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Convergent Synthesis of a $5HT_7/5HT_2$ Dual Antagonist

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Supporting Information

ABSTRACT: The development of an efficient and convergent route to 3-(4-fluorophenyl)-2-isopropyl-2,4,5,6,7,8-hexahydropyrazolo-[3,4-*d*]azepine (**1**), a potent $5HT_7/5HT_2$ dual antagonist, is described. Significant features of this route are: (a) a regioselective construction of a tetra-substituted pyrazole **6a** by reacting an *N*-monosubstituted hydrazone **4a** with an elaborated nitroolefin **5b** and (b) a unique Pd-catalyzed hydrogenation method that carries out the four-step, ring-closing reductive amination sequence in a notable one-pot operation to provide **1** in excellent overall yields.

INTRODUCTION

Serotonin (5-hydroxytryptamine, 5-HT), a biochemically derived monoamine neurotransmitter, is mostly produced and found in the intestine with the remainder in the central nervous system.[1] Serotonin regulates sleep, memory and learning, mood, behavior, muscle contraction, appetite, temperature, and function of the cardiovascular and endocrine system via activation of serotonin receptors (5-hydroxytryptamine receptors, 5-HT receptors).[2] These receptors are classified into seven distinct families termed $5HT_1$ through $5HT_7$ and all are G protein-coupled receptors with the exception of the 5-HT_3 receptor, which is a ligand-gated ion channel.[3] Within these general classes of serotonin receptors, at least 14 distinct subtype receptors have been identified by molecular cloning studies. The identification of several subtype 5-HT receptors has provided scientists with opportunities to characterize therapeutic agents believed to act via the serotonergic system.

Our interest to target serotonin receptors was directly related to one of our drug discovery programs. Recent efforts from our neuroscience group led to the discovery of a novel class of pyrazole compounds showing potent $5HT_7$ and/or $5HT_2$ antagonist activity.[4] Compound **1** was recognized as an important lead candidate for the potential treatment of depression, psychosis, anxiety, and sleep disorders (Figure 1).[5] The notable feature of **1** is the fused pyrazolo[3,4-*d*]azepane core structure. Several pharmacological compounds are also known to contain this core for potential indications of Alzheimer's, obesity, substance abuse, and other diseases.[6] The challenge associated with these molecules primarily consists of constructing the pyrazolo-[3,4-*d*]azepane core with its synthesis proceeding through one of two general linear strategies: (1) from commercially available 4-azepanone followed by protection, pyrazole formation, derivatizations then deprotection or (2) from a preassembled pyrazole followed by derivatizations then cyclization to the azepane ring. Unfortunately, both strategies suffer from lengthy routes and require expensive starting materials.

Early on, the medicinal chemistry team employed a sequence based on late-stage introduction of the fused pyrazole beginning with commercially available Boc-piperidone (Scheme 1). Ring expansion by treatment with ethyl diazoacetate[7] furnished the azepanone ester. A subsequent pyrazole synthesis[7] by condensation with isopropyl hydrazine followed by triflate formation with phenyl-bis-trifluoromethanesulfonamide, a palladium-catalyzed Suzuki−Miyaura reaction[8] with (4-fluorophenyl)boronic acid and then Boc-deprotection afforded compound **1**. Despite the efficiency of this route, there were potential drawbacks when considering large-scale process development. The major concerns were the following: (1) the use of hazardous ethyl diazoacetate[9] in the ring-expansion step; (2) the use of a homogeneous palladium catalyst in the Suzuki−Miyaura coupling reaction, as the need for removal of Pd in the final step may be necessary and expensive; and (3) use of chromatographic purifications in steps one and four. To circumvent all of the above concerns, we report a new convergent route based on a novel regioselective pyrazole synthesis that was designed and carried out in our lab on 200-g scale. Our synthetic approach demonstrates a regioselective reaction of hydrazone **4a** with nitroolefin **5b** to obtain pyrazole **6a**. Further development of the last stage led to a four-step, one-pot intramolecular ring closure of the azepane ring of product **1**. Overall, this route is high-yielding, inexpensive, chromatography-free, and adaptable for large-scale production.

RESULTS AND DISCUSSION

In our search for alternative ways to synthesize pyrazoles, we found sporadic examples in the literature describing the reaction of *N*-monosubstituted hydrazones and substituted nitroolefins affording pyrazole and/or pyrazolidine products.[10] Most recently, Deng and Mani[11] have demonstrated excellent regioselectivity in the reaction of *N*-monosubstituted hydrazones with various substituted nitroolefins in a variety of solvents and at various reaction temperatures under air atmosphere. The results of these studies prompted us to speculate that this particular pathway could be employed to regioselectively build the requisite pyrazole. By analyzing compound **1** retrosynthetically (Scheme 2), we chose to first disconnect the azepane ring at the C−N position where the linkages on both ends could be protected as in compound **6**. With intermediate **6** in hand, one could potentially conceive the synthesis of the azepane ring via deprotection on both ends followed by intramolecular reductive amination to give

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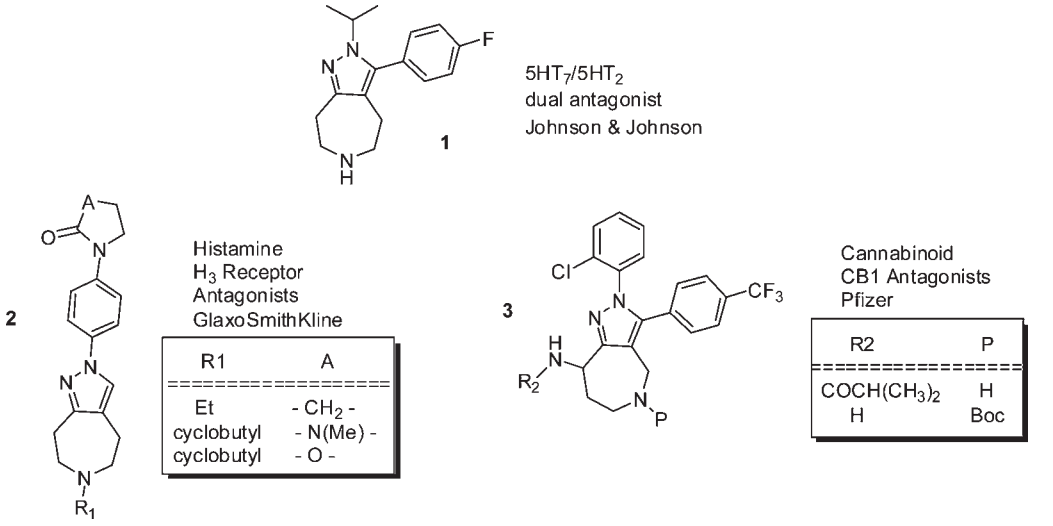
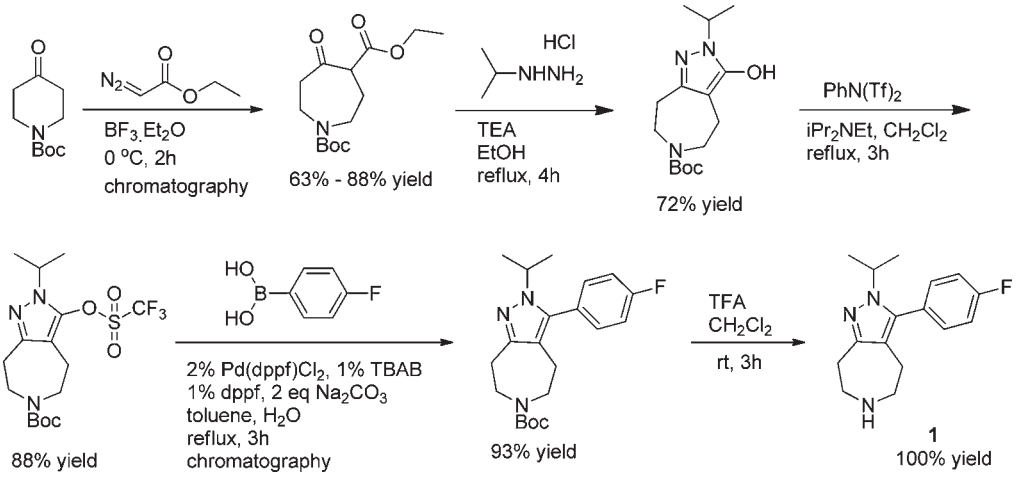
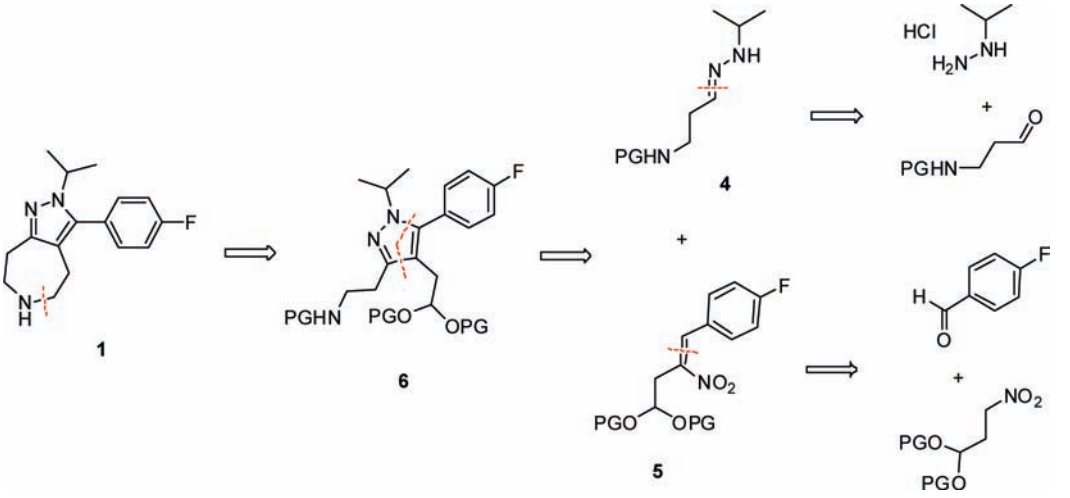


Figure 1. Structure of pyrazolo[3,4]azepanes of clinical interest.

Scheme 1. Original synthesis of 1



Scheme 2. Retrosynthetic analysis of compound 1



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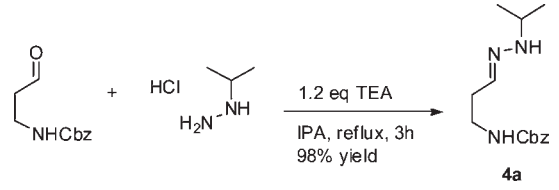
the final compound **1**. As for the formation of **6**, we envisaged the disconnection of the pyrazole at the C−N and C−C bonds. The synthesis of **6** would then derive from the key reaction of hydrazone **4** and nitroolefin **5** presumably through a stepwise cycloaddition pathway.[11a] Keep in mind, one of the challenges in the synthesis of both **4** and **5** was finding suitable protecting groups, which offered stability during the pyrazole synthesis and then facile deprotection during the cyclization step. We envisioned the synthesis of **5** utilizing the Knoevenagel condensation conditions or by Henry reaction of 4-fluoro-benzaldehyde with a protected nitro-propane acetal. For the synthesis of **4**, we anticipated utilizing commercially available isopropyl hydrazine reacting with an *N*-protected 3-amino propionaldehyde.

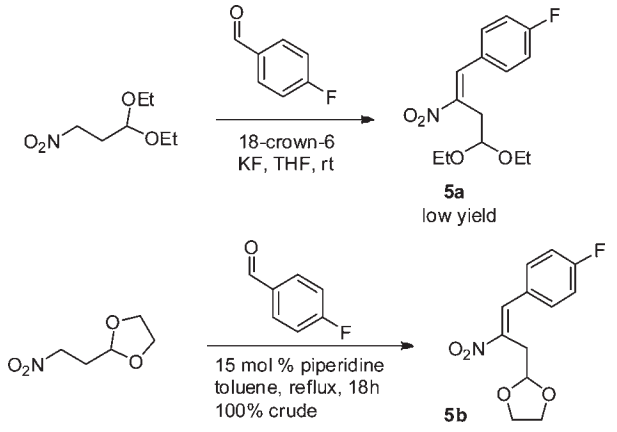
In the preparation of hydrazone **4**, we primarily selected benzyl *N*-(3-oxopropyl)carbamate as our starting material (Scheme 3). We reasoned that the use of Cbz protection would provide adequate stability during pyrazole formation and at the same time would be reasonably labile to removal prior to or possibly following the cyclization to the seven-membered ring. Our initial attempt using standard hydrazone formation conditions provided the requisite **4a** in 98% yield. The light-yellow oil was used directly without further purification.

Scheme 3. Preparation of hydrazone



For the protection of the nitroolefin **5**, we initially examined the diethyl acetal group (Scheme 4). Following literature procedures,[12] 1,1-diethoxy-3-nitropropane was prepared without difficulty but unfortunately, the subsequent Henry reaction-elimination step provided the desired olefin **5a** only in very low yield after silica gel chromatographic purification. Several other base-catalyzed reactions at varying temperatures were also evaluated without success, as most of the reactions afforded mixtures of starting material and nitro aldol compound. In addition, when the reaction was heated up to 80 °C, we observed slow decomposition of the starting material. It thus became apparent that 1,1-diethoxy-3-nitropropane was not a suitable material for our use. The problem was solved by the selection of 2-(2-nitroethyl)-1,3-dioxolane with the expectation that the ethylene acetal protecting group could endure elevated temperature conditions. By applying classic condensation conditions to 2-(2-nitroethyl)-1,3-dioxolane and 4-fluoro-benazldehyde, we successfully synthesized nitroolefin **5b** in quantitative crude yield.[13] The viscous brown oil was isolated in high purity and used directly in the next step.

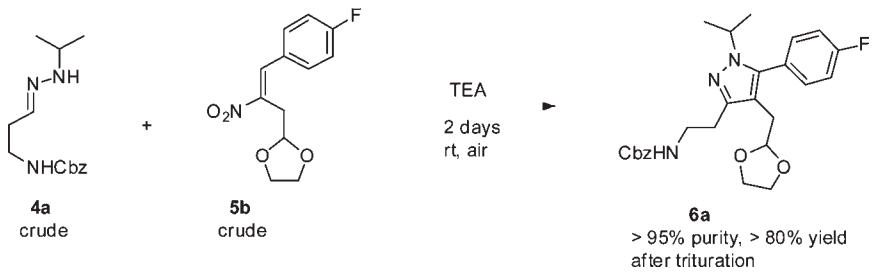
Scheme 4. Synthesis of nitroolefin



With two major building blocks **4a** and **5b** at hand, we directed our efforts to the important pyrazole synthesis. By combining **4a** and **5b** in THF at 60 °C, the reaction undergoes a slow oxidation step under open air for several days, followed by a fast elimination of HNO_2 to furnish pyrazole **6a** in quantitative crude yield. However, in order to drive the reaction to completion, several equivalents of **4a** were necessary. Presumably, the elimination of HNO_2 in the reaction gradually caused decomposition of **4a**.[11] We rationalized that the addition of a base to capture the nitrous acid could be helpful in preventing this decomposition. We were pleased to find that using triethylamine as the solvent indeed eliminated this undesirable decomposition and the reaction went to completion with 1.2 equiv of **4a**. After stirring for 2 days at room temperature in open air, the reaction afforded pyrazole **6a** in >80% yield (Scheme 5). Upon further optimization, we found that trituration from Et_2O/hexanes effectively increased the purity of the solid product to >95%. This reaction was successfully performed on 200-g scale.

With the completion of the pyrazole synthesis, we initially envisaged a stepwise cyclization of **6a** to azepane **1**. By employing 6 N HCl[14] to remove the Cbz and the acetal protecting group, our analysis of the reaction mixture by mass spectrometry indicated several possible compounds (Scheme 6). After workup of the crude intermediates, we proceeded with the reductive amination step utilizing $Na(OAc)_3BH$ to afford the final compound **1** in 80% crude yield. Although a valid route to

Scheme 5. Pyrazole formation



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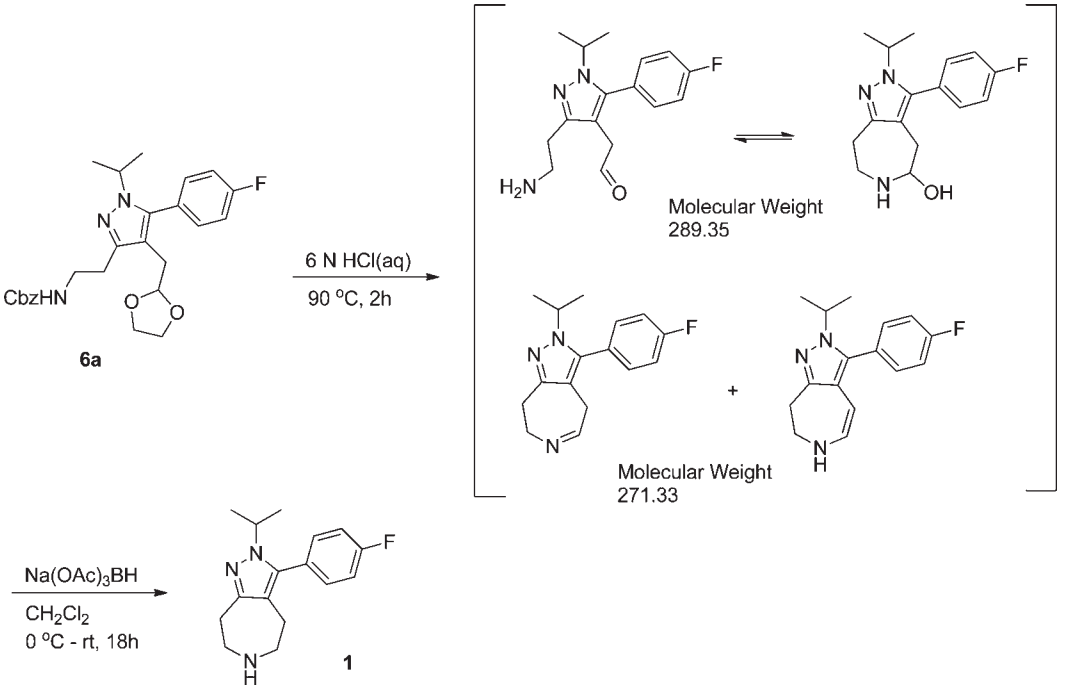
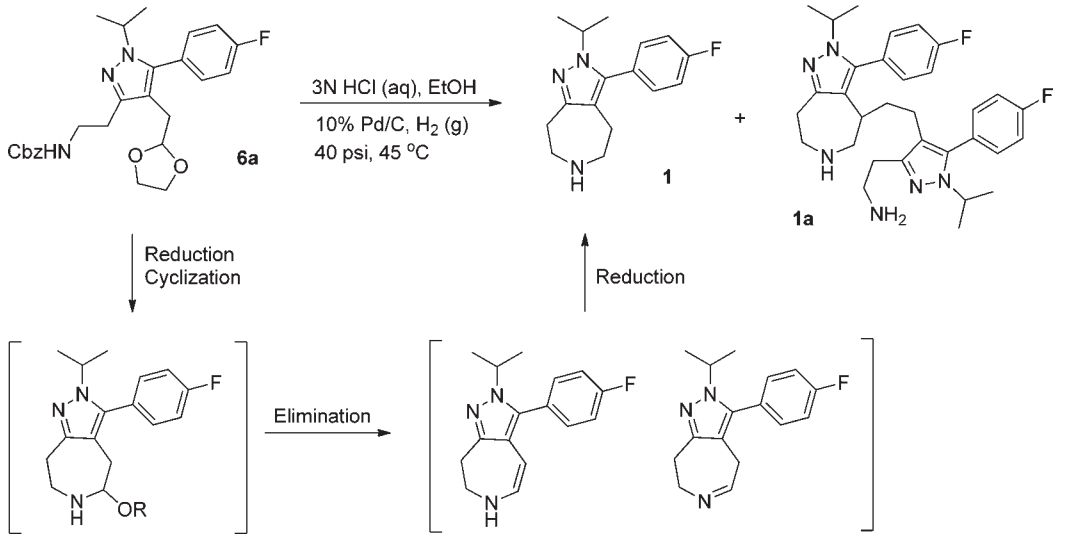
Scheme 6. Two-step sequence to compound 1



Scheme 7. One-step cyclization of compound 1



the complete synthesis of **1** was now established, the cyclization step still needed improvement. While examining the removal of the Cbz group by mild hydrogenolysis, we realized that we could perhaps achieve both Cbz and acetal deprotection, as well as reductive cyclization by hydrogenation in a mild aqueous HCl/alcohol mixture. The acidic medium should induce cyclization and subsequent elimination to form imine or enamine intermediates followed by hydrogenation again to provide compound **1**, all in a one-pot process (Scheme 7). Indeed, after some optimization on small scale, we eventually obtained >90% yield of **1** using a 3 N HCl/EtOH mixture with 10% Pd/C, hydrogenating at 40 psi and 45 °C. Interestingly, when the reaction was repeated on a 30-g scale, to our surprise, we only isolated 84% yield of crude product. Close examination of reaction products revealed 22% of dimer **1a**. Upon further investigation, we realized several factors contributed to dimer formation (Table 1). First, there was the concentration effect. A range of concentration levels in the reaction was screened to analyze the HPLC ratio of **1**/**1a**. We noticed that, when the concentration of **6a** in IPA was decreased from 0.3 to 0.2 M or 0.1 M with 10% by weight of catalysts (entries 4−6), greater intramolecular formation of **1** was observed. Second, there was the solvent effect. We examined several solvents such as EtOH, IPA, AcOH, EtOAc, and *tert*-amyl alcohol. Interestingly, we found that secondary and tertiary

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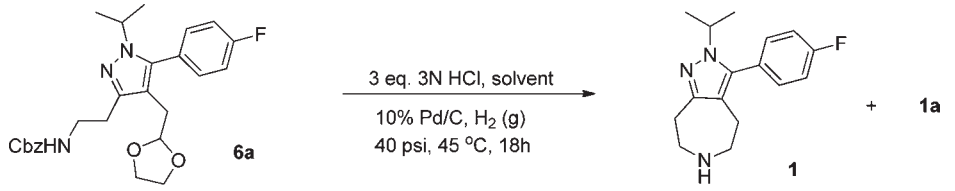
Table 1. Contributing factors to the formation of compound 1



entry	concentration (M)	solvents	weight 10% Pd/C (wt %)	HPLC ratio **1**/**1a**
1	0.2	EtOH	10	85/15
2	0.2	AcOH	10	60/40
3	0.2	EtOAc	10	85/15
4	0.3	IPA	10	65/35
5	0.2	IPA	10	90/10
6	0.1	IPA	10	99/1
7	0.2	*tert*-amyl OH	5	87/13
8	0.2	*tert*-amyl OH	10	93/7
9	0.2	*tert*-amyl OH	20	95/5
10	0.2	*tert*-amyl OH	25	99/1

alcohols such as IPA or *tert*-amyl alcohol decreased dimer formation while enhancing intramolecular cyclization to product **1**, whereas AcOH did not offer any significant advantage. As for EtOH and EtOAc, both solvents did facilitate the formation of **1** but less than IPA and *tert*-amyl alcohol. Last, there was an effect of catalyst loading (entries 7−10). We conducted several reactions with various quantities of 10% Pd/C and found that 20% and 25% by weight of catalysts increased the intramolecular formation of **1**. In comparison, 5% and 10% by weight of catalysts afforded the least amount of **1**. With all the factors taken into consideration, the synthesis of the azepane ring was finally optimized utilizing 3 equiv of 3 N HCl and 25% by weight of 10% Pd/C in 0.2 M of *tert*-amyl alcohol. The reaction was hydrogenated at 40 psi for 18 h at 45 °C to afford product **1** in 89% crude yield with <2% of impurity **1a** present. Purification was accomplished by recrystallization of **1** in MeOH/EtOAc as its citrate salt, followed by base liberation to provide the final compound **1** in 71% yield.

It should be noted that all of our operations described were performed in a research laboratory setting not in a process plant. Additional fine-tuning of the process work is necessary if further up-scaling is required. Due to time constraints, optimization of the synthesis route was not thoroughly investigated during the production campaign. In this case, the use of unsuitable solvents (hexane and MTBE) in the trituration step can be substituted with more process friendly solvents such as heptanes and MTBE. Additionally, the repeated stripping to dryness operations can also be circumvented by simple solvent exchange.

CONCLUSIONS

In summary, we have demonstrated a compelling route for the complete synthesis of compound **1** (Scheme 8). The convergent synthesis proceeds through a significantly less expensive, very efficient, and chromatography-free route that is adaptable to large-scale manufacture. The accomplishments include the following: (1) a regioselective pyrazole synthesis involving an *N*-monosubstituted hydrazone reacting with a disubstituted nitro olefin; (2) a direct four-step process of deprotection, intramolecular cyclization, elimination, and reduction all in a one-pot operation to obtain the final drug substance **1**. With several pharmacological compounds containing a similar pyrazolo-fused azepane core, we anticipate the utility of this sequence to be applicable to the syntheses of many other biologically active compounds.

EXPERIMENTAL SECTION

Benzyl 3-(2-Isopropylhydrazono)propylcarbamate (4a). A solution of isopropyl hydrazine hydrochloride (92.4 g, 0.84 mol) and benzyl (3-oxopropyl)carbamate (173 g, 0.84 mol) in isopropyl alcohol (1.7 L) was treated with Et_3N (140 mL, 1.0 mol) over 20 min. White solids precipitated to form a thick reaction mixture. The slurry mixture was heated to reflux temperature for 3 h then cooled down to room temperature. The solvent was concentrated under reduced pressure (30 Torr, 40 °C) and the recovered residue was diluted in EtOAc (700 mL). The organic layer was washed with water (3 × 500 mL), brine (300 mL) and dried over $MgSO_4$. After filtration and evaporation under reduced pressure, the title compound **4a** was isolated as a light-yellow oil (216 g, 0.82 mol, 98%). The crude product was used in the next reaction without further purification. The hydrazone **4a** is stable at room temperature for weeks. However, it is recommended to use it right away. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38−7.26 (m, 5H), 7.01 (t, J = 4.5 Hz, 1H), 5.11 (br s, 1H), 5.08 (s, 2H), 3.46−3.32 (m, 3H), 2.42−2.32 (m, 2H), 1.11 (d, J = 6.4 Hz, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 156.5, 139.4, 136.6, 128.7, 128.2, 66.7, 50.1, 38.4, 32.7, 22.0; HRMS-ESI (m/z) calcd for $C_{14}H_{21}N_3O_2$ $[M + H]^+$ 264.1707, undetectable.

2-(3-(4-Fluorophenyl)-2-nitroallyl)-1,3-dioxolane (5b). A solution of 2-(2-nitroethyl)-1,3-dioxolane (162.5 g, 1.10 mol), fluorobenzaldehyde (124 g, 1.0 mol), and piperidine (15 mL, 0.15 mol) in toluene (1.2 L) was heated to reflux under N_2 for 18 h using a Dean−Stark trap, then cooled to room temperature. Approximately, 15 mL of water was collected. The reaction mixture was washed with water (2 × 300 mL) and brine (2 × 300 mL). The

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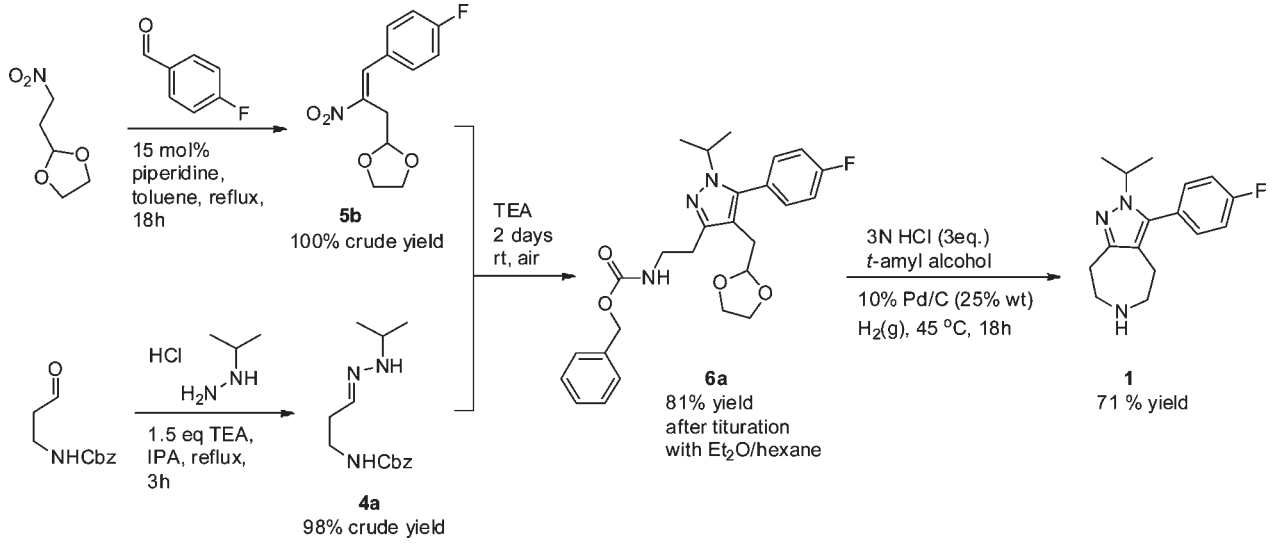
Scheme 8. Convergent synthesis of compound 1



extracted organic layer was dried over $MgSO_4$ and filtered. Activated powder charcoal (80.0 g) was added to the organic solution, and the suspension was stirred for 1 h. After filtration, the solvent was evaporated under reduced pressure to obtain the title compound **5b** as a brown, viscous oil (264 g, 1.04 mol, quantitative crude yield). The crude product was used in the next reaction without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.15 (s, 1H), 7.69−7.67 (m, 2H), 7.16−7.12 (m, 2H), 5.23 (t, J = 4.5 Hz, 1H), 4.02−3.98 (m, 2H), 3.94−3.89 (m, 2H), 3.26 (d, J = 4.5 Hz, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 165.0, 163.0, 146.8, 135.7, 132.3, (128.3, 128.3), (116.4, 116.3), 102.0, 65.3, 32.3; HRMS-ESI (m/z) calcd for $C_{12}H_{12}FNO_4$ $[M + H]^+$ 254.0823, found 254.0816.

Benzyl 2-(4-((1,3-Dioxolan-2-yl)methyl)-5-(4-fluorophenyl)-1-isopropyl-1*H*-pyrazol-3-yl)ethylcarbamate (6a). A solution of compound **4a** (216 g, 0.82 mol) in Et_3N (1 L) was treated with compound **5b** (173 g, 0.68 mol) over 20 min. The reaction was stirred open to air at room temperature for 2 days. *Caution!* Although air is needed for the reaction, care should be taken when stirring in open air due to potential safety hazard. Et_3N was evaporated by rotary evaporation (50 Torr, 40 °C), and the remaining residue was dissolved in EtOAc (1.2 L). Any remaining insoluble material was filtered off through filter paper. The organic solution was washed with water (3 × 500 mL) and brine (500 mL), dried over $MgSO_4$, and then filtered through a short pad of silica gel (~200 g). Evaporation of solvent under reduced pressure afforded the title compound **6a** as an orange, viscous oil (330 g, 100%). After 2 days under house vacuum (15 Torr), the crude oil **6a** solidified to form an orange solid. The solid was slurried in Et_2O (350 mL) and hexanes (600 mL) for 3 h at room temperature and then was collected by filtration. The solids were dried under house vacuum oven (15 Torr) at 40 °C overnight to obtain compound **6a** as an orange fine powder (260 g, 0.56 mol, 81%). To recover additional **6a**, the mother liquor was concentrated under reduced pressure, and the same trituration procedure was repeated. Sometimes the recovered material from the mother liquor did not solidify and required chromatography to isolate **6a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40−7.24 (m, 7H), 7.17−7.10 (m, 2H), 5.82 (br s, 1H), 5.10 (s, 2H), 4.75 (t, J = 4.8 Hz, 1H), 4.18 (sept, J = 6.6 *Hz*, 1H), 3.90−3.68 (m, 2H), 3.68−3.65 (m, 2H), 3.58 (q, J = 6.0 Hz, 2H), 2.85 (t, J = 6.0 Hz, 2H), 2.59 (d, J = 4.8 Hz, 2H), 1.35 (d, J = 6.6 *Hz*, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 163.8, 161.8, 156.5, 148.4, 140.5, 137.0, (131.91, 131.85), 128.4, (127.96, 127.88), 126.78, 126.75, (115.81, 115.64), 111.2, 104.2, 66.3, 64.8, 49.9, 40.3, 28.4, 26.6, 22.8; HRMS-ESI (m/z) calcd for $C_{26}H_{31}FN_3O_4$ $[M + H]^+$ 468.2295, found 468.2292; IR (film) 3305.90 1716.90, 1690.20, 1546.39, 1508.40, 1265.50 cm^{-1}; mp 99−100 °C.

3-(4-Fluorophenyl)-2-isopropyl-2,4,5,6,7,8-hexahydropyrazolo[3,4-*d*]azepine, (1). A 2.25-L, glass hydrogenation bottle was charged with pyrazole **6a** (90.0 g, 0.19 mol) in *tert*-amyl alcohol (910 mL) and 3 N HCl (190 mL, 0.57 mol). With compound **6a** in solution and the bottle under N_2, 10% Pd/C (22.2 g) was added into the mixture. The reaction mixture was hydrogenated to 40 psi for 18 h at 45 °C and then filtered through acid-treated low-metal filter paper. The filtrate was concentrated under reduced pressure (30 Torr, 50 °C) to an oil and then diluted with H_2O (500 mL). The aqueous solution was washed with EtOAc (3 × 250 mL) and then adjusted to pH 13−14 by adding KOH pellets under cold ice bath. The aqueous layer was washed with EtOAc (3 × 250 mL), and the extracted organic phase was filtered through acid-treated low-metal filter paper to remove any remaining solids. The filtrate was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to recover 46.2 g of crude **1** as a tan solid. The crude material was dissolved in MeOH (200 mL) and then treated with warm citric acid (35.4 g, 0.18 mol) in MeOH (120 mL). When additional EtOAc (250 mL) was added to the mixture, precipitation of citrate salt **1** began to develop. The slurry mixture was stirred for 18 h and then filtered to recover 63.8 g of the citrate salt of **1**. The solids thus obtained were stirred in EtOAc (400 mL) and 1 N NaOH (350 mL). After the solids dissolved, the aqueous phase was removed, and the organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to recover **1** as an off-white solid (36.9 g, 0.13 mol, 71% yield). Pd analysis of the final drug substance was less than 1 ppm. ^{1}H NMR (400 MHz, $CDCl_3$ δ: 7.20−7.25 (m, 2H), 7.13−7.18 (t, J = 8.6 Hz, 2H), 4.21−4.28 (sept, J = 6.6 Hz, 1H), 3.01−3.04 (m, 2H), 2.88−2.94 (m, 4H), 2.46 (t, J = 5.2 Hz, 2H), 1.40 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$ δ: 161.9, 151.9, 139.3, 132.0, 131.9,

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127.1, 118.3, 116.0, 115.8, 50.8, 49.9, 49.3, 33.8, 28.4, 23.0; HRMS-ESI (m/z) calcd for $C_{16}H_{20}FN_3$ $[M + H]^+$ 274.1714, found 274.1701; mp 145 −147 °C.

2-(5-(4-Fluorophenyl)-4-(2-(3-(4-fluorophenyl)-2-isopropyl-2,4,5,6,7,8-hexahydropyrazolo[3,4-*d*]azepin-4-yl)ethyl)-1-isopropyl-1*H*-pyrazol-3-yl)ethanamine, (1a). ^{1}H NMR (400 MHz, $CDCl_3$ δ: 7.10−7.05 (m, 8H), 4.21−4.05 (m, 2H), 3.26−3.20 (m, 1H), 3.03−3.00 (dd, J = 3.7, 13.5 Hz, 1H), 2.95−2.88 (m, 3H), 2.72−2.62 (m, 5H), 2.22−2.17 (m, 1H), 2.03−1.92 (m, 2H), 1.76−1.58 (m, 1H), 1.52−1.44 (m, 1H), 1.38−1.32 (m, 12H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 163.4, 161.8, 150.4, 147.6, 139.2, 139.1, 131.7, 131.4, 127.2, 127.0, 121.5, 117.1, 115.8, 115.7, 115.6, 115.6, 53.0, 49.6, 49.1, 41.9, 36.0, 34.6, 33.2, 31.0, 22.8, 22.7, 21.1; HRMS-ESI (m/z) calcd for $C_{32}H_{40}F_2N_6$ $[M + H]^+$ 547.3355, found 547.3355.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. ^{1}H NMR and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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