Process Development and Scale-Up of the SOS1 Inhibitor MRTX0902

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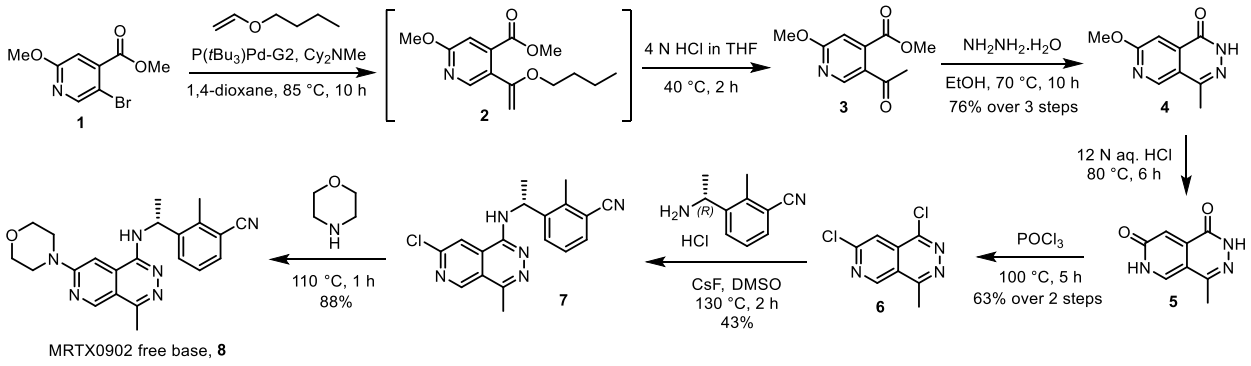
MRTX0902, a novel SOS1 inhibitor, is currently being evaluated in phase I trials for the treatment of cancer. The complexity of the molecule containing a pyrido[3,4-*d*]pyridazine core and a chiral amine moiety makes it a challenging target to prepare on multi-kilogram scale to support clinical development studies. An efficient and scalable synthesis to the key intermediate, 4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1(2*H*)-one and a much improved end-game to MRTX0902 was developed.

MRTX0902 is a brain-penetrant, orally bioavailable, selective, and potent inhibitor of the SOS1:KRAS complex. It can be used in combination with MRTX849[1,2] – adagrasib

(KRAZATI^{TM}) – leading to a significant increase in antitumor activity in comparison with their respective activity as a single agent.[3] The route to MRTX0902 developed by our drug discovery colleagues (Scheme 1) was used to deliver several kilograms of crucial intermediates while also providing sufficient amount of active pharmaceutical ingredient (API) to support early stage studies. However, while this route was effective for initial development, several improvements were necessary in order to prepare multi-kilogram amount of API for GLP toxicology and FIH studies.

Scheme 1. Drug Discovery Route to MRTX0902



The starting material used in the discovery team route, methyl 5-bromo-2-methoxyisonicotinate **1**, was not commercially available on multi-kilogram scale and had to be custom-synthesized in several steps with a lead time greater than 8 weeks. While acceptable for the first kilogram delivery, this proved challenging for future scale-up campaigns and therefore needed to be addressed. In addition, the key intermediate, 1,7-dichloro-4-methylpyrido[3,4-*d*]pyridazine **6**, was susceptible to hydrolysis upon storage under normal humidity level; therefore, it was flagged as a potential issue in the long run. Additionally, the first S_NAr towards intermediate **7** was reported to give only a moderate yield[3] of 43% due to inherent selectivity issues, and was

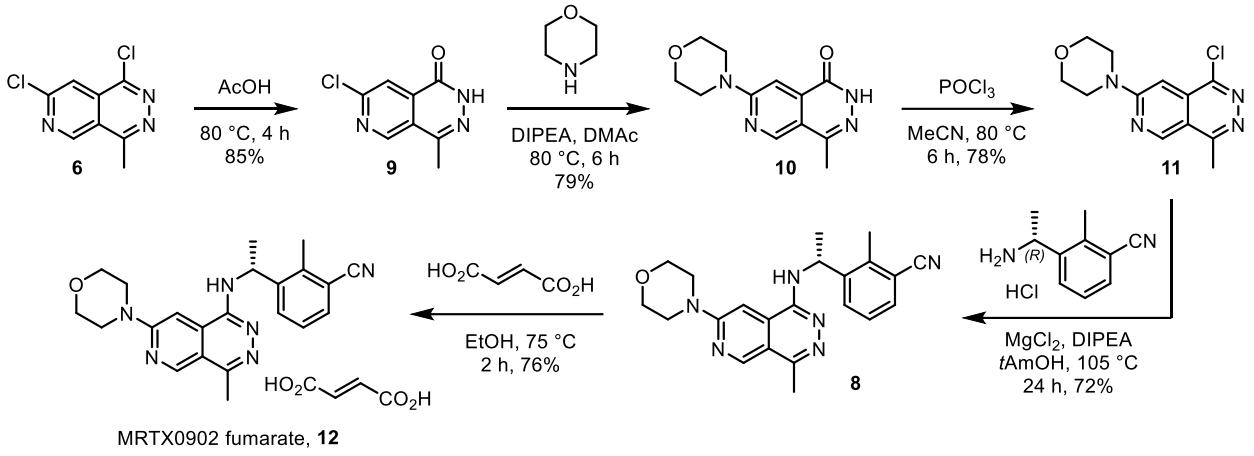
challenging to reproduce with the desired purity without resorting to preparative HPLC. Lastly, the order of the two final S_NAr reactions leading to MRTX0902 was suboptimal as the more expensive chiral benzylic amine was introduced before the inexpensive morpholine. Reversing the order of steps would directly reduce the cost of the overall synthesis.

Polymorph Control. Due to polymorphic promiscuity of MRTX0902 free base and its tendency to readily crystallize as a solvate, a salt screening was conducted. It resulted in the identification of anhydrous fumaric acid salt reproducibly isolated as the same crystalline form. However, the protocol for its synthesis proved unsuitable for scale-up and required further development work which will be discussed below.

The initial process development focused on addressing the most critical issues to enable the production of 1 kg of MRTX0902 fumarate salt to satisfy the initial program demand. A more in-depth development work and *de novo* synthesis will be presented later in this manuscript. The drug discovery approach was used to manufacture 6 kilograms of 1,7-dichloro-4-methylpyrido[3,4-*d*]pyridazine **6** while the final steps were modified and improved using the knowledge acquired during the initial steps of process development, see Scheme 2.

First Kilo Delivery. Taking advantage of the formerly noted hydrolytic instability of the chlorophthalazine **6,** the north-eastern chloride could be selectively replaced by hydroxyl with acetic acid at 80 °C to generate phthalazinone **9** in 85% isolated yield (see Scheme 2).

Scheme 2. Improved Synthetic Route to MRTX0902 Fumarate Used for the First Kilo Delivery



This key change allowed us to directly use morpholine by harnessing the reactivity of the chloropyridine moiety. Using phthalazinone **9** with morpholine and DIPEA in DMAc led to the clean formation of 4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1(2*H*)-one **10** in 79% isolated yield. The compound was isolated *via* trituration of the crude solid – an acceptable replacement for the chromatographic purification previously needed. In order to introduce the chiral benzylic amine, compound **10** was activated to the corresponding chlorophthalazine **11** by treatment with phosphorus oxychloride in acetonitrile in 78% isolated yield. Unfortunately, obtaining compound of high purity required chromatographic purification. Compound **11** was taken to the final S_NAr reaction with the expensive (*R*)-3-(1-aminoethyl)-2-methylbenzonitrile hydrochloride[3] in the presence of DIPEA and $MgCl_2$ in *t*AmOH to afford MRTX0902 free base **8** in 72% isolated yield via trituration. The introduction of the costly chiral benzylic amine at the later stage improved cost-efficiency as compared to the initial approach.[3] Last, the preparation of MRTX0902 fumarate **12** from the free base **8** was explored. Due to the poor solubility of MRTX0902 free base, the crystallization process required significant amount of solvent (EtOAc)

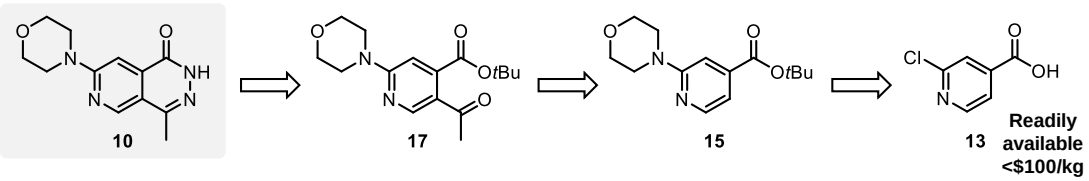
even at elevated temperature. In addition, the process required several days for the salt formation to complete. Solvent and temperature screening afforded two alternative hits: THF at room temperature or EtOH at 75 °C. Both solvents afforded MRTX0902 fumarate **12** in a couple of hours while keeping concentrations at acceptably high level. However, it was found that residual solvent was challenging to completely remove from the salt. EtOH was ultimately selected for the salt formation.[4] MRTX0902 free base **8** was treated in EtOH at 75 °C with solid fumaric acid to afford MRTX0902 fumarate **12** in 76% isolated yield via filtration. Non-negligible losses were observed in the mother liquor, an issue which was addressed in the subsequent iterations of process development work.

Route Design. Building on this first successful delivery for GLP toxicology studies, our next challenge was to address the commercial unavailability of the starting material used (compound **1**). Our second major challenge was to eliminate the need of the expensive Buchwald Pd precatalyst (P(*t*Bu)$_3$Pd-G2) used in the first step of the discovery synthesis.[5] The use of palladium very early in the synthesis has a direct impact on the overall cost effectiveness of the synthetic approach so the design of a new route and the choice of a readily available starting material were fundamental considerations in the development work for MRTX0902 fumarate.

Our goal was to intercept some of the endgame chemistry developed for the GLP delivery and showcased in this manuscript. 4-Methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1(2*H*)-one **10** was a suitable candidate devoid of the storage issues of chlorophthalazine **6**. With compound **10** as target, it was envisioned that installation of the morpholine at an earlier stage would negate the need for a methoxy protecting group. Relying on the strong directing group properties of the morpholine substituent and the substitution pattern of our pyridine core electrophilic bromination was expected to occur with great selectivity at the desired position. Halogen-metal exchange

followed by trapping of the organometallic species with an acetyl source would prime the resulting pyridine **17** for a facile condensation with hydrazine to afford phthalazinone **10**. The retrosynthetic analysis is shown on Scheme 3.

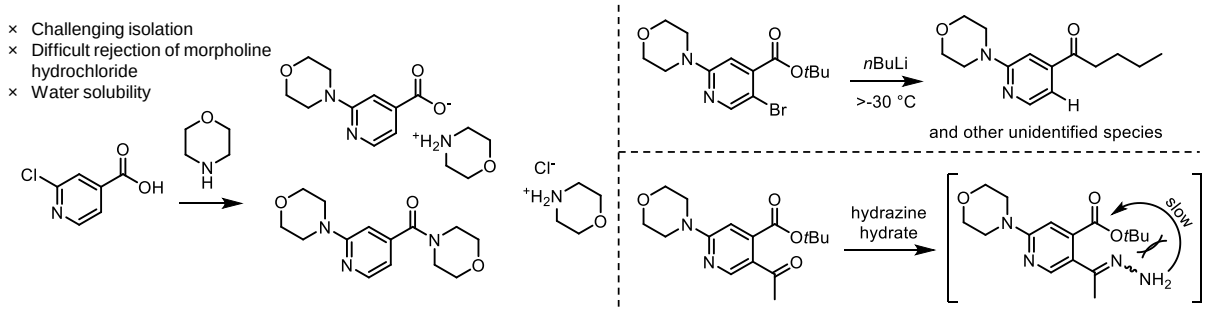
Scheme 3. Retrosynthetic Analysis to Key Intermediate 10



Preparation of Morpholino-Ester 15. The optimized preparation of compound **10** is described below. The readily available 2-chloroisonicotinic acid **13** was first transformed to the corresponding *tert*-butyl ester using Boc_2O and triethylamine in the presence of catalytic amount of DMAP in NMP to generate *tert*-butyl 2-chloroisonicotinate **14** in 91% corrected isolated yield. The formation of the *t*Bu ester was found to be beneficial for several reasons: a) to ease the isolation of each intermediate, b) minimize losses due to the zwitterionic properties of isonicotinic acid related species, c) to avoid incompatibilities with the organometallic species downstream (requiring extra organometallic reagent among other) and d) to prevent the formation of non–negligible amounts of morpholine amide during the S_NAr reaction of the free carboxylic acid moiety in the presence of morpholine (see Scheme 4). The S_NAr between compound **4** and morpholine was investigated in various solvents and bases, organic and inorganic. Interestingly, it was found that the reaction in morpholine as solvent, where it acts both as nucleophile and base, gave the best result. Compound **14** could be treated with morpholine to generate the corresponding *tert*-butyl 2-morpholinoisonicotinate **15** in 97% corrected isolated yield.

Bromination of Pyridine 15. The electrophilic bromination was studied on compound **15**. Encouragingly, the first attempt using NBS in DCM at 20 °C gave the desired regioisomer with a clean profile under 1 h reaction time with only traces amount of bis-brominated species. Employing strictly stoichiomeric amounts of NBS combined with optimized isolation afforded *tert*-butyl 5-bromo-2-morpholinoisonicotinate **16** in 93% corrected isolated yield.

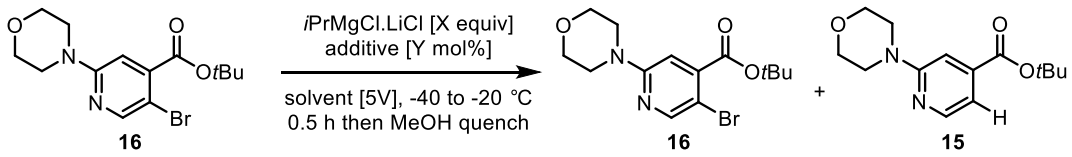
Scheme 4. Challenges Encountered During Process Development



Acylation of Bromo-Pyridine 16. The metal-halogen exchange turned out to be more challenging than anticipated. *n*BuLi could only be used if the reaction mixture was maintained at cryogenic conditions. Formation of the corresponding butyl ketone by displacement of the *tert*-butyl moiety along with other unidentified byproducts became an issue at higher temperatures (see Scheme 4). As a consequence, milder organometallic species such as *i*PrMgCl.LiCl ("Turbo Grignard", discovered and popularized by the Knochel group)[6] was pursued for this transformation. In the preliminary experiment treating **16** with *i*PrMgCl.LiCl at -30 °C in toluene or THF (Table 1 – Entry 1 and 2) for 1 hour followed by MeOH quench afforded significant amount (69% LCAP) of debrominated material **15** in THF (Entry 2) consistent with intermediacy of desired organomagnesium species. Building on this positive result the reaction was further optimized in hopes of avoiding cryogenic conditions. Unfortunately, extended reaction time did not furnish higher conversion and eventually led to the build-up of unknown impurities upon

temperature increase. The use of additives was then investigated in hopes to enhance the metalation. Pleasingly, it was discovered that catalytic (5 mol%) amount of copper(I) iodide was highly beneficial to the efficiency of the metal/halogen exchange either in toluene or THF (Entry 3 to 4). Better coordination and solubility in THF may explain the stronger effect observed (Entry 3 versus 4) therefore efforts were continued using THF. Additionally, the Lewis acid $ZnCl_2$ was used (Entry 5) in order to study a potential activation effect *via* coordination with the nitrogen atom of the pyridine. No drastic changes were observed and the reaction profile mimicked additive-free conditions in THF (Entry 2). Other copper (I) species (Entry 6 to 8) performed equally well. However, due to its inherent air stability, low cost and toxicity, optimization efforts were focused on CuI. Lowering the loading of the CuI to 0.5 mol% (Entry 11) could be achieved, but for reproducibility reasons, the CuI loading was set to 1.0 mol%. Lastly, reducing the equivalent of the Grignard reagent from 2.0 to 1.1 equivalent (Entry 12 to 14) did not lead to full conversion, thus 2.0 equivalents were used in subsequent runs. Efforts to further understand the dramatic effect of copper(I) species is still continuing in our laboratory.

Table 1. Optimization of the Metal/Halogen Exchange of **16**[a]



entry	*i*PrMgCl.LiCl (equiv)	additive [mol%]	solvent	conversion[b] 16/15 (%)
1	3.0	None	PhMe	complex[c]
2	3.0	None	THF	17/69

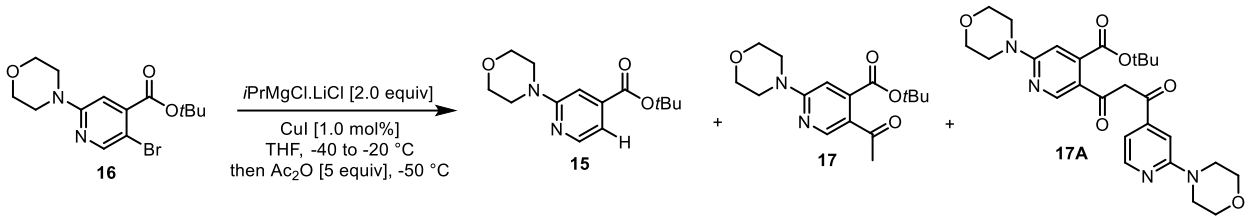
3	2.0	CuI [5.0]	PhMe	0/71
4	2.0	CuI [5.0]	THF	0/95
5	2.0	$ZnCl_2$ [5.0]	THF	29/61
6	2.0	CuBr [5.0]	THF	0/91
7	2.0	CuCN [5.0]	THF	1/95
8	2.0	CuCl.2LiCl [5.0]	THF	0/89
9	2.0	CuI [2.5]	THF	0/95
10	2.0	CuI [1.0]	THF	0/97
11	2.0	CuI [0.5]	THF	1/92
12	1.7	CuI [1.0]	THF	7/91
13	1.3	CuI [1.0]	THF	24/74
14	1.1	CuI [1.0]	THF	34/65

[a] Reactions were run for 0.5 h with *tert*-butyl 5-bromo-2-morpholinoisonicotinate **16** (3 mmol scale) and quenched by the addition of MeOH to generate **15**. [b]Determined by HPLC. [c]Magnesiation is very slow in toluene, leading to multiple byproducts.

With a highly efficient method to generate the heteroaryl magnesium species in hand, its reaction with various electrophilic acetyl source was subsequently investigated. Due to its higher stability upon storage and sufficiently strong electrophilic nature, acetic anhydride was the preferred source of acetyl moiety for our system. Next, with the consideration of scale-up in mind, utilization of a single reactor for the acylation step was determined to be preferred. Initial development of this process relied on an inverse-addition method at -50 °C to achieve the desired ketone. Fortunately, small-scale batches showed that the addition of acetic anhydride to the Grignard reagent provided comparable results (Table 2 – Entry 1 and 2). This result was confirmed on a 200-gram demo-batch scale and subsequent use-tests (Entry 3). While a new impurity resulting from Grignard addition to *tert*-butyl ester **16** to form adduct **17A** was identified, it was found to be acceptable (as long as its formation was minor) as it was confirmed to be fully rejected in the subsequent cyclization step. Unfortunately, the production batch did

not perform as well as expected and dione **17A** was formed as the major product (Entry 4). Mesomixing was established as the source of this impurity, which was accompanied by a moderate temperature spike (-50 to -25 °C) that had not been observed during development. With the drive to minimize reactor usage and facilitate the minimal processing time, it was found that increased agitation speeds and slower addition rates would preclude formation of this byproduct, but on scale-up, adduct **17A** was still observed in non-negligible amounts (Entry 5). To maintain the production schedule and due to tight timeline, this addition method was abandoned, and a two-reactor system was deployed thus avoiding formation of undesired **17A** in its entirety. This method was reproduced multiple times on various scales with no decrease in performance. (Entries 6 to 8). Ultimately, compound **16** was treated with *i*PrMgCl.LiCl in THF in the presence of catalytic amount of CuI. The *in-situ* generated organomagnesium species was then slowly added to acetic anhydride. After work-up, the desired *tert*-butyl 5-acetyl-2-morpholinoisonicotinate **17** was isolated in 77% corrected yield (average of several runs).

Table 2. Scale-up Optimization and Acylation to **7**[a]



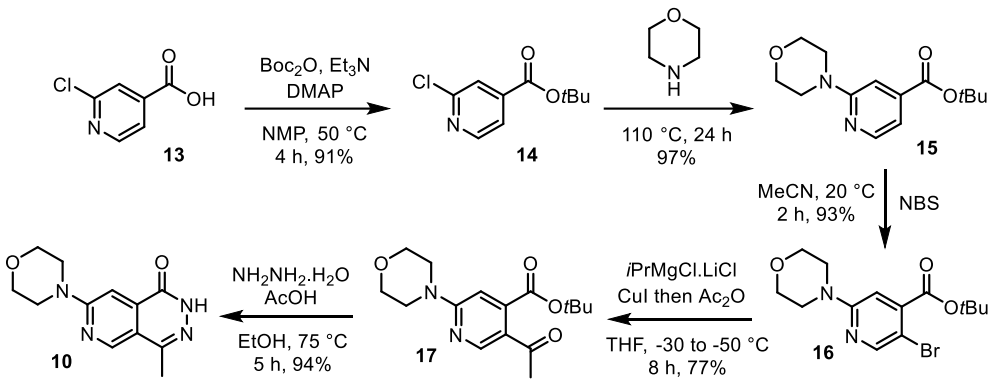
entry	scale (kg)	addition method	conversion[b] 5/7/7A (%)
1	0.01	inverse[c]	4/86/0
2	0.01	normal[d]	4/91/0
3	0.2	normal[d]	4/86/2
4	2.0	normal[d]	8/29/49
5	2.0	normal-slow[e]	9/66/17
6	1.0	inverse[c]	6/88/<1

7	2.5	inverse[c]	5/87/<1
8	3.1	inverse[c]	4/90/0

[a] Reactions were run at the indicated scale of *tert*-butyl 5-bromo-2-morpholinoisonicotinate **16** in THF (5V). [b]Determined by HPLC. [c]Inverse = Metalated species added to Ac_2O at -50 °C. [d]Normal = Ac_2O added to the metalated species at -50 °C. [e]Normal-slow = very slow addition (1-2 $L.h^{-1}$) of Ac_2O to the metalated species at -50 °C.

Phthalazinone 10 Core Formation. The last step of our envisioned synthesis to compound **10** was the condensation of hydrazine hydrate with compound **17**.[7] Using standard conditions with hydrazine hydrate in EtOH at high temperature, the corresponding hydrazone was cleanly generated. However, the final cyclization to the phthalazinone was found to be sluggish and proceeded to decent conversion only after extended reaction time of over 24 to 48 h (see Scheme 4). Several approaches were proposed to circumvent this issue. The use of higher boiling point solvent such as the longer chain alcohol *n*-butanol or carbonyl activator such as a Brønsted acid were tested. The later was found to be the most effective and using 1 equivalent of acetic acid, the cyclization rate could be drastically increased leading to complete reaction in 5 hours at 75 °C. Deprotection of the *t*Bu ester to the corresponding carboxylic acid or enhanced hydrazone isomerization cannot be ruled out with certainty under these reactions conditions. However, treatment of compound **17** in absence of hydrazine hydrate with acetic acid in EtOH at 75 °C showed complete stability of the *t*Bu ester moiety. The final optimized conditions were applied to compound **7** and hydrazine hydrate in the presence of acetic acid in EtOH to generate 4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1(2*H*)-one **10** in 94% corrected isolated yield. It is worth noting that due to the very low solubility of the azaphthalazinone core, this step is extremely efficient at removing impurities carried over the previous steps granting perfect entry into the endgame.

Scheme 5. Optimized and Cost-Effective Route to Intermediate I

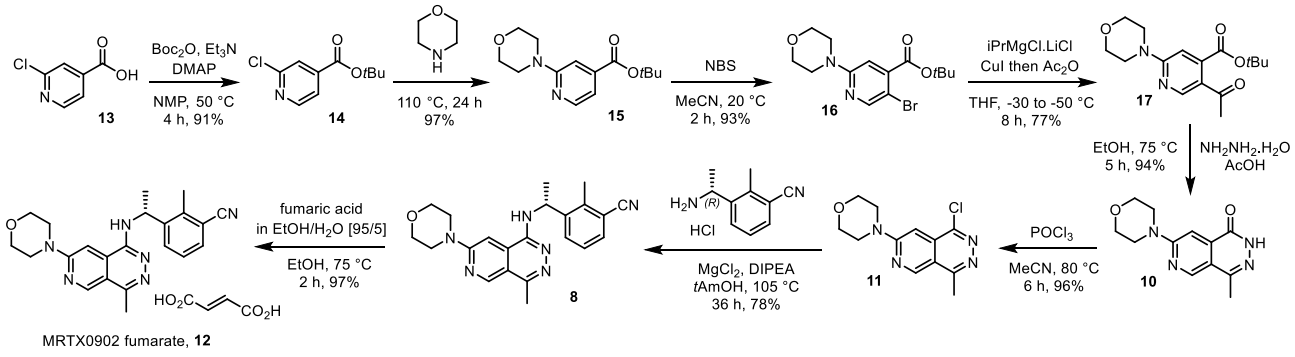


The new synthesis of 4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1(2*H*)-one **10** described in Scheme 5 has a 60% overall yield over 5 steps starting from the inexpensive and readily available 2-chloroisonicotinic acid, relies on inexpensive reagents while the use of extreme temperature (cryogenic or >120 °C) is circumvented. This sequence was performed multiple times in several kilograms scale to reliably produce the key intermediate **10** with a high purity profile, ideal to engage in the endgame of the synthesis of MRTX0902.

Endgame Optimization. The last 3 steps to MRTX0902 fumarate salt were already well established, see Scheme 2, but some attention was brought to polish them, especially increasing the yield at every step, crucial for cost-effectiveness and removing tedious purification methods. The activation of compound **10** to the corresponding heteroaryl chloride **11** was performed in the same manner as described above. However, to avoid the use of column chromatography on scale, it was found that quenching of the phosphorus oxychloride and related phosphate analogues using an inorganic base such as sodium hydroxide or carbonate allowed for an efficient removal of these species. The crude solid obtained after solvent removal could then be triturated in *i*PrOH increasing its purity to above 98%. Using this new isolation protocol, the compound **11** was isolated in 96% corrected isolated yield, a considerable increase from the 78% yield obtained via

column chromatography on silica gel. The final S_NAr reaction with (*R*)-3-(1-aminoethyl)-2-methylbenzonitrile hydrochloride was performed using the same protocol described above. However, a new crystallization method was identified. The acetonitrile/water crystallization system allowed us to reach a higher corrected isolated yield of 78% of MRTX0902 free base dihydrate. Last, some improvements were made to the fumarate salt formation **12**. The addition of fumaric acid as a solid, as discussed above, was deemed not ideal. Therefore, the fumaric acid was used as a 95/5 EtOH/water solution requiring generous amount of solvent due to its low solubility. In addition, seed material of MRTX0902 fumarate salt **12** was also used to initiate the crystallization upon controlled addition of the fumaric acid solution. Ultimately, MRTX0902 fumarate salt **12** was isolated in 97% corrected yield with minimal loss in the mother liquors. The overall sequence used for the production of multi kilograms quantity of MRTX0902 fumarate is shown in Scheme 6 below.

Scheme 6. Manufacturing Route to MRTX0902 Fumarate



In conclusion, a new, high yielding and cost-effective route to MRTX0902 fumarate salt was developed. Starting from the inexpensive and readily available 2-chloroisonicotinic acid, multi-kilograms of MRTX0902 fumarate were prepared with the same physical and chemical

properties in comparison with the drug discovery route. The 8 steps sequence has an overall yield of 44% as compared with 18% yield previously obtained relying on non-commercial starting material at scale. The fumarate salt formation process allowed a 3-fold time cycle reduction, cut the solvent usage by a factor 10, increased the scalability by more than 50x while maintaining a high level of reproducibility for API quality and physical properties. The purity of MRTX0902 fumarate salt using this new route is greater than 99.7% as a result of very efficient purging steps and careful process controls. This will ensure the clinical team with reliable API quality and quantity for incoming studies.

EXPERIMENTAL SECTION

***tert*-Butyl 2-chloroisonicotinate (14).** To a 150 L reactor was added 2-chloroisonicotinic acid (**13**) [7.0 kg, 44.4 mol, 1.0 equiv.] followed by NMP [24.5 L]. Then DMAP [1.1 kg, 8.9 mol, 0.2 equiv.] was added to the stirred solution and the temperature was cooled to 5 °C for 30 minutes. Boc anhydride [19.4 kg, 88.8 mol, 2.0 equiv.] was added followed by the dropwise addition of triethylamine [4.5 kg, 44.4 mol, 1 equiv.]. The temperature was then controlled at NMT 30 °C [actual 20 - 23 °C]. Then the mixture was allowed to react at 45 °C until the starting material was ≤1.0 area% by HPLC analysis (typically 3 - 5 h). The reaction was cooled to 5 °C. Brine 10 w/v% [14 L] was added slowly to the crude mixture while the temperature was controlled at NMT 20 °C [actual 10 – 15 °C]. The reaction temperature was then increased to 20 °C and a solution of heptane/MTBE 3/1 [42 L] was added followed by water [28 L]. The biphasic mixture was stirred for 30 minutes, and the aqueous phase was discarded. The organic layer was washed with an aqueous solution of KH_2PO_4 12 w/v% [35 L] and brine 10 w/v% [14 L]. The biphasic mixture was

stirred for 30 minutes, and the aqueous phase was discarded. The organic phase was then concentrated under reduced pressure to afford 12.4 kg of *tert*-butyl 2-chloroisonicotinate (**14**) as a pale-yellow oil in 91% corrected isolated yield [LCAP 99.7% - qNMR 69.5% potency – 8.6 kg]. A sample was purified by flash column chromatography on silica gel using 0 to 10% *i*PrOAc in heptane to obtain an analytically pure sample as a white solid which matched reported literature.[8] **TLC** (10% *i*PrOAc in heptane, Rf): 0.40 (UV). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.50 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.81 (m, 1H), 7.71 (dd, *J* = 5.0, 1.2 Hz, 1H), 1.60 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.8, 152.3, 150.3, 142.2, 124.0, 121.6, 83.2, 28.0. **LRMS** (0.8 kV, ESI): m/z (%): 216 (23) [$[M+H]^+$, ^{37}Cl], 214 (63) [$[M+H]^+$, ^{35}Cl], 160 (35) [$[M\text{-isobutene}+H]^+$, ^{37}Cl], 158 (100) [$[M\text{-isobutene}+H]^+$, ^{35}Cl].

***tert*-Butyl 2-morpholinoisonicotinate (15).** To a 150 L reactor was added *tert*-butyl 2-chloroisonicotinate (**14**) [8.6 kg, 40.3 mol, 1.0 equiv.] followed by morpholine [25.8 L]. The temperature was then increased to 115 °C [actual 110 - 115 °C]. The mixture was allowed to react at 115 °C until the starting material was ≤1.0 area% by HPLC analysis (typically 24 h). The reaction was cooled to 60 °C and water [4.3 L] was added. The reaction was then cooled to 30 °C and MTBE [51.6 L] was added followed by brine 10 w/v% [34.4 L]. The biphasic mixture was stirred for 30 minutes, and the aqueous phase was discarded. The organic layer was washed with an aqueous solution of KH_2PO_4 12 w/v% [43.0 L] and brine 10 w/v% [17.2 L]. The biphasic mixture was stirred for 30 minutes, and the aqueous phase was discarded. The organic phase was then concentrated under reduced pressure to afford 12.5 kg of *tert*-butyl 2-morpholinoisonicotinate (**15**) as a pale-yellow oil in 97% corrected isolated yield [LCAP 98.9% - qNMR 82.5% potency – 10.3 kg]. A sample was purified by flash column chromatography on silica gel using 0 to 25% *i*PrOAc in heptane to obtain an analytically pure sample as a colorless oil which matched reported

literature.[9] **TLC** (25% *i*PrOAc in heptane, *Rf*): 0.41 (UV). **^{1}H NMR** (400 MHz, DMSO-d_6) 8.26 (d, *J* = 5.1 Hz, 1H), 7.15 (s, 1H), 7.03 (dd, *J* = 5.1, 1.2 Hz, 1H), 3.75 – 3.66 (m, 4H), 3.51 – 3.44 (m, 4H), 1.54 (s, 9H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 164.8, 160.2, 149.1, 140.7, 112.2, 106.3, 82.2, 66.4, 45.4, 28.1. **LRMS** (0.8 kV, ESI): m/z (%): 265 (100) $[M+H]^+$, 209 (15) [M-isobutene+H]$^+$.

***tert*-Butyl 5-bromo-2-morpholinoisonicotinate (16).** To a 150 L reactor was added *tert*-butyl 2-morpholinoisonicotinate (**15**) [10.3 kg, 39.0 mol, 1.0 equiv.] followed by acetonitrile [51.5 L]. The temperature was then cooled to 0 °C and NBS [6.9 kg, 39.0 mol, 1.0 equiv.] was slowly added. The mixture was warmed to 20 °C and stirred until the starting material was ≤1.5 area% by HPLC analysis (typically 2 h). The reaction mixture was then concentrated to ca. 1.5 to 2V [ca. 15 - 20 L]. The temperature was then controlled at NMT 30 °C [actual 20 – 30 °C] and water [51.5 L] was added slowly. Stirring continued at the same controlled temperature for 2 hours. The reaction mixture was concentrated to ca. 5.5 to 6V [ca. 55 - 60 L]. The temperature was then controlled at NMT 30 °C [actual 20 – 30 °C] and was stirred for 12 to 24 h. The suspension obtained was filtered at 15 °C and the cake was washed with water [20.6 L]. The wet cake was then dried at 40 °C under vacuum to afford 12.8 kg of *tert*-butyl 5-bromo-2-morpholinoisonicotinate (**16**) as a pale-yellow solid in 93% corrected isolated yield [LCAP 98.9% - qNMR 97.3% potency – 12.5 kg]. **M.p.** 58.6 – 58.7 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 6.82 (s, 1H), 3.84 – 3.77 (m, 4H), 3.53 – 3.46 (m, 4H), 1.60 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.9, 158.4, 151.0, 142.4, 107.3, 104.9, 83.7, 66.6, 45.4, 28.1. **HRMS** (ESI) calculated for $C_{14}H_{20}BrN_2O_3$: 343.0657 $[M+H]^+$, Found: 343.0651.

***tert*-Butyl 5-acetyl-2-morpholinoisonicotinate (17).** To a 500 L reactor [R1] was added *tert*-butyl 5-bromo-2-morpholinoisonicotinate (**16**) [26.0 kg, 75.8 mol, 1.0 equiv.] followed by CuI

[152 g, 0.8 mol, 0.01 equiv.] and THF [130 L]. The temperature was then cooled to -30 °C and iPrMgCl.LiCl 1.3M in THF [116.6 L, 151.6 mol, 2.0 equiv.] was added dropwise. The mixture was maintained at -30 °C and stirring was continued for 7 hours. Aliquot of the reaction mixture quenched in MeOH were used to control the level of metalation. To another 500 L reactor [R2] was added acetic anhydride [38.7 kg, 379 mol, 5.0 equiv.] and the temperature was cooled to -50 °C. The reaction mixture from R1 was transferred to R2 slowly while controlling the temperature to NMT -45 °C. The reaction mixture was stirred for 30 minutes and was then slowly added to water [130 L]. After stirring for 30 minutes, the aqueous layer was discarded. The organic phase was then concentrated until no distillate was observed. EtOAc [104 L] was added to the crude mixture followed by brine 10 w/v% [52 L]. The biphasic mixture was stirred for 30 minutes, and the aqueous phase was discarded. The organic layer was concentrated to 1.5 – 2V [40 – 50 L] and heptane [78 L] was added. Stirring continued for 12 hours. The suspension obtained was filtered and the cake was washed with heptane [52 L]. The wet cake was then dried at 50 °C under vacuum to afford 17.6 kg of *tert*-butyl 5-acetyl-2-morpholinoisonicotinate (**17**) as a pale-yellow solid in 77% corrected isolated yield [LCAP 98.2% - qNMR 97.7% potency – 17.2 kg]. **M.p.** 126.4 – 126.5 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 6.54 (s, 1H), 3.84 – 3.75 (m, 4H), 3.71 – 3.64 (m, 4H), 2.51 (s, 3H), 1.59 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.9, 167.7, 160.0, 150.9, 144.4, 120.9, 104.4, 83.0, 66.6, 44.9, 28.0, 26.9. **HRMS** (ESI) calculated for $C_{16}H_{23}N_2O_4$: 307.1658 $[M+H]^+$, Found: 307.1652.

4-Methyl-7-morpholinopyrido[3,4-d]pyridazin-1(2H)-one (10). To a 100 L reactor was added *tert*-butyl 5-acetyl-2-morpholinoisonicotinate (**17**) [7.90 kg, 25.8 mol, 1.0 equiv.] followed by EtOH [55.3 L]. Then acetic acid [1.58 kg, 25.8 mol, 1.0 equiv.] was added to the stirred suspension at 20 °C. Hydrazine hydrate 80% [3.2 kg, 51.6 mol, 2.0 equiv.] was added slowly while the

temperature was controlled at NMT 35 °C. At the end of the addition the temperature was increased to 75 °C. The mixture was allowed to react at 75 °C until the starting material was ≤1.0 area% by HPLC analysis (typically 5 - 10 h). The reaction was cooled to 20 °C. The precipitated solid was filtered, and the cake was washed with EtOH (7.9 L x 2). The wet cake was then dried at 50 °C under vacuum to afford 5.96 kg of 4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1(2*H*)-one (**10**) in 94% yield. **M.p.** 249.0 °C (dec.). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 8.89 (s, 1H), 7.23 (s, 1H), 3.74 – 3.72 (m, 4H), 3.67 – 3.64 (m, 4H), 2.46 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 156.0, 159.2, 149.4, 143.2, 135.2, 116.2, 98.4, 66.3, 45.2, 18.1. **HRMS** (ESI) calculated for $C_{12}H_{15}N_4O_2$: 247.1190 $[M+H]^+$, Found: 247.1190.

4-(1-Chloro-4-methylpyrido[3,4-*d*]pyridazin-7-yl)morpholine (11). To a 100 L reactor was added 4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1(2*H*)-one (**10**) [5.93 kg, 24.1 mol, 1.0 equiv.] followed by MeCN [59.3 L]. Then phosphorus oxychloride [7.40 kg, 48.2 mol, 2.0 equiv.] was added at the controlled temperature 15 to 30 °C. At the end of the addition the temperature was increased to 80 °C. The mixture was allowed to react at 80 °C until the starting material was ≤1.0 area% by HPLC analysis (typically 4 - 7 h). The reaction was cooled to 20 °C and volatiles were removed under reduced pressure then CH_2Cl_2 [29.5 L] was added. Water [56.9 L] was added followed by sodium carbonate to reach pH = 7 to 8. The aqueous phase was discarded, and volatiles were removed under reduced pressure. Then 2-propanol was added [26.7 L] and heated to 50 °C for 2 h. Reaction was cooled to 20 °C over 3 h. The precipitated solid was filtered, and the cake was washed once with 2-propanol [5.9 L]. The wet cake was then dried at 50 °C under vacuum to afford 6.12 kg of 4-(1-chloro-4-methylpyrido[3,4-*d*]pyridazin-7-yl)morpholine (**11**) in 96% yield. **M.p.** 184.1 – 184.2 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.29 (s, 1H), 6.90 (s, 1H), 3.74 (m, 8H),

2.82 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 160.1, 157.5, 152.6, 151.7, 131.4, 115.2, 93.4, 66.3, 45.2, 18.7. **HRMS** (ESI) calculated for $C_{12}H_{14}ClN_4O$: 265.0851 $[M+H]^+$, Found: 265.0852.

(*R*)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1-yl)amino)ethyl)benzonitrile - MRTX0902 free base (8). To a 100 L reactor was added 4-(1-chloro-4-methylpyrido[3,4-*d*]pyridazin-7-yl)morpholine (**11**) [6.12 kg, 23.1 mol, 1.0 equiv.] and *t*AmOH [61.2 L]. Then (*R*)-3-(1-aminoethyl)-2-methylbenzonitrile hydrochloride [5.02 kg, 25.5 mol, 1.1 equiv.] was added followed by $MgCl_2$ [3.30 kg, 34.7 mol, 1.5 equiv.] and DIPEA [9.04 kg, 69.9 mol, 3.0 equiv.]. At the end of the addition the temperature was increased to 75 °C for 1 h. The reaction was then heated to 100 °C and allowed to react until the starting material was ≤3.0 area% by HPLC analysis (typically 36 - 48 h). The reaction mixture was cooled to 25 °C and ethyl acetate [55.2 L] was added to the reaction mixture. Water [61.2 L] was added to the mixture at the controlled temperature 20 to 30 °C. The aqueous phase was discarded, and volatiles were removed under reduced pressure. Acetonitrile [36.7 L] were added to the obtained mixture and the precipitate was filtered. The filtrate was concentrated under reduced pressure. Acetonitrile [18.4 L] was added and the mixture was heated to 50 °C. Upon addition of water, seeding and cooling to 20 °C, crystallization was observed. The precipitated solid was filtered, washed once with a pre-mixed solution of water [6.1 L] and acetonitrile [3.0 L]. The wet cake was then dried at 50 °C under vacuum to afford 7.85 kg of (*R*)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1-yl)amino)ethyl)benzonitrile (**8**) in 87% yield (dihydrate obtained - 78% anhydrous (**8**) corrected yield). **M.p.** 122.3 – 122.4 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.99 (s, 1H), 7.71 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.61 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.53 (d, *J* = 6.8 Hz, 1H), 7.40 (s, 1H), 7.31 (m, 1H), 5.52 (p, *J* = 6.9 Hz, 1H), 3.78 (dd, *J* = 5.8, 3.8 Hz, 4H), 3.68 (dd, *J* = 5.8, 3.8 Hz, 4H), 2.65 (s, 3H), 2.55 (s, 3H), 1.54 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 159.8,

151.2, 149.4, 147.6, 146.4, 139.2, 131.3, 129.7, 127.4, 125.1, 119.0, 114.5, 112.7, 93.6, 66.3, 47.1, 45.5, 21.9, 18.5, 17.2. **HRMS** (ESI) calculated for $C_{22}H_{25}N_6O$: 389.2085 $[M+H]^+$, Found: 389.2085.

(*R*)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1-yl)amino)ethyl)benzonitrile fumarate – MRTX0902 hemifumarate (12). To a 500 L reactor was added (*R*)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1-yl)amino)ethyl)benzonitrile dihydrate (**8**) [7.85 kg, 20.2 mol, 1.0 equiv.] and EtOH [86.4 L]. The suspension was heated to 75 °C. Crystalline seed material [39.5 g] of the final product was added. Then a prepared solution of fumaric acid [2.40 kg, 20.2 mol, 1.0 equiv.] in 95% aqueous ethanol [52.2 L] was added dropwise. Crystallization was observed upon addition of the fumaric acid solution and stirring was continued at 75 °C for 2 h after the end of the addition. The reaction mixture was cooled to 20 °C over 4 h and then stirring was continued for 4 h at the same temperature. The suspension was filtered and the collected solid was rinsed with EtOH [23.6 L]. The wet cake was then dried at 50 °C under vacuum to afford 8.93 kg of (*R*)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1-yl)amino)ethyl)benzonitrile fumarate (**12**) in 97% yield. **M.p.** 253.2 – 253.3 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.01 (s, 1H), 7.71 (dd, J = 7.9, 1.4 Hz, 1H), 7.64 – 7.55 (m, 2H), 7.42 (s, 1H), 7.32 (t, J = 7.8 Hz, 1H), 6.61 (s, 2H), 5.51 (s, 1H), 3.80 – 3.74 (m, 4H), 3.73 – 3.66 (m, 4H), 2.65 (s, 3H), 2.56 (s, 3H), 1.54 (d, J = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 166.6, 159.9, 151.3, 149.7, 147.7, 146.3, 139.2, 134.6, 131.3, 129.7, 127.4, 125.3, 119.0, 114.3, 112.7, 93.7, 66.3, 47.1, 45.5, 21.8, 18.2, 17.2. **HRMS** (ESI) calculated for $C_{22}H_{25}N_6O$: 389.2085 $[M+H]^+$, Found: 389.2085.

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Notes

The authors declare the following competing financial interest(s): MRTX0902 is owned by Mirati Therapeutics Inc., for which the authors are either employees or contractors.

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ABBREVIATIONS

SOS1, Son of Sevenless homolog 1; KRAS, Kirsten RAt Sarcoma; GLP, Good Laboratory Practice; FIH, First-In-Human; DMAP, 4-DiMethylAminoPyridine; Boc, *tert*-Butyloxycarbonyl; NBS, *N*-BromoSuccinimide.

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