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A Highly Efficient Synthesis of a Naphthalenoid Histamine-3 Antagonist

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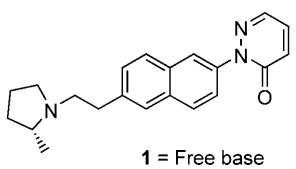
Abstract: A highly efficient synthesis of the potent and selective histamine-3 receptor antagonist **1A** was accomplished in four chemical steps and a salt formation step in 36% overall yield from 6-bromo-2-naphthalenol **9**. The key features are a regioselective Suzuki coupling protocol for selective vinylation of **12** with potassium vinyltrifluoroborate in high yield (92%) with excellent regioselectivity (90:2) and a base-catalyzed hydroamination reaction of **11** in an anti-Markovnikov fashion under mild reaction conditions. An optimized copper-catalyzed cross coupling reaction is used to incorporate the pyridazinone **4**.

Keywords: copper-catalyzed cross coupling; histamine-3 antagonist; hydroamination; pyridazinone; regioselective Suzuki vinylation

Introduction

Histamine-3 receptor antagonists modulate the release of a variety of neurotransmitters.[1] Hence histamine-3 antagonists may have greater efficacy and broader scope than drugs targeting a single neurotransmitter and offer therapeutic benefits in disorders of cognition.[2] Several new classes of high-potency non-imidazole-based histamine-3 antagonists have been described recently.[3] Compound **1**,[3b] a member of new class of naphthalene-based histamine-3 antagonists, has been reported.[3] In order to further evaluate this compound we needed to develop a more efficient and scalable synthesis. In the present report, we describe a highly efficient and practical process for the synthesis of **1A** involving new protocols of a regioselective Suzuki coupling for selective vinylation of ther triflate group *vs.* bromide, and a base-catalyzed hydroamination in an anti-Markovnikov fashion under mild reaction conditions.



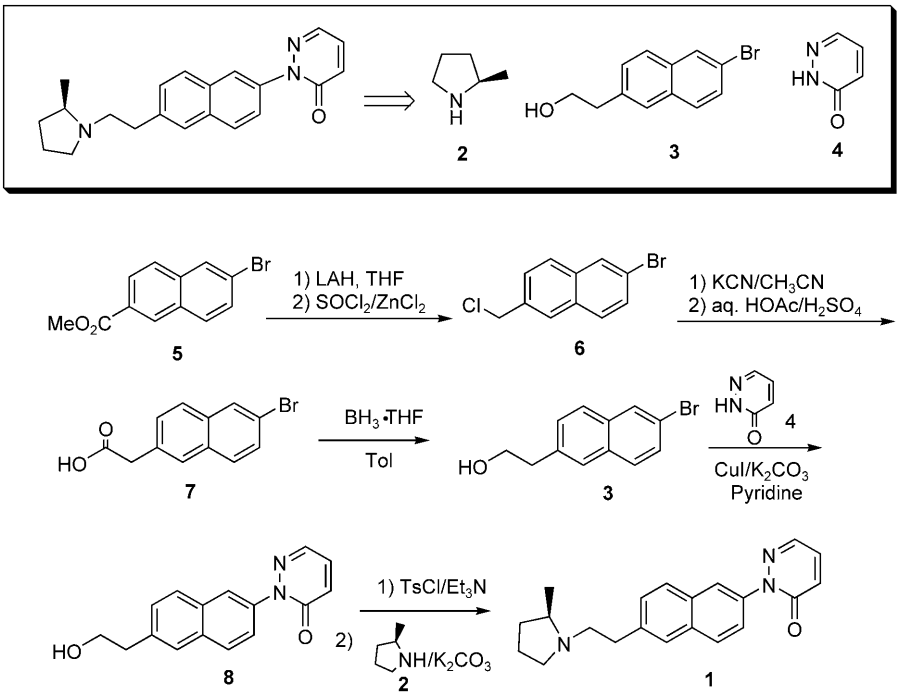
1 = Free base
1A = Bis-Citrate Salt

Results and Discusstion

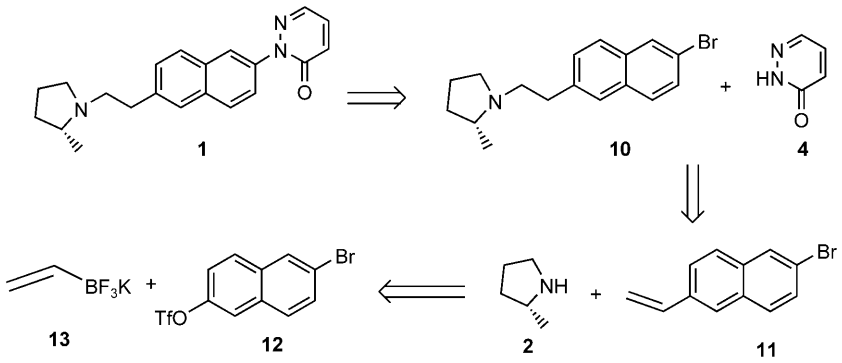
Compound **1** was initially assembled *via* three key components: 2-(*R*)-methylpyrrolidine **2**, naphthalene alcohol **3** and pyridazinone **4** as summarized in Scheme 1. Although the early work allowed use of **2** and **4** in bulk quantities, the preparation of **3** required five chemical transformations starting from 6-bromo-2-napthoic acid methyl ester **5**.[3c] The lengthy synthesis and the high cost of **5** necessitated a more efficient process for **1**. The ready availability of 6-bromo-2-naphthalenol **9** in bulk quantities and its low cost led us to investigate the use of **9** as a starting material.

Retrosynthetically, **1** can be envisioned from a cross-coupling reaction of **10** with pyridazinone **4**. The β-arylethylamine **10** could arise from the hydroamination reaction of **11.** Subsequently, the vinylnaphthalene **11** could be derived from a selective vinylation reaction of **12** which could be prepared from the commercially available 6-bromo 2-naphthalenol **9** (Scheme 2).

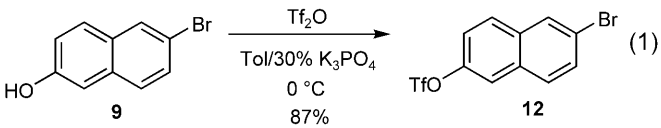
Preparation of triflate **12** was straightforward under biphasic reaction conditions (toluene and 30% K_3PO_4) using triflic anhydride at 0 °C [Eq. (1)].[4] Triflate **12** was isolated in good yield (87%) and high purity (>97%), and was used in the next step without further processing.



Scheme 1. The initial eight-step process.



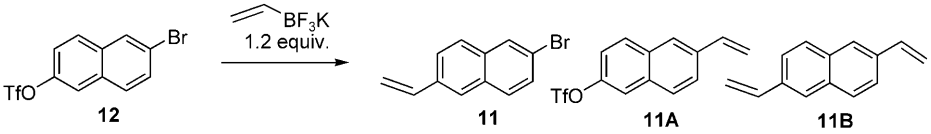
Scheme 2. Retrosynthesis of **1**.



Preparation of the triflate

A regioselective vinylation of the triflate group of **12** was necessary due to the inability to cross-couple the triflate group with pyridazinone **4**. Of the commonly used coupling reactions for vinylation are the Stille coupling[5] with vinyltin reagents and the Suzuki coupling[6] with vinylboron derivatives. Our efforts were focused on a regioselective vinylation of triflate **12** with vinylboron derivatives to avoid producing a tin by-product. Although several boronic vinyl derivatives have been used for the vinylation of triflates or bromides,[7] achieving high regioselectivity could be challenging. The similar reactivity of bromide and triflate groups under palladium-catalyzed cross-coupling conditions often produced mixed results. For example, the regioselective Suzuki coupling favoring the bromide over triflate group was reported,[8a,b,c] while the opposite selectivity was also reported for Kumada and Stille couplings.[8d,e] To the best of our knowledge, no information about the selectivity of vinylation of a triflate group in the presence of a bromide was available. In order to achieve the necessary selective vinylation of **12**, a number of reaction conditions were investigated. Several commercially available vinylboron reagents (vinylboronate pinacol ester,[7a] trivinylcyclo-

Table 1. Selected results of the vinylation reaction.



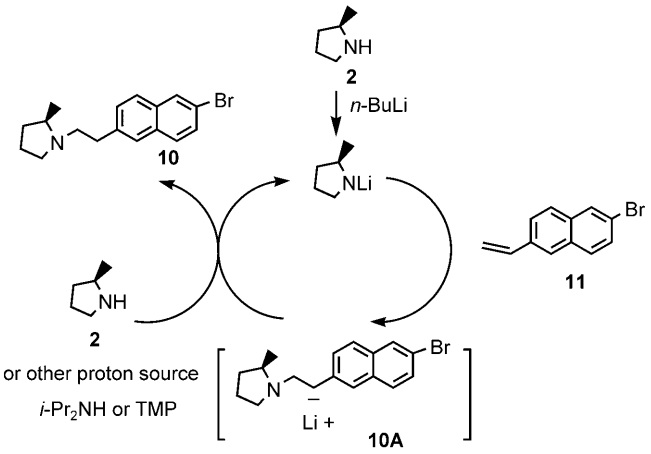
	Reaction Conditions[a]	Yield [%][b]			
		12	**11**	**11A**	**11B**
1	$PdCl_2(dppf)\cdot CH_2Cl_2/Et_3N$ (1.0 equiv.)/*n*-PrOH/97 °C/15 h	1	53	4	6
2	$Pd(OAc)_2/P(o\text{-tolyl})_3$ (1:2)/Et_3N (1.0 equiv.)/*n*-PrOH/95 °C/15 h	1	1	59	9
3	$Pd(PPh_3)_4/Et_3N$ (1.0 equiv.)/*n*-PrOH/95 °C/15 h	5	52	4	9
4	$Pd(PPh_3)_4/Et_3N$ (2.0 equiv.)/Cs_2CO_3 (2.0 equiv., 1 M)/EtOH/45 °C/15 h	0	90	2	0
5	$Pd(PPh_3)_4/Cs_2CO_3$ (2 equiv., 1 M)/EtOH/45 °C/15 h	17	77	5	0

[a] 2 mol% of Pd catalysts were used.
[b] The HPLC assay yields of the reaction mixture were determined using quantitative HPLC analysis by comparison to a known amount of analytical pure reference standards.

triboroxane,[7c] potassium vinyltrifluoroborate[7d]) were evaluated under the established protocols.[7] From these studies, potassium vinyltrifluoroborate was found to produce the best overall results in respect to the yield and selectivity and was selected for the further optimization. Under the established protocol using potassium vinyltrifluoroborate [$PdCl_2(dppf)\cdot CH_2Cl_2/Et_3N$/*n*-PrOH/reflux],[7d] the desired product was obtained in 53% yield (Table 1, entry 1). The low yield is presumably due to the product oligomerization under the reaction conditions. Other commonly used palladium systems were then investigated [$PdCl_2(CH_3CN)_2$, $PdCl_2(PPh_3)_2$, $Pd_2(dba)_3$, $Pd(dba)_2$, $PdCl_2(dppe)_2$, $Pd(PPh_3)_4$, $Pd(OAc)_2/P(Cy)_3$, $Pd(OAc)_2/P(o\text{-Tolyl})_3$] with the most interesting results being listed in Table 1.

Of the screened catalysts, $Pd(PPh_3)_4$ produced comparable results (Table 1, entry 3) to $PdCl_2(dppf)\cdot CH_2Cl_2$ and was used for further optimization. It is interesting that with $Pd(OAc)_2/P(o\text{-tolyl})_3$, the vinylation took place preferentially at the bromide (Table 1, entry 2). Solvent screening (THF, DMA, DMF, NMP, dioxane, *i*-PrOH, toluene, EtOH and *n*-PrOH) indicated that the alcoholic solvents, *n*-PrOH and EtOH were optimal. No noticeable difference was observed when other organic bases including *i*-Pr_2NH, *n*-Pr_2NH, *i*-Pr_2NEt, morpholine, and piperidine were used in the place of Et_3N. However, a substantial rate acceleration was observed when 2.0 equivalents of Cs_2CO_3 (1.0 M) aqueous solution was added to the reaction mixture of **12** (1.0 equiv.)/$Pd(PPh_3)_4$ (2 mol%)/Et_3N (2.0 equiv.)/EtOH. The reaction could then be carried out at a lower temperature (45 °C instead of 97 °C), which consequently led to considerable yield increase to 92% (Table 1, entry 4), with no hydrolysis of the triflate group and less than 2% of the bromo-coupling regioisomer formed. Addition of an aqueous Cs_2CO_3 solution to the reaction mixture allowed for milder reaction conditions, which contributed to the improved regioselectivity and reduced oligomerization, and thus subsequently resulted in the yield improvement. Interestingly, when Et_3N was omitted from the optimized reaction conditions, the reaction was slower and failed to go to completion (Table 1, entry 5). This combination of an organic base and an aqueous inorganic base to accelerate the vinylation reaction might be applicable to other Suzuki cross-coupling reactions. The coupling product **11** is a highly crystalline solid and can be easily isolated in high purity by a simple precipitation procedure with water. This material was used directly in the next step without further processing.

The introduction of the 2-(*R*)-methylpyrrolidine **2** *via* a hydroamination reaction of **11** in an anti-Markovnikov fashion was the next challenging step. The transition metal-catalyzed hydroamination of styrenes leading to β-arylethylamines has been reported in several recent studies,[9] since this class of amines is prevalent in many biologically important compounds.[10] Hydroamination of styrenes is an elegant and simple method to prepare β-arylethylamines due to its high atom-efficiency. We were particularly interested in the base-catalyzed hydroamination for its simplicity. Although the methodology has been reported,[11] it has been restricted to simple styrenes and not been widely used for the molecules containing additional functional groups. This is perhaps due to the incompatibility of the harsh reaction conditions with molecules containing functional groups. When we carried out the initial hydroamination under the "typical" reaction conditions[11c] using one equivalent of 2-(*R*)-methylpyrrolidine **2** and 10 mol% of *n*-BuLi in THF at 120 °C under pressure, a very complex reaction mixture was obtained and no desired product was detected. When *n*-BuLi was increased to a stoichiomet-



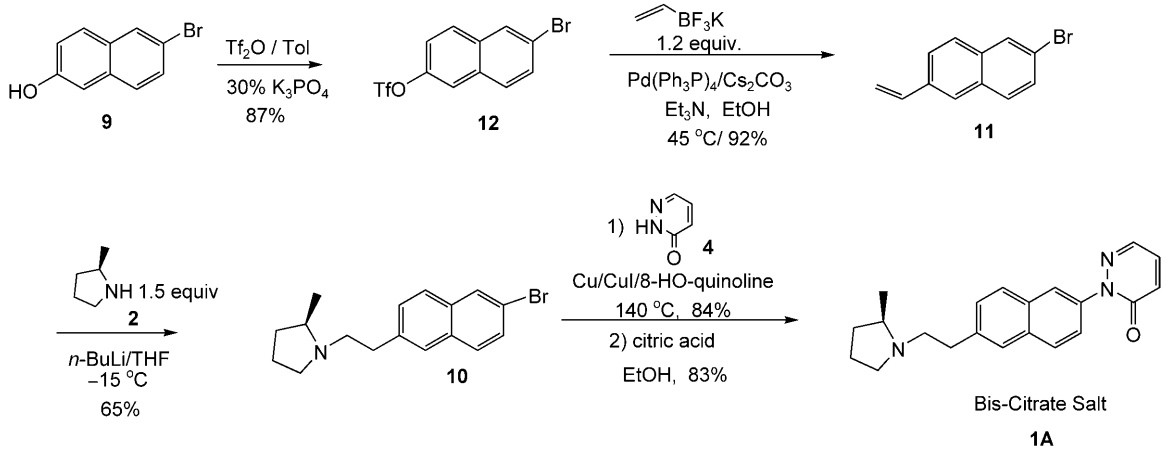
Scheme 3. Proposed hydroamination pathway.

ric amount at 22 °C, the desired product was formed in 14% yield. With further reducing the reaction temperature to 0 °C, the product was obtained in 34% yield, although it was not necessary to use a stoichiometric amount of *n*-BuLi according to the reaction mechanism (Scheme 3). Aryl bromides are known to form benzyne intermediates with strong bases,[12] and likewise the presence of the bromo group in the molecule could generate benzyne intermediates, which could subsequently react with the amine **2** leading to the by-products. This coupled with the polymerization could be the main reason for the low yield and the need to use more than a catalytic amount of *n*-BuLi.

To improve the reaction yield, an excess amount of amine **2** was added to facilitate the protonation of the initial formed carbanion **10A** and drive the reaction to the desired pathway. When more than 5 equiv. of **2** was used at 0 °C with 1.0 equiv. of *n*-BuLi, the reaction yield was increased to 55%. Further optimization of the reaction conditions revealed that when less *n*-BuLi (0.5 equiv.) was used at the temperature range of −15 °C to −20 °C with a minimum of 1.5 equiv. of amine **2** under a slow addition (~15 min) of vinylnaphthalene to the amide, the desired product can be obtained in 65% yield. Use of less than 0.5 equiv. of *n*-BuLi and less than 1.5 equiv. of amine **2** resulted in incomplete conversion. When the reaction was carried out at lower temperatures (below −25 °C) or at higher temperatures (above 0 °C), inferior results were produced. Among of the solvents (THF, MTBE, DME) evaluated, THF was the solvent of choice. Also, reverse addition of 2-(*R*)-methylpyrrolidine amide to the vinylnaphthalene resulted in low yield.

The above results suggest that facilitating protonation of the carboanion **10A** with an excess of amine **2** improves the reaction yield. It was then attempted to use different external secondary amines as the proton source for this improvement provided these amines would not to undergo addition to the olefin. When diisopropylamine or tetramethylpiperidine (TMP) were used under the optimized conditions using 1.0 equiv. of amine **2**, the desired product was obtained in ~65% yield. No by-products resulting from the addition of amides (*i*-Pr_2NLi and TMPLi) to the double bond were detected. This result is comparable with the reaction using excess of 2-(*R*)-methylpyrrolidine **2** and this protocol should be more useful when it is undesirable to use an excess of a valuable amine. These results demonstrate the synthetic utility of base-catalyzed hydroamination reaction under mild conditions using functionalized vinyl aromatics, thus expanding the scope of this methodology.

A simple and efficient purification procedure for **10** was developed. The HCl salt of the desired product **10** was found to have very low solubility in aqueous solution and even lower in a brine solution, and it was easily crystallized from the aqueous solution leaving all the HCl salts of impurities in the solution. The final incorporation of the pyridazinone **4** was accomplished with an optimized copper-catalyzed coupling reaction.[3c] After screening a variety of ligands and solvents, it was found that use of 8-hydroxyquinoline



Scheme 4. The new four-step process.

as ligand in DMF gave the best result producing the desired product in 84% yield (Scheme 4). The crude coupling product was further purified by an extractive work-up procedure, salt formation and crystallization of its bis-citrate salt **1A** to high purity (>99%).

Conclusions

In summary, we have developed a highly efficient and practical process for the synthesis of **1A** with an overall yield of 36%. The process is highlighted by the development of a regioselective Suzuki coupling protocol for the selective vinylation of **12** using potassium vinyltrifluoroborate in high yield 92% and excellent regioselectivity (90:2). The successful hydroamination of 6-bromovinylnaphthalene **11** was achieved under mild reaction conditions. In addition, an efficient cross-coupling reaction between the bromide **10** and pyridazinone **4** was accomplished with the optimized copper-catalyzed reaction using 8-hydroxyquinoline as ligand. This column chromatography-free process involving several simple work-up and purification procedures is amendable to the large-scale preparation of **1A**

Experimental Section

The NMR spectra were recorded at a Varian 400 MHz instrument at 400 MHz for ^{1}H and 100 MHz for ^{13}C. The electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) mass spectra were obtained using a Hewlett Packard 1100, LC-MS, HPLC-mass spectrometer and fast atom bombardment (FAB) mass spectra were obtained using a JEOL SX102A spectrometer. All the reactions were performed under a positive pressure of nitrogen. Commercial grade anhydrous solvents and reagents were used without further purification. All reactions were monitored by HPLC (Zorbax SB-C8, 4.6 mm×25 cm column) with purities being determined by peak area % at the UV detector wavelengths of 215 and 230 nm and NMR analysis. The HPLC assay yields of the reaction mixture were determined using quantitative HPLC analysis by comparison to a know amount of analytical pure reference standards and potency refers to a wt% assay by HPLC *versus* a purified standard. The enantiomeric purity of the product was determined by the chiral HPLC analysis using a Chiral Pak-AD column, 10 μm, 250 mm×4.6 mm (Chiralcel Technologies) at the UV detector wavelength of 223 nm. The elemental analysis was performed by Quantitative Technologies Inc.

Trifluoromethanesulfonic Acid 6-Bromonaphthalen-2-yl Ester (12)[4]

To a mixture of 6-bromonaphthalen-2-ol **9** (100 g, 0.448 mol) in toluene (1200 mL) was added a solution of potassium phosphate (300 g) in H_2O (700 mL). The mixture was cooled to 0 °C, to the mixture was added trifluoromethanesulfonic anhydride (171.7 g, 0.609 mol) dropwise keeping the temperature below 5 °C within 0.5 h. The resulting mixture was stirred at 5 °C for 1 h. The aqueous layer was separated and the organic layer was washed with 5% $NaHCO_3$ (1200 mL), 20% brine (800 mL×2) and dried over Na_2SO_4. The organic solution was concentrated to ~200 mL volume under reduced pressure, and azeotroped with heptane (500 mL×2) to ~200 mL volume. The slurry was diluted with heptane (300 mL) and cooled to −10 °C, and mixed for 3 h. The product was collected by filtration, and dried under vacuum to afford 145.0 g of the title compound as an off-white solid (the product was analyzed against pure reference standard and determined to have a 96% w/w potency, resulting in a 87% potency adjusted isolated yield). The crude product is used in the next step without further purification.

A small pure reference sample was obtained by column chromatography purification to obtain the pure product as a solid: mp 54–55 °C. ^{1}H NMR ($CDCl_3$): δ=8.04 (s, 1H), 7.82 (d, J=9.1 Hz, 1H), 7.62–7.66 (dd, J=8.8, 1.9 Hz, 1H), 7.39 (dd, J=9.1, 2.5 Hz, 1H); DCI-MS: m/z=356 $[M+NH_4-H_2O]^+$.

2-Bromo-6-vinylnaphthalene (11)

A mixture of trifluoromethanesulfonic acid 6-bromonaphthalen-2-yl ester (**12**) (96.0 g, 96 w/w% potency, 260 mmol), potassium vinyltrifluoroborate (42.6 g, 318 mmol) in EtOH (2.6 L) and a 1.0 M aqueous solution of cesium carbonate (530 mL) was purged with nitrogen, to the mixture was then added tetrakis(triphenylphosphine)palladium (3.1 g, 3 mmol) followed by triethylamine (74 mL, 530 mmol). The mixture was heated to 45 °C for 15 h under nitrogen (HPLC indicated complete consumption of the starting material) and cooled to room temperature. To the mixture was added H_2O (1.5 L), the resulting suspension was stirred at room temperature for 2 h and filtered. The wet-cake was washed with H_2O (500 mL) and dried in the vacuum oven at 45 °C for 48 hour to give the product as a beige solid; yield: 61.3 g (the product was analyzed against pure reference standard and determined to have a 91% w/w potency, resulting in a 90% potency adjusted isolated yield).

The crude product is used in the next step without further purification. A small pure reference sample was obtained by column chromatography purification to obtain the pure product as a solid: ^{1}H NMR ($CDCl_3$): δ=7.86 (d, J=2.0 Hz, 1H), 7.54–7.61 (m, 4H), 7.42–7.44 (dd, J=8.7, 2.0 Hz, 1H), 6.73–6.80 (dd, J=17.5, 11.0 Hz, 1H), 5.79 (d, J=17.5 Hz, 1H), 5.28 (d, J=11.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ= 136.18, 135.12, 133.77, 131.62, 129.42, 129.32, 129.29, 126.93, 125.84, 124.00, 119.55, 114.54; GC-MS (DEI): MW=232: anal. calcd. for $C_{12}H_9Br$: C 61.83, H 3.89, Br 34.28; found: C 61.76, H 3.69, Br 34.25.

1-[2-(6-Bromonaphthalen-2-yl)-ethyl]-2-methylpyrrolidine (10)

To a cooled solution of 2-(*R*)-methylpyrrolidine (9.53 g, 112 mmol) in THF (200 mL) at −15 °C was added *n*-BuLi (1.6 M in hexane, 23 mL, 37 mmol) dropwise keeping the temperature below −10 °C. The resulting mixture was stirred at −15 °C for 10 min. To the cooled solution was added a solution of 2-bromo-6-vinylnaphthalene (**11**) (17.5 g, 91 w/w% potency, 68.3 mmol) in THF (200 mL) dropwise keeping the

temperature below −15 °C (this took about 30 min). After addition, the resulting mixture was stirred at −15 °C for 10 min and quenched with H_2O (5 mL) and allowed to warm to room temperature. The organic solution was filtered through a pad of Celite to remove some solid. The filtrate was concentrated to about 30 mL volume, EtOAc (200 mL) was added followed by 5% $NaHCO_3$ (150 mL). The organic layer was separated, washed with 5% $NaHCO_3$ (2×150 mL), and extracted with 2 N HCl (3×150 mL). The HCl salt of the desired product slowly precipitated out from the aqueous solution upon addition of brine (150 mL). The resulting suspension was cooled to 0 °C, stirred at 0 °C for 1 hour and filtered. The product was dried in a vacuum oven at 50 °C for 24 hour to obtain the product as an HCl salt; yield: 18.1 g (the product was analyzed against pure reference standard and determined to have a 87% w/w potency, resulting in a 65% potency adjusted isolated yield).

The crude product is used in the next step without further purification. A small pure reference sample was obtained by recrytallization to obtain the pure product as a solid. The NMR spectra were taken using the free base obtained from the purified HCl salt. ^{1}H NMR ($CDCl_3$): δ = 7.95 (d, J = 1.8 Hz, 1H), 7.63–7.68 (m, 3H), 7.49–7.51 (dd, J = 8.6, 1.9 Hz, 1H), 7.36–7.38 (dd, J = 8.3, 1.8 Hz, 1H), 3.36–3.41 (m, 1H), 3.16–3.23 (m, 1H), 3.01–3.07 (m, 2H), 2.47–2.58 (m, 2H), 2.40 (m, 1H), 1.98–2.05 (m, 1H), 1.87–1.93 (m, 1H), 1.76–1.82 (m, 1H), 1.52–1.61 (m, 1H), 1.21 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 137.69, 132.86, 131.66, 129.34, 129.04, 128.82, 128.10, 126.84, 126.54, 118.93, 60.78, 55.37, 53.62, 34.80, 32.58, 21.88, 18.24; APCI-MS: m/z = 319 $(M+H)^+$; anal. calcd. for $C_{17}H_{21}BrClN$: C 57.56, H 5.97, N, 3.95; found: C 57.54, H 5.98, N 3.91.

2-{6-[2-(Methyl-1-pyrrolidin-1-yl)-ethyl]-2-naphthalen-2-yl}-2*H*-pyridazin-3-one (1A)[3c]

To a reaction vessel were charged 1-[2-(6-bromonaphthalen-2-yl)-ethyl]-2(*R*)-methylpyrrolidine hydrochloride (**10**) (12.5 g, 87 w/w% potency, 36.8 mmol), CuCl (174 mg, 1.75 mmol, 5 mol%), 8-hydroxyquinoline (514 mg, 3.54 mmol, 10 mol%), K_2CO_3 powder (12.19 g, 88.0 mmol), *2H*-pyridazin-3-one (**4**) (5.06 g, 52.7 mmol), and DMF (57 mL). The reaction vessel was evacuated, and backfilled with N_2 (repeated 3 times). The reaction vessel was then pressurized with N_2 to 5 psi, and the mixture was heated to 140 °C, and maintained for 18 h (HPLC indicated complete consumption of the starting material) (***Caution:*** the internal pressure will rise, and must be vented as needed). The reaction mixture was cooled to 20 °C, and isopropyl acetate (200 mL), 30% NH_4OH (100 mL), 4% Na_2EDTA-23% NaCl solution (100 mL) were added. The mixture was agitated for 0.5 h, filtered through a pad of filter aid, rinsed with isopropyl acetate (20 mL). The lower aqueous solution was extracted with isopropyl acetate (50 mL). The combined organic layers were washed with 4% Na_2EDTA-23% NaCl solution (250 mL×3) and analyzed against reference standard to contain 9.80 g of the free base of **1** (84% assayed yield). It was then concentrated to ~200 mL volume and extracted with a mixture of H_2O:CH_3SO_3H:NMP (70:10:20 by volume) (150 mL followed by 50 mL). Isopropyl acetate (200 mL) was added to the combined aqueous extract, and the mixture was cooled to <10 °C. 50% NaOH aqueous solution was charged into the mixture until the pH of the mixture is ~13. The upper organic phase was separated, and the lower aqueous solution was extracted once with isopropyl acetate (50 mL). The combined organic solution was washed with 5% $NaHCO_3$ (250 mL x2), and 25% brine (200 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated to dryness, and ethyl acetate (170 mL) was added. The resulting solution was heated to 40 °C, and salicylic acid (4.80 g, 34.7 mmol) was added. The solution was stirred at 40 °C for 2 h, and cooled to 20 °C. The slurry was mixed for 2 h, filtered, washed with ethyl acetate (50 mL), dried under vacuum at 55 °C overnight to afford 12.7 g of the salicylate. This salt was then freed up in a mixture ethyl acetate (150 mL) and 10% Na_2CO_3 aqueous solution (100 mL). The organic solution was washed with 20% brine (150 mL×2), dried over Na_2SO_4, filtered. The filtrate was concentrated to dryness, and azeotroped with absolute ethanol (100 mL) to dryness. The residue was dissolved in absolute ethanol (200 mL), and the solution was heated to 40 °C. Anhydrous citric acid (18.1 g, 94.3 mmol) was added all at once, and the solution seeded with small amount of bis-citrate salt. The solution was mixed at 40 °C for 5 h, and the slurry was cooled to 25 °C, and mixed for 2 h. The product was isolated by filtration, washed with absolute ethanol (100 mL), dried under vacuum at 50 °C overnight to give the bis-citrate salt as an off-white solid; yield: 18.4 g (70% overall); mp 150–152 °C. ^{1}HNMR (DMSO-d_6): δ = 8.12 (d, J = 1.7 Hz, 1H), 8.10 (dd, J = 3.8, 1.5 Hz), 7.98 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.9 Hz, 1H), 7.90 (s, 1H), 7.68 (dd, J = 8.6, 2.1 Hz, 1H), 7.55 (dd, J = 8.4, 1.4 Hz, 1H), 7.52 (dd, J = 9.6, 3.8 Hz, 1H), 7.11 (dd, J = 9.5, 1.6 Hz, 1H), 3.60 (m, 2H), 3.47 (m, 1H), 3.21 (m, 4H), 2.67 (d, J = 15.3 Hz, 4H), 2.58 (d, J = 15.3 Hz, 4H), 2.18 (m, 1H), 1.95 (m, 2H), 1.62 (m, 1H), 1.35 (d, J = 6.5 Hz, 3H); ^{13}C NMR (DMSO-d_6): δ = 175.89, 171.36, 159.50, 138.90, 137.68, 135.80, 132.51, 132.12, 131.53, 130.71, 128.51, 128.02, 127.75, 126.91, 124.17, 123.85, 71.91, 63.16, 52.58, 43.59, 31.31, 30.90, 21.08, 15.58; APCI-MS (ESI): m/z = 334 (M+1); anal. calcd. for $C_{33}H_{39}N_3O_{15}$: C 55.23, H 5.48, N 5.86; found: C 55.26, H 5.31, N 5.87; Pd = 8 ppm, Cu = 3 ppm.

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