitrile + 0.05% TFA) and detection at 220 nm; flow: 1.0 mL/min; temp. 25 °C; and gradient: 0 min: A = 95%, B = 5%; 10 min: A = 5%, B = 95%; 20 min: A = 5%, B = 95%; and 22 min: A = 95%, B = 5%. Chiral purity was evaluated by HPLC analysis using a Chiralpak IA (250 nm × 4.6 nm) with isocratic mobile phase 60% heptanes/EtOH + 0.1% DEA and detection at 260 nm; flow: 1.0 mL/min; and temp. 25 °C.

4-(Benzothiophen-5-yl)-7-bromo-2-methyl-1,2-dihydroisoquinolin-3(4*H*)-one (6). A mixture of benzothiophene **5** (386 g, 1.81 mol), $Pd(OAc)_2$ (14.0 g, 62.5 mmol), $P(i\text{-}BuNCH_2CH_2)_3N$ (42.7 g, 125 mmol), and toluene (2.0 L) was degassed for 10 min to afford a dark solution. NaO*t*-Bu (180 g, 1.88 mol) was added, followed by a solution of **4** (300 g, 1.25 mol) in toluene (1.0 L). The reaction mixture was purged with nitrogen and heated to 60 °C, at which point an exotherm to 70 °C was observed. It was heated at 70 °C for 2.5 h and analyzed by HPLC, which indicated that the reaction was complete (<1% of **4**). The reaction mixture was cooled to 20 °C, diluted with DCM (5.0 L), and washed with water (8.0 L). The organic layer was concentrated to ∼600 mL of volume. The resulting solution was purified by a silica gel column (2.5 kg silica) using DCM (6.0 L) and 3:4 DCM/EtOAc (10.5 L) as eluent. The fractions containing pure product were concentrated to afford a semisolid, which was suspended in EtOAc (800 mL) and diluted with heptanes (2.0 L). The resulting suspension was stirred at ambient temperature for 2 h and filtered. The filter cake was rinsed with heptanes (2 × 200 mL) and dried under vacuum to afford the desired product as an off-white solid (220 g, 47% yield). ^{1}H NMR (300 MHz, $CDCl_3$) 7.80 (d, 1 H, J = 8.4 Hz), 7.47−7.40 (m, 4 H), 7.22 (t, 1 H, J = 5.7 Hz), 7.18 (dd, 1 H, J_1 = 1.8 Hz, J_2 = 8.4 Hz), 7.03 (d, 1 H, J = 8.7 Hz), 4.93 (s, 1 H), 4.63 (d, 1 H, J = 15.9 Hz), 4.30 (d, 1 H, J = 15.9 Hz), 3.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 169.8, 140.3, 139.2, 135.2, 134.9, 134.1, 131.6, 130.7, 128.8, 127.5, 124.7, 124.2, 123.2, 123.1, 121.3, 52.4, 52.3, 35.3; MS m/z 371.80 $[M + H]^+$; HPLC 95.2%.

4-(Benzothiophen-5-yl)-7-bromo-2-methyl-1,2,3,4-tetrahydroisoquinoline (7). A solution of **6** (289 g, 776 mmol) and THF (5.0 L) was treated with BMS (171 mL, 1.71 mol) and the reaction mixture was heated at 50 °C for 1 h. It was allowed to cool to 45 °C over 1 h, and 6 N HCl (500 mL) was added. The resulting mixture was stirred at 50 °C for 2 h and cooled to ambient temperature. It was diluted with EtOAc (3.0 L) and water (1.0 L) and basified using 2 N NaOH (1.55 L) to pH 10. The layers were separated, and the aqueous layer was extracted with EtOAc (1.0 L). The combined organic layers were concentrated, and the residue was purified by silica gel column using 3:1 heptanes/EtOAc as eluent. The fractions containing pure product were concentrated to afford the desired product as a light-yellow oil (218 g, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) 7.79 (d, 1 H, J = 8.1 Hz), 7.63 (d, 1 H, J = 1.5 Hz), 7.43 (d, 1 H, J = 5.4 Hz), 7.27 (d, 1 H J = 5.4 Hz), 7.25 (s, 1 H), 7.15 (dt, 1 H, J_1 = 1.5 Hz, J_2 = 8.4 Hz), 6.76 (d, 1 H, J = 8.4 Hz), 4.32 (t, 1 H, J = 7.5 Hz), 3.74 (d, 1 H, J = 15.0 Hz), 3.61 (d, 1 H, J = 15.0 Hz), 3.06 (ddd, 1 H, J_1 = 1.2 Hz, J_2 = 5.7 Hz, J_3 = 11.4 Hz), 2.61 (dd, 1 H, J_1 = 8.7 Hz, J_2 = 11.4 Hz), 2.42 (s, 3 H), 1.72−1.65 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 140.7, 140.3, 137.9, 136.9, 131.7, 129.9, 129.4, 127.2, 125.9, 124.4, 124.1, 122.9, 120.2, 62.2, 58.4, 46.3, 45.9; MS m/z 357.97 $[M + H]^+$; HPLC 91.1%.

4-(4-(Benzothiophen-5-yl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)morpholine (9) via Coupling of 7 and 8. A mixture of **7** (214 g, 599 mmol), $Pd(OAc)_2$ (13.3 g, 59.4 mmol), **8** (208 g, 2.4 mol), BINAP (37.3 g, 59.9 mmol), KO*t*-Bu (148 g, 1.32 mol), and toluene (3.0 L) was degassed for 10 min and purged with nitrogen. The reaction was heated at 85 °C for 1 h, at which point HPLC analysis indicated that the reaction was complete (<1% of **7**). It was allowed to cool to ambient temperature and diluted with EtOAc (4.0 L). The mixture was washed with water (4.0 L) and brine (4.0 L), and the organic layer was concentrated to afford a residue, which was purified by silica gel column using 0−10% MeOH in EtOAc as eluent. The fractions containing the desired product (contaminated with an unknown impurity) were collected and concentrated to dryness. The residue was repurified by silica gel column using 0−10% MeOH in EtOAc as eluent to afford the desired product as a brown solid after concentration of the pure fractions (173 g, 79% yield). ^{1}H NMR (300 MHz, $CDCl_3$) 7.78 (d, 1 H, J = 8.1 Hz), 7.65 (d, 1 H, J = 1.5 Hz), 7.41 (d, 1 H, J = 5.4 Hz), 7.25 (d, 1 H, J = 5.4 Hz), 7.18 (dd, 1 H, J_1 = 1.5 Hz, J_2 = 8.1 Hz), 6.79 (d, 1 H, J = 8.4 Hz), 6.68−6.62 (m, 2 H), 4.33 (dd, 1 H, J_1 = 6.0 Hz, J_2 = 8.1 Hz), 3.85 (t, 4 H, J = 4.8 Hz), 3.73 (d, 1 H, J = 14.7 Hz), 3.61 (d, 1 H, J = 14.7 Hz), 3.12 (t, 4 H, J = 4.8 Hz), 3.07 (ddd, 1 H, J_1 = 0.9 Hz, J_2 = 5.4 Hz, J_3 = 11.4 Hz), 2.60 (dd, 1 H, J_1 = 8.1 Hz, J_2 = 11.4 Hz), 2.43 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 149.9, 141.7, 140.2, 138.3, 136.3, 130.6, 129.4, 126.9, 126.1, 124.3, 124.2, 122.7, 115.0, 113.1, 67.4, 62.7, 59.3, 49.9, 46.4, 45.5; MS m/z 365.21 $[M + H]^+$; HPLC 91.3%.

2-Methyl-7-morpholino-1,2-dihydroisoquinolin-3(4*H*)-one (10). A mixture of **4** (3.80 kg, 15.8 mol), potassium carbonate (4.37 kg, 31.7 mol), CuI (300 g, 1.58 mol), *L*-proline (1.05 kg, 9.5 mol), **8** (11.0 L, 127 mol), and DMSO (7.6 L) was heated at 85 °C for 30 h, at which point HPLC analysis indicated that the reaction was complete (<3% of **4**). The reaction mixture was cooled to ambient temperature over 2.5 h and charged into brine solution (40.0 L) over 100 min while maintaining the internal temperature below 30 °C. DCM (20.0 L) was added, and the resulting mixture was agitated for 15 min. The layers were separated, and the aqueous layer was extracted with DCM (2 × 5.0 L). The combined layers were concentrated until no more DCM was removed to afford a thick slurry, which was passed through a silica gel plug using 5% MeOH/EtOAc as eluent. The fractions containing product were combined and concentrated to afford the desired product **10** as a yellow solid (2.58 kg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) 7.06 (d, 1 H, J = 8.4 Hz), 6.84 (dd, 1 H, J_1 = 2.1 Hz; J_1 = 8.4 Hz), 6.68 (d, 1 H, J = 2.1 Hz), 4.46 (s, 2 H), 3.87 (t, 4 H, J = 4.8 Hz), 3.55 (s, 2 H), 3.13 (t, 4 H, J = 4.8 Hz), 3.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 169.2, 150.2, 131.6, 128.1, 123.6, 115.6, 112.1, 66.9, 53.3, 49.6, 36.0, 34.4; MS m/z 247.15 $[M + H]^+$; HPLC 98.5%.

4-(Benzothiophen-5-yl)-2-methyl-7-morpholino-1,2-dihydroisoquinolin-3(4*H*)-one (11). A mixture of **10** (300 g, 1.22 mol), **5** (272 g, 1.28 mol), $Pd(OAc)_2$ (13.6 g, 60.7 mmol), BINAP (37.9 g, 60.7 mmol), and 1,4-dioxane (1.5 L) under nitrogen was stirred for 10 min at ambient temperature. NaO*t*-Bu (175 g, 1.83 mol) was added portionwise over 30 min, and the reaction mixture was heated to 60−65 °C, at which point the system became self-heating, requiring removal of the heating mantle until the exotherm subsided (**CAUTION**: this reaction

dx.doi.org/10.1021/op3000064 | *Org. Process Res. Dev.* 2012, 16, 499−506

has the possibility of overheating). Heating was then reapplied, and the reaction was stirred at 80 °C for 1.5 h, at which point HPLC analysis indicated that the reaction was complete (<1% of **10**). The reaction mixture was allowed to cool to ambient temperature, quenched into water (6.0 L), and extracted with DCM (3.0 L, 1.5 L). The combined organic extracts were washed with brine (3.0 L), and the organic layer was concentrated to afford crude product as a brown residue. It was combined with the crude product from a 170-g scale reaction for purification as follows.

The combined crude product was suspended in IPAc (700 mL) at 60 °C for 15 min, cooled to 5 °C, and filtered. The filter cake was dissolved in DCM (1.5 L) and passed through a silica gel plug using EtOAc as eluent. The product containing fractions was concentrated to dryness to afford the desired product as a brown solid [480 g, 66% yield (average for two reactions)]. ^{1}H NMR (300 MHz, $CDCl_3$) 7.77 (d, 1 H, J = 8.4 Hz), 7.50 (s, 1 H), 7.39 (d, 1 H, J = 5.4 Hz), 7.26−7.18 (m, 2 H), 7.49 (d, 1 H, J = 8.4 Hz), 6.87 (dd, 1 H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 6.77 (d, 1 H, J = 2.4 Hz), 4.91 (s, 1 H), 4.64 (d, 1 H, J = 15.9 Hz), 4.28 (d, 1 H, J = 15.9 Hz), 3.88 (t, 4 H, J = 4.8 Hz), 3.19 (t, 4 H, J = 4.8 Hz), 3.08 (s, 3 H); MS m/z 379.12 $[M + H]^+$; HPLC 99.1%.

4-(4-(Benzothiophen-5-yl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)morpholine (9) via Reduction of 11. A solution of **11** (565 g, 1.49 mol) and THF (11.4 L) was stirred for 10 min, and the reaction temperature was adjusted to 35 °C. BMS (300 mL, 3.16 mol) was added over 25 min while maintaining the internal temperature at <40 °C. The reaction was stirred at 40 °C for 4 h, at which point HPLC analysis indicated that the reaction was complete (<1% of **11**). It was combined with 2 N HCl (2.24 L) over 25 min, and the resulting mixture was stirred at 40 °C for 1 h. The mixture was cooled to ambient temperature and basified using 2 N NaOH (2.5 L) to pH 13. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 3.0 L). The combined organic layers were concentrated, and the residue was passed through a silica gel plug using 10% MeOH/EtOAc as eluent. The fractions containing product were combined and solvent-swapped to acetonitrile (11.5 L). The resulting solution was treated with activated charcoal (95 g) and heated at reflux for 40 min. The suspension was cooled to 40 °C and filtered through a Celite pad. The Celite pad was rinsed with acetonitrile (2 × 500 mL), and the combined filtrates were concentrated to afford the desired product **9** as a yellow solid (360 g, 66% yield). HPLC 95.4%. Spectroscopic analysis was in agreement with that obtained via the coupling of **7** and **8**.

7-Amino-2-methyl-1,2-dihydroisoquinolin-3(4*H*)-one (15). A 500-mL Parr bottle was charged with **14** (7.4 g, 36 mmol), Pd/C (10%, 740 mg), EtOAc (74 mL), and EtOH (74 mL) under nitrogen. The mixture was purged with nitrogen and hydrogen sequentially and agitated under 20 psi of hydrogen for 2 h. The reaction was cooled to ambient temperature and filtered through a Celite pad. The filtrate was concentrated to afford the desired product **15** as a white solid (5.6 g, 89% yield). ^{1}H NMR (300 MHz, $CDCl_3$) 6.93 (d, 1 H, J = 8.1 Hz), 6.59 (dd, 1 H, J_1 = 2.4 Hz, J_2 = 8.1 Hz), 6.48 (d, 1 H, J = 2.4 Hz), 4.39 (s, 2 H), 3.66 (bs, 1 H), 3.51 (s, 2 H), 3.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 169.8, 145.4, 132.1, 128.6, 122.4, 115.1, 111.6, 53.4, 36.4, 34.8; MS m/z 177.10 $[M + H]^+$.

2-Methyl-7-morpholino-1,2-dihydroisoquinolin-3(4H)-one (10) from 15. A mixture of **15** (2.50 g, 14.2 mmol), **16** (6.48 g, 15.6 mmol), K_2CO_3 (4.70 g, 34.1 mmol), and acetone (50 mL) was heated at reflux for 7 h, at which point HPLC analysis indicated that it was complete (<5% of **15**). The reaction was cooled to ambient temperature and filtered. The filter cake was rinsed with acetone (2 × 10 mL), and the combined filtrates were concentrated to dryness. The residue was purified by a silica gel plug using 5% MeOH/EtOAc as eluent to give the desired product **10** as a light-yellow solid (2.62 g, 75% yield). Spectroscopic analysis was in agreement with that obtained via the coupling of **4** and **8**.

(+)-4-(4-(Benzothiophen-5-yl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)morpholine DTTA Salt (17). A solution of **9** (650 g, 1.78 mo1) and acetone (10.2 L) was heated to 50 °C, and a solution of di-*p*-toluoyl-D-tartaric acid (690 g, 1.78 mol) in acetone (1.5 L) was added over 10 min. The solution was stirred at reflux for 10 min; at this point a white precipitate formed. The suspension was cooled to ambient temperature over 2 h and further to −5 °C over 1 h. The resulting slurry was stirred at −5 °C for 1 h and filtered. The filter cake was rinsed with acetone (2 × 1.3 L) and dried under vacuum at ambient temperature for 16 h to afford a white solid (1.12 kg, 84%). HPLC 97.2%.

The solid obtained above was suspended in 1:9 EtOH/THF (20.0 L) and heated at 65 °C for 1 h; then heptane (10.0 L) was added. The resulting slurry was heated at 65 °C for 1 h and allowed to cool to ambient temperature over 1 h, then further cooled to −5 °C over 1.5 h and stirred at −5 °C for 1 h. The suspension was filtered, and the filter cake was rinsed with heptane (2 × 1.1 L) and dried under vacuum at ambient temperature for 72 h to afford **17** as a white solid (523 g, 47%). Mp (DSC): 166 °C; ^{1}H NMR (500 MHz, CD_3OD) 8.00 (d, 4 H, J = 8.0 Hz), 7.87 (d, 1 H, J = 8.5 Hz), 7.70 (d, 1 H, J = 1.5 Hz), 7.60 (d, 1 H, J = 5.5 Hz), 7.33 (d, 1 H, J = 5.5 Hz), 7.27 (d, 4 H, J = 8.0 Hz), 7.13 (dd, 1 H, J_1 = 1.5 Hz, J_2 = 8.5 Hz), 6.83 (dd, 1 H, J_1 = 2.5 Hz, J_2 = 9.0 Hz), 6.77 (d, 1 H, J = 2.5 Hz), 6.71 (d, 1 H, J = 9.0 Hz), 5.86 (s, 1 H), 4.59 (dd, 1 H, J_1 = 6.0 Hz, J_2 = 11.0 Hz), 4.46 (s, 2 H), 3.81 (t, 4 H, J = 5.0 Hz), 3.74 (dd, 1 H, J_1 = 6.0 Hz, J_2 = 12.0 Hz), 3.43 (t, 1 H, J = 12.0 Hz), 3.12 (t, 4 H, J = 5.0 Hz), 2.98 (s, 3 H), 2.39 (s, 6 H); ^{13}C NMR (125 MHz, CD_3OD) 171.6, 167.4, 152.1, 145.5, 141.7, 140.5, 138.4, 131.2, 131.1, 130.5, 130.2, 128.6, 123.4, 126.9, 126.1, 125.4, 124.8, 124.0, 117.5, 113.4, 74.8, 67.9, 59.6, 56.8, 50.3, 43.5, 43.4, 21.7; HRMS calculated for $C_{22}H_{25}N_2OS$ (free base + H): 365.1688, found: 365.1695; HPLC 95.3%; 93.3% ee.

(+)-4-(4-(Benzothiophen-5-yl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)morpholine (18). A mixture of **17** (825 g, 1.10 mol), acetone (8.25 L), and water (10.3 L) was stirred for 10 min, and a solution of Na_2CO_3 (700 g, 6.60 mol) in water (4.0 L) was added. The resulting suspension was stirred at ambient temperature for 75 min and filtered. The filter cake was rinsed with water (2 × 2 L) and dried under vacuum (>30 in Hg) to afford the desired product **18** as a white solid (394 g, 102% theory). Mp (DSC): 145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 7.82 (d, 1 H, J = 8.0 Hz), 7.68 (d, 1 H, J = 2.0 Hz), 7.44 (d, 1 H, J = 5.5 Hz), 7.29 (d, 1 H, J = 5.5 Hz), 7.21 (dd, 1 H, J_1 = 1.5 Hz, J_2 = 8.5 Hz), 6.82 (d, 1 H, J = 8.5 Hz), 6.70 (dd, 1 H, J_1 = 2.5 Hz, J_2 = 8.5 Hz), 6.66 (d, 1 H, J = 2.5 Hz), 4.37 (dd, 1 H, J_1 = 6.0 Hz, J_2 = 8.0 Hz), 3.88 (t, 4 H, J = 5.0 Hz), 3.77 (d, 1 H, J = 14.5 Hz), 3.67 (d, 1 H, J = 14.5 Hz), 3.16 (t, 4 H, J = 5.0 Hz), 3.09 (dd, 1 H, J_1 = 5.5 Hz, J_2 = 11.5 Hz), 2.64 (dd, 1 H, J_1 = 8.5 Hz, J_2 = 11.5 Hz), 2.47 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) 149.5, 141.2, 139.8, 137.9, 135.9, 130.2, 129.0, 126.5, 125.7, 123.9, 123.8, 122.3, 114.6, 112.7, 66.9, 62.3, 58.8, 49.5, 46.0, 45.1; HRMS calculated for $C_{22}H_{25}N_2OS$ (M + H): 365.1688, found: 365.1697; HPLC 97.1%; 94.3% ee.

dx.doi.org/10.1021/op3000064 | *Org. Process Res. Dev.* 2012, 16, 499−506

(+)-4-(4-(Benzothiophen-5-yl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)morpholine maleate salt (1). A solution of **18** (393 g, 1.08 mol) and ethanol (7.0 L) was heated to reflux (~78 °C). A solution of maleic acid (140 g, 1.21 mol) in EtOH (1.0 L) was added over 5 min. The solution was refluxed for 5 min and allowed to cool to ambient temperature over 2 h and further to −5 °C over 1.5 h. The mixture was stirred at −5 °C for 1 h and filtered. The filter cake was rinsed with cold EtOH (2 × 1.0 L) and dried under vacuum (>30 in Hg) at ambient temperature for 48 h to afford **1** as a white solid (470 g, 91%). Mp (DSC): 196 °C; ^{1}H NMR (300 MHz, CD_3OD) 7.90 (d, 1 H, J = 8.4 Hz), 7.73 (s, 1 H), 7.61 (d, 1 H, J = 5.4 Hz), 7.34 (d, 1 H, J = 5.4 Hz), 7.18 (dd, 1 H, J_1 = 1.5 Hz, J_2 = 8.4 Hz), 6.88 (dd, 1 H, J_1 = 2.4 Hz, J_2 = 8.7 Hz), 6.81 (s, 1 H), 6.79 (d, 1 H, J = 8.7 Hz), 4.88 (bs, 4 H), 4.65−4.47 (m, 3 H), 3.87−3.79 (m, 5 H), 3.54 (t, 1 H, J = 12 Hz), 3.13 (t, 4 H, J = 5.1 Hz), 3.06 (s, 3 H); ^{13}C NMR (75 MHz, CD_3OD) 171.2, 152.5, 142.1, 141.0, 138.7, 137.0, 131.6, 130.7, 129.1, 127.0, 126.4, 125.7, 125.2, 124.5, 118.0, 113.7, 68.3, 60.0, 57.3, 43.9, 43.8; HRMS calculated for $C_{22}H_{25}N_2OS$ (free base + H): 365.1688, found: 365.1690; HPLC 98.1%; >99.9% ee; Karl Fisher: 1.5% water; Pd: 5 ppm.

AUTHOR INFORMATION

Corresponding Author

*Telephone: (518) 512-2522. E-mail: qiang.yang@amriglobal.com.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to our drug discovery colleagues for their support during this program. We thank our colleagues in the analytical group for their invaluable support in method development and the AMRI kilo lab team members for assisting in the scale-up of this project.

REFERENCES

(1) The World Health Organization. The World Health Report 2004: Changing History, Annex Table 3: Burden of disease in DALYs by cause, sex, and mortality stratum in WHO regions, estimates for 2002. Geneva: WHO, 2004.

(2) Kessler, R. C.; Chiu, W. T.; Demler, O.; Walters, E. E. *Arch. Gen. Psychiatry* **2005**, *62* (6), 617.

(3) Greenberg, P. E.; Kessler, R. C.; Birnbaum, H. G.; Leong, S. A.; Lowe, S. W.; Berglund, P. A.; Corey-Lisle, P. K. *J. Clin. Psychiatry (Memphis, TN U.S.)* **2003**, *64* (12), 1465.

(4) Walter, M. W. *Drug Dev. Res.* **2005**, *65*, 97.

(5) Liu, S.; Molino, B. F. *Annu. Rep. Med. Chem.* **2007**, *42*, 13.

(6) D'Aquila, P. S.; Collu, M.; Gessa, G. L.; Serra, G. *Eur. J. Pharmacol.* **2000**, *405*, 365.

(7) Molino, B. F.; Liu, S.; Guzzo, P. R.; Beck, J. P. U.S. Patent 7,541,357, 2009.

(8) Ulysse, L. G.; Yang, Q.; McLaws, M. D.; Keefe, D. K.; Guzzo, P. R.; Haney, B. P. *Org. Process Res. Dev.* **2010**, *14*, 225.

(9) Yang, Q.; Ulysse, L. G.; McLaws, M. D.; Keefe, D. K.; Guzzo, P. R.; Haney, B. P. *Org. Synth.* **2012**, *89*, 44.

(10) Hu, M.; Guzzo, P. R.; Zha, C.; Nacro, K.; Yang, Y.-L.; Hassler, C.; Liu, S. *Tetrahedron Lett.* **2012**, *53*, 846.

(11) Christensen, H.; Kiil, S.; Dam-Johansen, K.; Nielsen, O.; Sommer, M. B. *Org. Process Res. Dev.* **2006**, *10*, 762.

(12) Christensen, H.; Kiil, S.; Dam-Johansen, K.; Nielsen, O. *Org. Process Res. Dev.* **2007**, *11*, 956.

(13) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742.

(14) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.

(15) Calkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.

(16) Hamada, T.; Chieff, A.; Ahman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124* (7), 1261.

(17) Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195.

(18) Grasa, G. A.; Colacot, T. J. *Org. Process Res. Dev.* **2008**, *12*, 522.

(19) Lim, J. O.; Jin, M. K.; Ryu, H. C.; Kang, D. W.; Lee, J.; Pearce, L. V.; Tran, R.; Toth, A.; Blumberg, P. M. *Eur. J. Med. Chem.* **2009**, *44*, 322.

(20) Lee, J.; Kim, J. Y.; Song, K. S.; Kim, J.; Ahn, K. W.; Kong, Y. PCT Int. Appl. 2011014003, 2011.

(21) Robinson, D. I. *Org. Process Res. Dev.* **2010**, *14*, 946.

(22) Snodin, D. J. *Org. Process Res. Dev.* **2010**, *14*, 960.

(23) Teasdale, A.; Delaney, E. J.; Eyley, S. C.; Jacq, K.; Taylor-Worth, K.; Lipczynski, A.; Hoffmann, W.; Reif, V.; Elder, D. P.; Facchine, K. L.; Golec, S.; Oestrich, R. S.; Sandra, P.; David, F. *Org. Process Res. Dev.* **2010**, *14*, 999.