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Process Development and Large-Scale Synthesis of a c-Met Kinase Inhibitor

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Abstract:

A highly convergent synthesis of c-Met kinase inhibitor 1 has been demonstrated on a multikilogram scale using three key fragments: dihalotricyclic core 2, chiral sulfamide side chain 3, and pyrazole boronic ester 4. The chirality in sulfamide side chain 3 was installed using the cheap and readily available starting material (*S*)-epichlorohydrin. A total of 2.71 kg of 1 were isolated in seven steps (the longest linear sequence).

Introduction

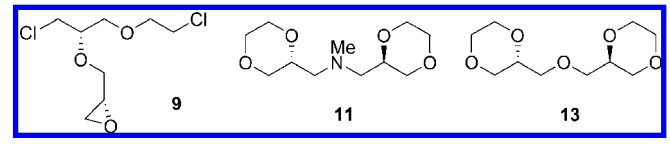
The receptor for hepatocyte growth factor (HGF), which is also known as scatter factor (SF), is c-Met (Mesenchymal epithelial transition factor). Activation of c-Met by HGF can induce a variety of cellular responses, including proliferation, survival, motility, invasion, and changes in morphology.[1−3] Aberrant activation of c-Met can increase the tumorigenicity and metastatic potential of tumor cells.[4,5] Such activation can occur through several mechanisms, including overexpression of c-Met and increased expression of HGF. Such overexpression has been reported in cancers of many organs and shown to increase with tumor progression for several,[3] correlating with shorter patient survival. It is therefore hypothesized that inhibitors of c-Met could suppress tumor aggressiveness and increase survival. Compound **1** has undergone clinical investigation as an orally dosed c-Met kinase inhibitor at Merck.[6] We report herein an efficient and practical synthesis of **1** that is amenable to multikilogram operation.

The medicinal chemistry synthesis of **1** was convergent and proceeded using three key fragments: dihalotricyclic core **2**, chiral sulfamide side chain **3**, and the pyrazole boronic ester **4** (Scheme 1).[7] The challenges of the route for large scale implementation were the high temperature polyphosphoric acid-mediated cyclisation to afford the tricyclic core and the synthesis of the chiral sulfamide side chain. The synthesis of the sulfamide side-chain **3** (Scheme 2) involved a chiral stationary phase HPLC separation of the racemic Cbz-protected analogue of amine **5**, which was available in sufficient quantities within our department for the Medicinal Chemistry delivery. However, the supplies of **5** were insufficient for a bulk delivery and, in addition, the 3-step protection-resolution-deprotection sequence was undesirable. Therefore, an alternative route to sulfamide **3** was required. It was thought that the correct enantiomer of amine **5** could be obtained from (*S*)-epichlorohydrin, a cheap and readily available starting material (Scheme 3).

Results and Discussion

The conversion of (*S*)-epichlorohydrin to alcohol **6** *via* a low yielding three-step procedure has been reported in the literature[8] and this would provide a good starting point for further development. Reaction of epichlorohydrin with 2-chloroethanol (Scheme 3) in the presence of $BF_3 \cdot OEt_2$ at 40 °C gave complete conversion to intermediate alcohol **7**, which was then re-epoxidised to **8** using 8 M aqueous sodium hydroxide at ambient temperature (67% yield over two steps). However, significant levels of dimer **9** were present. A screen of alternative Lewis acids in various solvents was performed but conversions were poor.

Upon further investigation, it was discovered that inverse addition of the epichlorohydrin to three equivalents of 2-chloroethanol was optimal, and that formation of dimer **9** could be minimized by performing the reaction with $BF_3 \cdot OEt_2$ in toluene.



Because of the volatile nature of epoxide **8**, a concentrated toluene solution of this compound was used for the next step. The assay yield for epoxide **8** over 2 steps was 74%.

Laboratory scale reactions of epoxide **8** with aqueous sodium hydroxide at 90 °C led to ring-opening and subsequent cyclization to the desired alcohol **6**. To complete the synthesis

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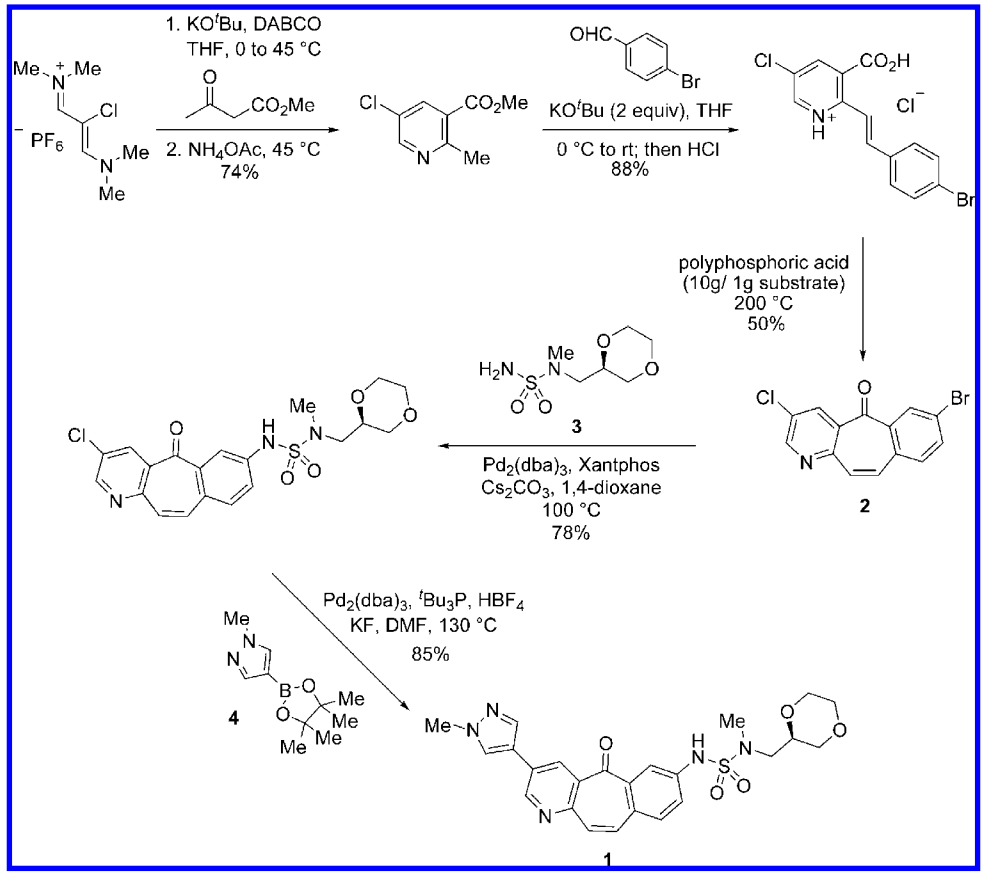
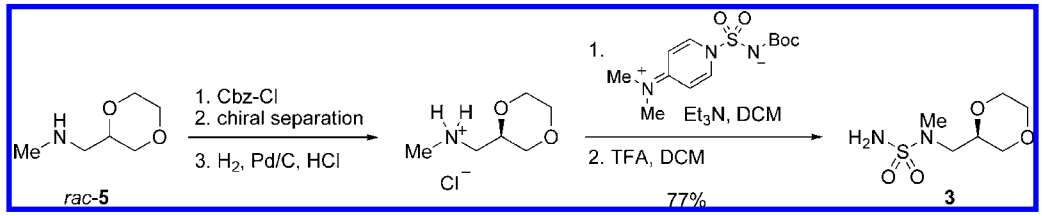
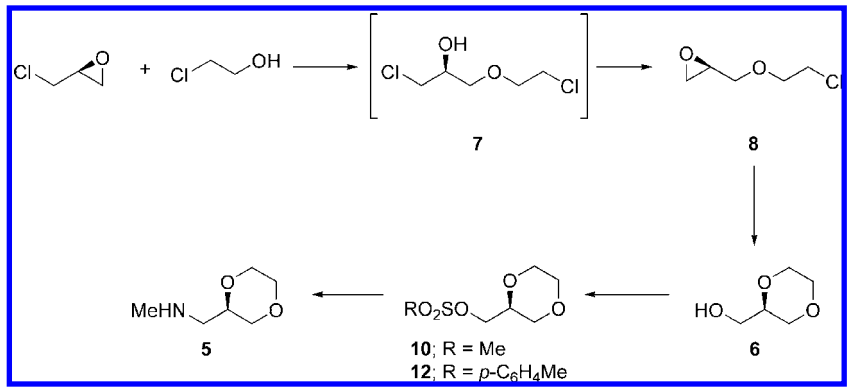
Scheme 1. **Medicinal Chemistry Synthesis of 1**



Scheme 2. **Medicinal Chemistry Side Chain Synthesis**

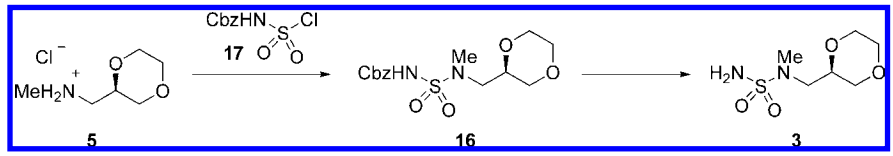


Scheme 3. **New Route to Amine**



of this fragment, activation of alcohol **6** with a suitable leaving group and subsequent displacement with methylamine was required. Initially, the mesylate (**10**) was investigated, however, on treatment with methylamine in methanol at 80 °C (sealed tube), a mixture of desired amine **5** and tertiary amine **11** was formed and further optimization did not lead to significant improvements. The corresponding tosylate (**12**) was found to be a crystalline solid that could be cleanly converted into desired amine **5** upon reaction with methylamine under the conditions described above. Subsequent development efforts therefore focused on tosylate **12**. Due to the fact that alcohol **6** is highly water-soluble, a through process from epoxide **8** to tosylate **12** was developed. The equivalents and concentration of sodium hydroxide used were optimized to reduce formation of ether **13** and maximize conversion of alcohol **6** to tosylate **12**, respectively. After workup and a solvent switch to toluene,

Scheme 4. **Preparation of Sulfamide 3**

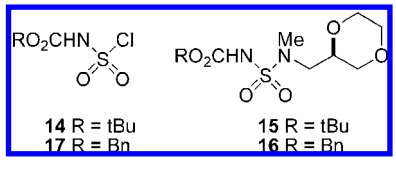


tosylate **12** could be crystallized by simply adding heptane at low temperature (64% corrected yield over 2 steps).

After examining various combinations of reaction solvent, concentration, and temperature for the reaction of tosylate **12** with methylamine, it was found that 4 M methylamine in ethanol at 60 °C gave the highest yield of amine **5** with minimal formation of tertiary amine **11** (<3 GCAP [gas chromatography area percent]). Once the reaction was complete, the *p*-toluenesulfonic acid, which is generated in this reaction, could be simply removed by adding sodium ethoxide and filtering off the sodium tosylate formed (using MTBE as an antisolvent). The resulting solution of amine **5** was then solvent-switched to propan-2-ol (which also served to remove excess methylamine) and desired product **5** was then isolated as its HCl salt in 68% corrected yield.

Conversion of Amine 5 to Sulfamide 3. The most direct method of converting amine **5** to sulfamide **3** (Scheme 4) would be to displace ammonia from sulfamide ($H_2NSO_2NH_2$). A number of examples of this reaction using secondary dialkylamines have been reported in the literature,[9] typically with a large excess of sulfamide in polar solvents at elevated temperatures. Initial attempts at reacting amine **5** with 5 equiv of sulfamide in either diglyme or dioxane (at 110 °C) looked promising; however, the lack of a good analytical method and pressing deadlines meant that this approach was put on hold.

As an alternative strategy, it was decided to modify the Medicinal Chemistry procedure. Thus, the HCl salt of amine **5** was free-based in DCM by addition of 3.0 equiv of Hünig's base (Et_3N or Cy_2NMe gave insoluble HCl salts, which would have required an additional filtration). The resulting solution of **5** was then added to a solution of (chlorosulfonyl)carbamate **14** in DCM (prepared by treatment of ^{t}BuOH in DCM at ~0 °C with chlorosulfonylisocyanate) to afford Boc-protected sulfamide **15**, which was isolated by crystallization in 93% yield. The Boc group was then removed, using the Medicinal Chemistry conditions (22 equiv of TFA in DCM), to afford sulfamide **3-TFA** as a stable mono-TFA salt. Prolonged attempts to flush out the residual TFA by either regular or azeotropic distillation were unsuccessful.



It was anticipated that using a Cbz group in place of the Boc group for this chemistry would provide two major benefits: Cbz-protected sulfamide **16** would have a chromophore, facilitating HPLC analysis and quantification, and the deprotection, via hydrogenolysis, would afford the free sulfamide (**3**), which was known to be crystalline (unlike the TFA salt, which was an oil). Thus, Cbz-sulfamide **16** was prepared from **17** by repeating the conditions described above to prepare **15**, except BnOH was substituted for ^{t}BuOH. Sulfamide **16** was then isolated in 83% yield by crystallization from IPAc. However, this crystallization gave very fine hair-like needles, which resulted in a gelatinous mixture that was very slow to filter. The same morphology was observed from toluene/heptane. A through-process from amine salt **5-HCl** to sulfamide **3** was therefore pursued. Hydrogenolysis of Cbz-sulfamide **16** to sulfamide **3** was found to proceed smoothly, using as little as 1 mol % of 10% Pd/C (50 wt % water) at 1 atm hydrogen in methanol, to afford an essentially quantitative yield of **3** after 6 h. Sulfamide **3** was readily isolated by crystallization from IPA, and recovery could be maximized when heptane was used as an antisolvent. On scale, **3** was isolated in 89% yield over 2 steps. In summary, 3.13 kg of **3** were isolated over seven steps in 29% overall yield

Preparation of the Tricyclic Core 2. The tricyclic core **2** was prepared using a modified version of the Medicinal Chemistry procedure. In the first step, nicotinate **18** was synthesized from vinamidinium salt **19** (Scheme 5) using chemistry previously reported by Merck Process Research.[10] Thus, vinamidinium salt **19** (1.2−1.5 equiv) was reacted with the potassium enolate of methyl acetoacetate (formed using 1.0 equiv of KO^{t}Bu) in THF at 45 °C, in the presence of 1.0 equiv of DABCO. Ammonium acetate (2.4 equiv) was then added to the resulting reaction mixture, and it was aged overnight at ≥60 °C. In the Medicinal Chemistry procedure, crude nicotinate **18** (~65% assay yield in our hands) was then isolated as a dark brown oil via an extractive workup and purified by column chromatography. With the aim of running this chemistry in the large scale preparative laboratory on 50 kg of vinamidinium salt **19**, the need to remove this silica treatment was imperative. It was quickly discovered that the nicotinate **18** was soluble in heptane, or at least heptane containing low levels of ethyl acetate, and this provided the basis for a more practical means of purifying the crude product of this reaction. Initially, nicotinate **18** was obtained by simply extracting the concentrated dark-brown oil with heptane; however, it was subsequently shown that it could also be extracted into heptane directly from the crude final reaction mixture. Nicotinate **18** (13.2 kg; 96.4 LCWP [liquid chromatography weight percent]; 63% corrected yield) was then isolated by solvent-switching to methanol and adding water to crystallize.

Nicotinate **18** was then condensed with 4-bromobenzaldehyde upon dissolving in THF and adding 2 equiv of KO^{t}Bu. Following the Medicinal Chemistry procedure, Friedel−Crafts substrate **20** could then be isolated in 76−81% yield (uncorrected) by crystallization from 3 M HCl-EtOH. However, using

(9) For example Alker, D.; Campbell, S. F.; Cross, P. E.; Burges, R. A.; Carter, A. J.; Gardiner, D. G. *J. Med. Chem.* **1990**, *33*, 585–591.

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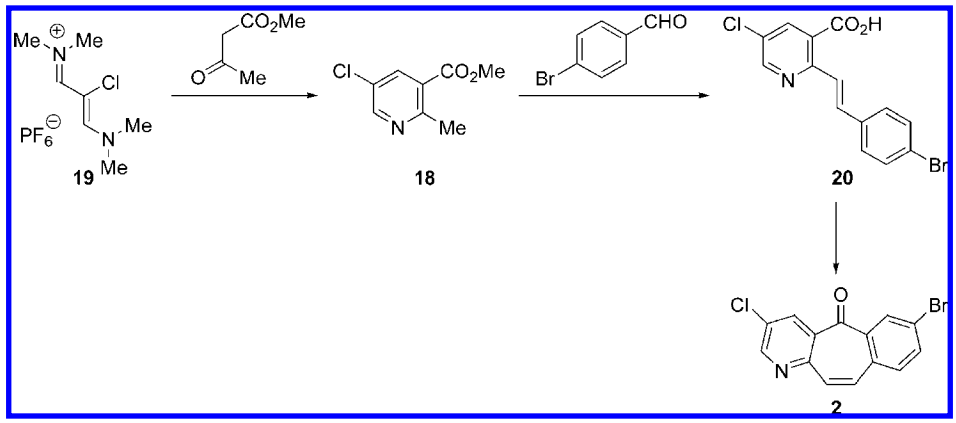
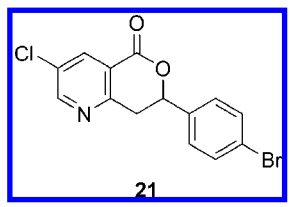
Scheme 5. **Preparation of Tricyclic Core 2**



this material (or material provided by the Medicinal Chemistry group) in the subsequent Friedel−Crafts cyclization led to significant foaming upon mixing with hot polyphosphoric acid (PPA). The same problem was also observed when substrate **20** and PPA were mixed cold and then heated to reaction temperature. This was eventually attributed to the large amounts of KCl and HCl present in the isolated Friedel−Crafts substrate (>40 000 ppm K; >86 000 ppm Cl). To avoid this problem, the isolation of Friedel−Crafts substrate **20** was changed to a combination of several aqueous washes followed by a solvent switch to methanol, from which the desired product crystallized in 67% corrected yield.

The Medicinal Chemistry group carried out the Friedel−Crafts cyclization of acid **20** to tricyclic ketone **2** by heating a solution of **20** in PPA to 200−220 °C overnight (63% yield). Such high temperatures would restrict operations to 20 L glassware, with a heating mantle, and hence running the reaction at lower temperatures was initially investigated. However, repeating this reaction at a range of temperatures confirmed that formation of **2** was only observed at temperatures of ≥180 °C, and 200 °C was required for a reasonable reaction rate—at 215 °C, complete conversion was observed after ∼4 h. Interestingly, under acidic conditions, a significant amount of what is believed to be lactone **21** is rapidly formed. It appears, however, that this compound is in equilibrium with acid **20** as both are consumed as the Friedel−Crafts reaction progresses and the ratio of the two remains unchanged. Other conditions (Eaton's Reagent; $MeSO_3H$; H_2SO_4; TfOH; Tf_2O; P_2O_5; TFA-TfOH; PhSH-$MeSO_3H$) were screened for this Friedel−Crafts reaction without success. Similarly, attempts to carry-out the cyclization on the analogous acyl chloride (prepared from acid **20** and $SOCl_2$) were unsuccessful using a variety of conditions (TfOH in DCE; $MeSO_3H$; $AlCl_3$ in nitrobenzene; $TiCl_4$ in nitrobenzene; AgOTf in nitrobenzene).



On the basis of these results, it was decided to run multiple batches of the Friedel−Crafts reaction in PPA at 210−220 °C and then combine these for a single workup. Thus, after quenching the reaction with water, the resulting slurry could be readily transferred out of the reaction vessel at ambient temperature. Diluting this slurry with acetonitrile and then filtering rejected essentially all of the UV active impurities (increased LCAP [liquid chromatography area percent] from ∼70% to >95%) and afforded desired product **2** as a crude dark-brown solid. Although the LCAP purity of this material was very high, the LCWP purity was only 60−70%, and it is believed that **2** is isolated here as a phosphate salt. Therefore, triethylamine was added to a suspension of this crude solid in DCM and the resulting solution treated with 20 wt % EcoSorb C-941. After removal of the EcoSorb, a solvent-switch to acetonitrile resulted in tricyclic ketone **2** (97 LCWP; >99 LCAP) crystallizing from solution in up to 76% yield.

The Friedel−Crafts cyclization was run in six batches (1.2 kg of 93 wt % **20** per batch) at ∼210 °C. Reactions were complete after 4 h (average assay yield was 80%), and after quenching with water, the six batches were combined. Work-up was carried out as described above to afford 5.4 kg of a black solid (70% yield of **2** corrected for purity). During this workup, 4% of tricyclic ketone **2** was lost to the initial isolation, and 5% was lost to the second. After a carbon treatment to remove triethylamine salts, **2** was isolated in 67% yield from acid **20** (corrected for purities). In summary, 4.28 kg of **2** were isolated over 3 steps in 28% overall yield.

Coupling of the Tricyclic Core with the Sulfamide Side Chain. The Medicinal Chemistry coupling of tricyclic ketone **2** with the TFA salt of sulfamide **3** to give penultimate **22** (Scheme 6) was carried out using 5 mol % $Pd_2(dba)_3$, 15 mol % Xantphos, and 4.0 equiv of Cs_2CO_3 in dioxane (40 mL/g). Dioxane was replaced with THF or toluene, and various permutations of catalyst and base were then screened for this reaction (Table 1), thus confirming that $Pd_2(dba)_3$, Xantphos, and Cs_2CO_3 was the optimum catalyst-base combination. Xantphos consistently gave higher yields than BINAP, and $Pd_2(dba)_3$ was found to be superior to $Pd(OAc)_2$ (entries 1−8). The reaction failed when using $Pd(dppf)Cl_2.CH_2Cl_2$ as a catalyst (entries 9−10). Cs_2CO_3 gave higher assay yields than the other bases tested (K_2CO_3, K_3PO_4, $^iPr_2NEt$).

Since reactions run in toluene became thick slurries, requiring higher dilution than those in THF and necessitating multiple batches, THF was chosen for scale-up. At the end of the

Scheme 6. **Pd-Mediated Coupling of Bromide 2 and Sulfamide 3**

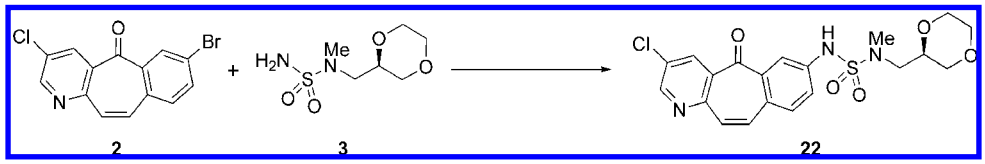
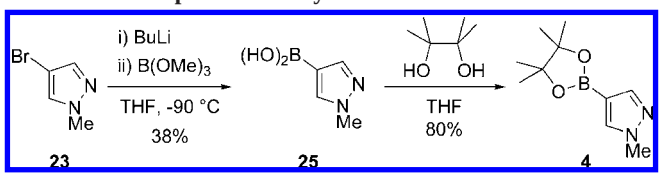


Table 1. **Screen of Pd Catalyst/Ligand/Base/Solvent**

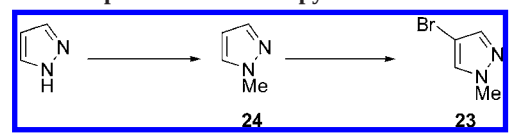
entry	Pd source	ligand	base	solvent	assay yield of **22**[a]
1	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	Tol.	61%
2	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	THF	0%
3	$Pd(OAc)_2$	BINAP	Cs_2CO_3	Tol.	0%
4	$Pd(OAc)_2$	BINAP	Cs_2CO_3	THF	11%
5	$Pd_2(dba)_3$	Xantphos	Cs_2CO_3	Tol.	96%
6	$Pd_2(dba)_3$	Xantphos	Cs_2CO_3	THF	87%
7	$Pd_2(dba)_3$	BINAP	Cs_2CO_3	Tol.	34%
8	$Pd_2(dba)_3$	BINAP	Cs_2CO_3	THF	24%
9	$Pd(dppf)Cl_2.CH_2Cl_2$	-	Cs_2CO_3	Tol.	0%
10	$Pd(dppf)Cl_2.CH_2Cl_2$	-	Cs_2CO_3	THF	0%
11	$Pd_2(dba)_3$	Xantphos	K_2CO_3	Tol.	64%
12	$Pd_2(dba)_3$	Xantphos	K_3PO_4	Tol.	64%
13	$Pd_2(dba)_3$	Xantphos	K_3PO_4	Tol. + 0.5 eq. H_2O	40%
14	$Pd_2(dba)_3$	Xantphos	DIPEA	Tol.	1%
15	$Pd_2(dba)_3$	Xantphos	K_2CO_3	THF	76%
16	$Pd_2(dba)_3$	Xantphos	K_3PO_4	THF	49%
17	$Pd_2(dba)_3$	Xantphos	K_3PO_4	THF + 0.5 eq. H_2O	57%
18	$Pd_2(dba)_3$	Xantphos	DIPEA	Tol.	0%

[a] All reactions were run on 100 mg scale at 80 °C using 0.20 equiv of Pd, 0.30 equiv of ligand, 1.50 equiv of base, and 1.1−1.2 equiv of **3** in 20 mL/g solvent for 18 h. Reactions were homogenised using DMAc prior to assaying.

Scheme 7. **Preparation of Pyrazole Boronate 4**



Scheme 8. **Preparation of Bromopyrazole 23**



reaction, the resulting slurry was simply filtered to give a solid which was ~40 wt % desired product **22**, with the remainder being cesium salts. Interestingly, although the solubility of **22** in THF is 116 mg/mL, at a reaction volume of 18 mL/g only 3% remains in the liquors after this filtration—presumably this is due to **22** existing as its less soluble cesium salt under these conditions. Although the product from this reaction had very low wt% purity, it could be successfully used in the subsequent Suzuki coupling. In addition, this isolation procedure removed nearly all of the organic byproduct, including unreacted starting materials and des-bromo tricyclic core. Coupled product **22** was isolated in 69% corrected yield.

Synthesis of the Pyrazole Boronate. Another compound which we were unable to source in sufficient amounts, and within the necessary timelines, was boronate **4** (Scheme 7). Thus, a process was required in order to support the preparation of 5 kg of this Suzuki coupling reagent. The synthesis of **4** from 4-bromo-1-methyl-1*H*-pyrazole (**23**) has previously been reported,[11] and it was hoped that this chemistry could be used as the basis for developing a viable process.

Initially, bromopyrazole **23** was prepared from pyrazole in 75% yield via a two-step *N*-methylation (MeI, KOH, water) and bromination (Br_2, DCM) sequence (Scheme 8). Although the methylation was successfully demonstrated on 200 g scale, for the bulk campaign it was decided to buy in commercially available 1-methylpyrazole (**24**) and to perform only the bromination step in-house. It was found that 1.5 equivalents of bromine was required to achieve complete consumption of 1-methylpyrazole and, after a standard extractive workup and solvent-switch, the desired product (**23**) could be obtained as a concentrated solution in THF that was suitable for direct use in the following step. This bromination was run on scale to afford a 47 wt % THF solution of **23** (11.6 kg) in 90% assay yield.

Conversion of bromopyrazole **23** to the corresponding lithio species, using BuLi under the literature conditions, was found to be poor. In particular, alkylation of the lithiated pyrazole with 1-bromobutane generated a significant byproduct during the lithium-halogen exchange. Despite these problems, quenching with trimethylborate allowed isolation of **25** as a complex mixture of oligomers and hydrates in approximately 20% yield. Subsequent treatment with an excess of pinacol in THF lead to formation of the desired **4**.

Related research from within our department[12] had previously demonstrated the superiority of an *in situ* quench with tri*iso*-propylborate ($B(O^iPr)_3$) over a stepwise lithiation-quench procedure using trimethylborate. Applying these conditions,

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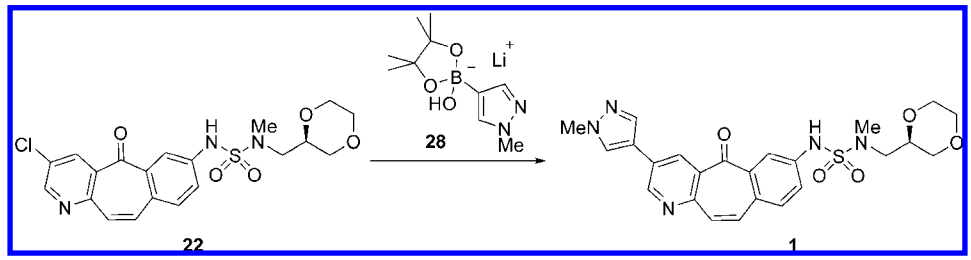
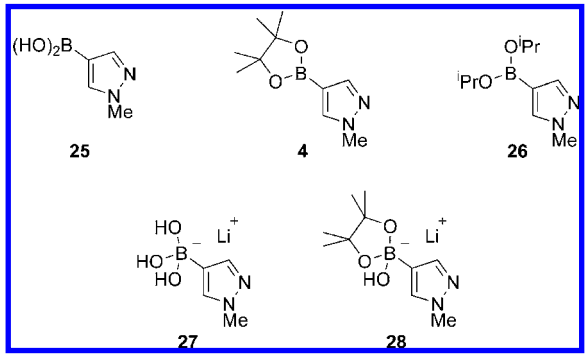
Scheme 9. **Suzuki Coupling of Chloride 22 and -ate Complex 28**



namely, adding 1.2 equiv of BuLi to a mixture of **23** and 1.2 equiv of $B(O^iPr)_3$ in THF/toluene at −70 °C to bromopyrazole **23**, resulted in a 90% conversion to boronate **26** (observed as boronic acid **25** on reverse-phase HPLC). Increasing the BuLi and tri-*iso*-propylborate charges, to 1.5 and 1.3 equiv respectively, gave essentially complete conversion. The solvent composition was also adjusted from 1:4 to 1:1 THF/toluene to reduce the viscosity of the reaction mixture at low temperature.



Despite these improvements in conversion, the isolation of acid **25** still proved difficult. Forming boronate **4** directly, by quenching the reaction with 2-propanol followed by pinacol, was therefore investigated as a means of avoiding the problematic isolation of **25**. Unfortunately, despite obtaining an encouraging 75% assay yield of boronate **4** (from bromopyrazole **23**) via this method, the isolation of this compound by an extractive workup procedure proved equally unsuccessful. All attempts were hampered by the high aqueous solubility of boronate **4** and/or decomposition of **4** to boronic acid **25** and 1-methylpyrazole (**24**). However, a significant breakthrough was realised when a reaction to form boronic acid **25** was quenched with 5 equiv of water rather than the large excess usually employed. In this case, a white solid crystallized from solution which, after isolation by a simple filtration, was tentatively assigned as trihydroxyborate complex **27**. Quenching instead with pinacol, and then warming to room temperature before adding the water, resulted in -ate complex **28** crystallizing from solution. A simple filtration provided 81.5 wt % **28** in up to 88% yield (on 100 g scale). The balance of the wt% was a combination of water (10.4 wt %), LiOH (4.6 wt %), and residual solvents (3.9 wt %). Whilst it was possible to convert -ate complex **28** to boronate **4** (in ∼80% recovery), this material was found to be much more active than **4** in Suzuki couplings and was therefore used as is.[13] Using this procedure, **28** was isolated in 75% yield. In summary, 16.6 kg of **27** were isolated over 3 steps in 71% overall yield.

Final Coupling. Using -ate complex **28** (∼ 1.70 equiv), the Suzuki coupling with chloride **22** (Scheme 9) consistently ran to completion within 1 h using 5 mol % $Pd(P^tBu_3)_2$ in DMF at 100 °C. Furthermore, no additional base was required. Initially, **1** was crystallized directly from the reaction mixture by simply adding hydrochloric acid. Not surprisingly, material isolated in this way was found to have very high residual palladium levels (up to 14 000 ppm). After screening various resins/carbons, it was found that addition of 2 M aqueous sodium hydroxide to the final reaction mixture followed by treating with EcoSorb C-941 reduced residual palladium in isolated **1** considerably. Residual palladium in the isolated product was reduced further when it was found that only 0.5 mol % $Pd(P^tBu_3)_2$ was actually needed for the reaction to reach completion in 1 h at 100 °C. This chemistry was run on scale (using 0.6 mol % catalyst) to afford an 80% yield of **1** (2.81 kg) with the material containing 150 ppm residual palladium.

Carbon-treating the aqueous solution of **1** sodium salt, during the final salt formation, was briefly examined as a means of reducing the residual palladium content down to acceptable levels (<50 ppm). However, in the time frame required, we were unable to identify a practical procedure that reliably gave sufficient palladium reduction as well as high recovery and, therefore, it was decided to include a separate palladium removal step. We immediately focused on use of the MP-TMT (macroporous polystyrene-2,4,6-trimercaptotriazine) resin, which had proven to be very successful for palladium reduction in other projects within the department. Since the solubility of **1** is highest in polar aprotic solvents, resin treatments were assessed using solvents such as DMF, DMSO, DMAc, and NMP. It was found that an overnight age with 20 wt % MP-TMT resin in any of these solvents (10 mL/g) gave an order of magnitude reduction in the Pd level (from 330 ppm to ∼10−30 ppm), with the treatment in DMF proving the most effective. After removal of the resin, **1** (>95% recovery) was crystallized by slow addition of water. This process was run using 17 wt % resin, to afford 2.71 kg of **1** (97% recovery) with only 7 ppm residual palladium. Residual Cs levels were also measured at this point and found to be 9 ppm.

Conclusion

A highly convergent synthesis of c-Met kinase inhibitor **1** has been demonstrated on scale. The key feature of the synthesis was the installation of chirality in sulfamide side chain **3** using the cheap and readily available starting material (*S*)-epichlorohydrin. A total of 2.71 kg of **1** were isolated in 29% yield over seven steps (the longest linear sequence) with the average yield per step being 85%.

(13) Mullens, P. R. *Tetrahedron Lett.* **2009**, *50*, 6783–6786.

Experimental Section

General. Starting materials were obtained from commercial suppliers and were used without further purification. HPLC analyses were performed on an Agilent Series 1100 liquid chromatograph equipped with a UV detector. NMR spectra were obtained at 400 MHz for ^{1}H and 100.6 MHz for ^{13}C. All coupling constants are reported in hertz (Hz).

(2*R*)-2-[(2-Chloroethoxy)Methyl]Oxirane (8). A solution of 2-chloroethanol (10.9 L, 162.5 mol) and $BF_3 \cdot OEt_2$ (0.34 L, 2.7 mol) in toluene (20 L) was heated to an internal temperature of 33 °C. The jacket temperature was decreased to 20 °C and epichlorohydrin (4.2 L, 53.6 mol) was added dropwise at a rate sufficient to maintain the reaction temperature at 36−38 °C. The resulting mixture was then aged at 36 °C for 20 min. The reaction was then cooled to 16 °C and aqueous NaOH (12.5 L of 46/48% aqueous NaOH and 12.5 L of water) was added over 1 h, with vigorous stirring, maintaining the reaction temperature below 20 °C. The batch was aged for 1 h at ambient temperature, and GC analysis was then used to confirm that cyclization was complete. The remaining water (10 L) was then added. The two layers were separated, combining the rag with the toluene phase. The aqueous phase was extracted with toluene (13 L), and the combined organic layers were washed with water (10 L). The resulting organic layer was distilled to low volume, monitoring the distillate for loss of product. The final crude mass was 9.10 kg (60 GCWP ≡ 5.43 kg of epoxide **8**; 74% yield). The NMR data obtained were identical to those reported in the literature.[14]

(2*S*)-1,4-Dioxan-2-ylmethyl 4-Methylbenzenesulfonate (12). Water (15.7 kg) was charged to a 50 L vessel, followed by 46/48% aqueous NaOH (19.6 kg). The resulting solution was heated to 90 °C, and epoxide **8** (9.10 kg of 60 GCWP solution ≡ 5.43 kg of epoxide, 39.8 mol) was then added. The reaction mixture was aged at 90 °C for 1 h. The reaction mixture was cooled to ambient temperature, and DCM (13.9 kg) was then added followed by solid TsCl (3.73 kg, 19.2 mol), in a single portion. The biphasic mixture was aged overnight at ambient temperature. Water (10.5 kg) was added, and the lower DCM layer was separated off. The aqueous phase was then extracted twice with DCM (2 × 13.9 kg). The combined organic layers were washed with 5% brine (0.52 kg NaCl in 10.5 kg water), and then solvent-switched to toluene to a final concentration of 2 L/kg (based on assay). A second batch was run on an identical scale, and the two batches were combined before proceeding. Heptane (7 L) was added, followed by 1 wt % of seed. The resulting batch was then cooled to 0 °C, another 1 wt % seed was added, and it was left to age over the weekend at ambient temperature. The batch was then recooled to 4 °C and aged for 2 h. The resulting solid was collected by filtration, washing the wet-cake with 4 L of 8:1 heptane/toluene. After drying at 25 °C under vacuum overnight (with a nitrogen sweep), tosylate **12** was obtained as a white solid (8.05 kg, 82.4 LCWP, 64% corrected yield, 88.6 LCAP). Mp 55−57 °C; $[\alpha]_D$ −13.0 (c = 0.1, $CHCl_3$); 99.3% ee by chiral HPLC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (3 H, s), 3.37 (1 H, dd, J = 9.6, 11.2 Hz), 3.70 (6 H, m), 3.97 (1 H, dd, J = 4.8, 10.4 Hz), 4.03 (1 H, dd, J = 5.4, 10.6 Hz), 7.37 (2 H, d, J = 8.1 Hz), 7.81 (2H, d, J = 8.3 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 145.1, 132.6, 129.9, 127.9, 72.3, 68.8, 67.5, 66.3, 66.2, 21.6; HRMS (ESI+) calcd for $C_{12}H_{17}O_5S$ 273.0797, found 273.0797. Anal. Calcd for $C_{12}H_{17}O_5S$: C, 52.93; H, 5.92. Found: C, 52.53; H, 5.83.

(2*R*)-1,4-Dioxan-2-yl-*N*-methylmethanaminium Chloride (5). A solution of tosylate **12** (7.76 kg of 82 LCWP material, 23.4 mol), methylamine (46.9 kg of a 33 wt % solution in ethanol, 499 mol), and ethanol (49.0 kg) was heated to 65 °C overnight in a sealed standard Pfaudler glass-lined vessel fitted with a 5 barg bursting disk. The resulting solution was concentrated, by atmospheric distillation, to a volume of ∼15 L. Sodium ethoxide (8 kg of a 21 wt % solution in ethanol, 24.7 mol) and MTBE (34.5 kg) were then added at 50 °C in the following manner: Half the NaOEt was added over 30 min, then half the MTBE, followed by the rest of the NaOEt, and finally the remaining MTBE. The resulting slurry was cooled to 20 °C, aged for 30−60 min, and then filtered, washing the wet-cake with MTBE (11.5 kg). The combined filtrate and washes were solvent-switched to IPA (using 30.5 kg IPA), by atmospheric distillation, to a final volume of ∼30 L. Concentrated hydrochloric acid (2.46 kg) was then added, keeping the batch temperature <60 °C. IPA (91.4 kg) was added, and the batch was concentrated, by atmospheric distillation, to a volume of ∼30 L. It was then aged at 50 °C until a seedbed formed. The resulting slurry was cooled to 20 °C and then filtered, washing the wet-cake with 1:1 heptane/IPA (15.5 L). The filtercake was dried to afford HCl salt **5** (2.83 kg, 95 GCWP, 68% corrected yield) as a white solid. Mp 218−219 °C; $[\alpha]_D$ +28.9 (c = 0.1, CH_3OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.51 (3 H, s), 2.84 (1 H, dd, J = 8.8, 13.1 Hz), 2.95 (1 H, dd, J = 3.5, 12.9 Hz), 3.25 (1 H, dd, J = 9.8, 11.3 Hz), 3.47 (1 H, m,), 3.59 (1 H, m,), 3.66 (1 H, d, J = 11.7 Hz), 3.74 (1 H, dd, J = 2.7, 11.3 Hz), 3.78 (1 H, d, J = 11.7 Hz), 3.89 (1 H, m,); 9.12 (2 H, s, br); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 71.0, 68.1, 66.1, 66.0, 48.6, 33.3; HRMS (ESI+) calcd for $C_6H_{14}NO_2$ 132.1025, found 132.1022. Anal. Calcd for $C_6H_{14}ClNO_2$: C, 42.99; H, 8.42; N, 8.36. Found: C, 42.71; H, 8.44; N, 8.32.

Benzyl{[[(2*R*)-1,4-Dioxan-2-ylmethyl](methyl)amino]-sulfonyl}carbamate (16). Dichloromethane (4.5 L/kg based on HCl salt **5** [2.80 kg, 16.7 mol], 12.6 L, 16.7 kg,) was charged to a vessel, and then cooled to −20 °C. Chlorosulfonylisocyanate (2.95 kg, 20.9 mol) was added in a single portion, and benzyl alcohol was then added over approximately 20 min, maintaining the internal temperature at <3 °C. The resulting batch was aged for 15 min whilst recooling to −20 °C. In a second vessel, *N*,*N*-diisopropylethylamine (8.63 kg, 66.8 mol) was added over 5 min to a stirred mixture of HCl salt **5** in dichloromethane (12 L/kg based on HCl salt **5**, 33.5 L, 44.4 kg). Once the contents of this second vessel were homogenized, they were added to original vessel over ∼45 min, such that the internal temperature remained <3 °C. The second vessel and addition line were rinsed through with dichloromethane (0.3 L/kg based on salt **5**, 1.1 kg). The resulting reaction mixture was then aged for 20 min at −5 to 0 °C. The reaction was carefully quenched with 4 M hydrochloric acid (10.57 L; prepared from 1.93 kg of 38% hydrochloric acid and 9.32 kg

(14) Halil, H.; Colak, N.; Oeztuerkmen, N. *Collect. Czech. Chem. Commun.* **1994**, *59*, 239–242.

of water), maintaining the internal temperature <3 °C (typically takes 10−15 min). The two layers were separated, and the organic phase was washed with water (18.6 kg). The resulting organic layer was then solvent-switched to MeOH (using ∼165 L MeOH) to a final concentration of 20 L/kg (based on assay of sulfamide **16**).

***N*-[(2*R*)-1,4-Dioxan-2-ylmethyl]-*N*-methylsulfamide (3).** To the methanol solution of Cbz sulfamide **16** (20 L/kg in MeOH, ∼5.17 kg (15.0 mol) of **16** by assay, ∼106 L) that was prepared above was added the palladium on carbon catalyst (801 g, 0.38 mol). The mixture was degassed and then stirred under hydrogen (1 atm, 15 psi) until the reaction was complete. The resulting reaction mixture was filtered, washing the vessel and catalyst residue through with MeOH (1−2 L/kg, approximately 5−10 L). The combined filtrate and wash was then solvent-switched to isopropanol, at 35−40 °C under vacuum, to a final volume of 10 L/kg (based on assay of product). The resulting mixture was aged, allowing a seedbed to form. Heptane (15 L/kg, ∼47.3 L, 32.4 kg) was then added, and the resulting slurry was filtered, washing the wet-cake with 1:3 isopropanol/heptane (2.7 and 7.2 kg, respectively). The filter-cake was dried under vacuum at 50 °C (18 h) to afford sulfamide **3** (3.13 kg, 95.2 LCWP, 89% corrected yield from amine HCl salt **5**) as a white solid. Mp 233 °C dec.; $[\alpha]_D$ +8.25 (c = 0.08, DMF); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.68 (3 H, s), 2.91 (1 H, s), 2.92 (1 H, s), 3.21 (1 H, m), 3.44 (1 H, m), 3.56 (1 H, m), 3.65 (4 H, m), 6.71 (2 H, s); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 73.5, 69.1, 66.3, 66.2, 51.6, 37.1; HRMS (ESI+) calcd for $C_6H_{15}N_2O_4S$ 211.0753, found 211.0744. Anal. Calcd for $C_6H_{15}N_2O_4S$: C, 34.28; H, 6.71; N, 13.32. Found: C, 34.28; H, 6.71; N, 13.19.

Methyl 5-Chloro-2-methylnicotinate (18). Methyl acetoacetate (12.6 kg, 108.5 mol) and THF (247.3 kg) were charged to a vessel, put under a nitrogen atmosphere, and then cooled to −10 °C. Solid potassium *tert*-butoxide (12.9 kg, 114.5 mol) was then carefully added in four equal portions, ensuring that the internal temperature remained <0 °C. Once this addition was complete, the batch was warmed to 25 °C over a period of 35 min, and then aged at this temperature for another 70 min. Solid vinamidinium salt **19** (50.0 kg, 163.1 mol) was then added, followed by DABCO (12.2 kg, 108.7 mol). The resulting reaction mixture was warmed to 45 °C, and then left to age at this temperature for 3 h. At this point, solid ammonium acetate (20.1 kg, 260.7 mol) was added, the temperature of the batch was increased to 60 °C, and it was aged at this temperature overnight (16 h). The resulting reaction mixture was cooled to 20 °C, and water (120 kg) was then added. After stirring for 5 min, the lower aqueous phase was removed. Brine (14.4 kg NaCl in 40 kg water) was then added, the biphasic mixture was stirred for 5 min, and the lower aqueous layer was separated off. The resulting THF layer was extracted three times with heptane. The combined heptane extracts were then washed twice with 3:1 v/v water/acetonitrile (2 × 37.6 and 9.8 kg, respectively). The resulting heptane layer was concentrated to minimum stirred volume, using partial vacuum and maintaining the batch temperature between 30 and 40 °C. Heptane (34.1 kg) was added, and the batch was reconcentrated to minimum stirred volume. Methanol (39.6 kg) was added, the batch was concentrated to minimum stirred volume, as described above, and a second portion of methanol (39.6 kg) was then added. The batch was cooled to 20 °C, and water (50 kg) was slowly added over a period of 30 min. Once this addition was complete, the batch was seeded and then cooled to 0 °C. Once a slurry had formed (45 min), a second portion of water (37.5 kg) was added and the batch was aged at 0 °C for another 1 h. The slurry was then filtered, washing the wet-cake with 5:9 methanol/water (14 L). The resulting filter-cake was dried under vacuum at ambient temperature to afford nicotinate **18** (13.22 kg, 96.4 LCWP, 63% corrected yield) as a light brown solid. Mp 45−47 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.68 (3 H, s), 3.87 (3 H, s), 8.21 (1 H, d, J = 2.4 Hz), 8.69 (1 H, d, J = 2.4 Hz); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 165.5, 157.5, 150.6, 137.4, 128.8, 126.2, 52.9, 24.0; HRMS (ESI+) calcd for $C_8H_9NO_2Cl$ 186.0322, found 186.0319. Anal. Calcd for $C_8H_9NO_2Cl$: C, 51.77; H, 4.34; N, 7.55. Found: C, 51.55; H, 4.25; N, 7.54.

2-[(*E*)-2-(4-Bromophenyl)vinyl]-5-chloronicotinic Acid (20). Nicotinate **18** (7.0 kg, 37.7 mol), 4-bromobenzaldehyde (7.0 kg, 37.7 mol), and THF (99.5 kg) were charged to a vessel. The resulting stirred solution was put under a nitrogen atmosphere, and then cooled to −5 °C. To a second vessel were charged potassium *tert*-butoxide (8.46 kg, 75.4 mol) and THF (47.3 kg). Once the KO^{t}Bu had dissolved, this solution was added via a 1 μm in-line filter to the contents of original vessel, whilst maintaining the internal temperature in this vessel at <0 °C. The second vessel and transfer lines were rinsed through with THF (7.1 kg) into the batch. The resulting reaction mixture was then warmed to 25 °C over a period of 1 h. After aging at this temperature for 1.5 h, the reaction was quenched by addition of water (53.8 kg), ensuring the batch temperature remained <30 °C. The biphasic mixture was stirred for 10 min, and the lower aqueous layer was then separated off. To the remaining THF layer was added ethyl acetate (48.6 kg) and 2 M hydrochloric acid (5.3 kg of conc. HCl diluted with 22.4 kg water). The resulting biphasic mixture was stirred for 10 min, and the lower aqueous layer was then separated off. The organic layer was washed with half-saturated brine (2.0 kg NaCl in 19.5 kg water) and then concentrated, using partial vacuum at <40 °C, to ∼27 L. The distillation was then continued whilst slowly adding ethyl acetate to maintain a constant batch volume of ∼27 L, until 48.5 kg of ethyl acetate had been added. This procedure was then repeated with methanol (42.6 kg). Once this was complete, the batch volume was adjusted to 56 L by adding additional methanol (15.0 kg), and the batch temperature was adjusted to 25 °C. The slurry was then filtered, washing the wet-cake with methanol (8.5 kg). The resulting filter-cake was dried under vacuum at 50 °C to afford acid **20** (9.21 kg, 93.1 LCWP, 67% corrected yield) as a yellow solid. Mp 238−240 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.60 (4 H, m), 7.81 (1 H, d, J = 16.2 Hz), 8.05 (1 H, d, J = 16.2 Hz), 8.25 (1 H, d, J = 2.5 Hz), 8.78 (1 H, d, J = 2.5 Hz), 13.82 (1 H, s, br); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 166.8, 152.6, 150.7, 138.1, 135.9, 134.4, 132.3, 129.6, 129.3, 126.3, 125.4, 122.4; HRMS (ESI+) calcd for $C_{14}H_{10}NO_2ClBr$ 337.9583, found 337.9574.

7-Bromo-3-chloro-5H-benzo[4,5]cyclohepta[1,2-b]pyridin-5-one (2). Polyphosphoric acid (12.0 kg) was charged to a 20 L round-bottom flask, fitted with an overhead stirrer, N_2 inlet, N_2 bubbler, and temperature probe. The flask was put under a nitrogen atmosphere, and then heated to ~180 °C (internal temperature). Solid acid **20** (1.12 kg, 3.3 mol) was added portion-wise, and the reaction mixture was then heated to 215 °C (internal temperature). The resulting dark brown mixture was left to age at this temperature (210−220 °C) until the reaction was complete. After 5 h, the heating mantle was removed and the reaction mixture was allowed to cool to 90 °C. Water (10.8 kg) was then VERY CAREFULLY added to the stirred batch at a rate sufficient to maintain the internal temperature at 80−100 °C. Once the addition was complete, the batch was allowed to cool to <50 °C, and then poured into a workup vessel, rinsing the 20 L flask into the vessel with 4.8 kg of water. In total six batches of this Friedel−Crafts cyclization was run, using the above procedure, and these were then combined at this stage in a 400 L vessel for a single workup. To the combined aqueous slurry was added acetonitrile (113.8 kg) over a period of 1 h at 20−25 °C. Once the addition was complete, the resulting mixture was stirred for 15 min and then filtered, washing the wet-cake with acetonitrile (28.4 kg). The filter-cake was dried on the filter overnight under a stream of nitrogen. The dried dark green-brown solid (9.10 kg) was charged back to the empty 400 L vessel. Dichloromethane (280 kg) and triethylamine (3.4 kg, 33.6 mol) were added, and the resulting mixture was stirred for 30 min at ambient temperature. A slurry of EcoSorb C-941 (0.9 kg) in dichloromethane (13.3 kg) was then added, rinsing in with a second portion of dichloromethane (13.3 kg), and the batch was left to age for a further 1 h. The resulting mixture was filtered through a pad of Hyflo Super-Cel (followed by a 1 μm in-line filter), washing the filter pad twice with dichloromethane (31 and 28 kg). The combined filtrate and washes were concentrated to a volume of 50 L, at atmospheric pressure, and then solvent-switched to acetonitrile to a final volume of 120 L, also at atmospheric pressure. The resulting slurry was cooled to 20 °C, via a linear ramp over a period of 6 h, and then aged at this temperature overnight. The slurry was then filtered, washing the wet-cake three times with acetonitrile (3 × 23 kg). The resulting filter-cake was dried under vacuum at 60 °C to afford 5.44 kg of crude tricyclic ketone **2** (82.1 LCWP, 94.2 LCAP) as a slightly tacky black solid. This crude solid was charged to a vessel, and dichloromethane (224.7 kg) and EcoSorb C-941 (0.81 kg) were added. The resulting stirred mixture was heated to a gentle reflux, aged at this temperature for 1 h, and then cooled to ambient temperature. The batch was then filtered through a pad of Solka-Floc (followed by a 1 μm in-line filter), washing the filter pad with dichloromethane (11.4 kg). The combined filtrate and wash were concentrated to a volume of 55 L, at atmospheric pressure, and then solvent-switched to heptane to a final volume of 47 L (used 88 kg heptane), also at atmospheric pressure. The resulting slurry was allowed to cool to ambient temperature overnight and then filtered, washing the wet-cake twice with heptane (2 × 11.0 kg). The resulting filter-cake was dried under vacuum at 40 °C to afford tricyclic ketone **2** (4.28 kg, >100 LCWP relative to standard, 99.6 LCAP, 67% corrected yield) as a beige-coloured solid. Mp 185−186 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.36 (1 H, d, J = 12.7 Hz), 7.49 (1 H, d, J = 12.7 Hz), 7.81 (1 H, d, J = 8.6 Hz), 8.05 (1 H, dd, J = 2.2, 8.6 Hz), 8.24 (1 H, d, J = 2.2 Hz), 8.47 (1 H, d, J = 2.6 Hz), 9.03 (1 H, d, J = 2.6 Hz); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 188.0, 152.6, 150.4, 139.1, 137.9, 136.5, 134.9, 134.2, 134.0, 133.9, 132.9, 132.8, 131.3, 123.8; HRMS (ESI+) calcd for $C_{14}H_8NOClBr$ 319.9478, found 319.9469. Anal. Calcd for $C_{14}H_8NOClBr$: C, 52.45; H, 2.20; N, 4.37. Found: C, 52.57; H, 2.20; N, 4.26.

***N′*-(3-Chloro-5-oxo-5H-benzo[4,5]cyclohepta[1,2-b]pyridin-7-yl)-*N*-[(2R)-1,4-dioxan-2-ylmethyl]-*N*-methylsulfamide (22).** Tricyclic ketone **2** (3.4 kg, 10.6 mol), sulfamide **3** (2.88 kg, 13.7 mol), Xantphos (937 g, 1.6 mol), $Pd_2(dba)_3$ (674 g, 0.7 mol), cesium carbonate (5.5 kg, 16.8 mol), and THF (53.7 kg) were charged to a vessel. The resulting mixture was degassed, by three vacuum/nitrogen purge cycles followed by subsurface degassing for 30 min, heated to 60 °C, and then aged at this temperature for 24 h. The bright yellow slurry obtained was cooled to 20 °C and filtered, washing the wet-cake with toluene (2 × 15 kg). The resulting filter-cake was dried, over the weekend, under vacuum at 60 °C to afford crude sulfamide **22** (9.6 kg, 34 LCWP, 96 LCAP, 69% corrected yield) as a yellow solid. Mp 167−169 °C; $[\alpha]_D$ −35.0 (c = 0.002, DMF); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.80 (3 H s), 3.15 (3 H, m), 3.42 (2 H, m), 3.62 (4 H, m), 7.24 (1 H, d, J = 12.7 Hz), 7.43 (1 H, d, J = 12.7 Hz), 7.60 (1 H, dd, J = 2.4, 8.6 Hz), 7.81 (1 H, d, J = 8.6 Hz), 7.99 (1 H, d, J = 2.4 Hz), 8.51 (1 H, d, J = 2.4 Hz), 8.98 (1 H, d, J = 2.4 Hz), 10.53 (1 H, s); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 188.5, 152.3, 150.6, 140.7, 138.6, 137.9, 134.6, 134.5, 133.5, 130.8, 130.6, 130.0, 123.5, 118.7, 73.5, 68.7, 66.2, 66.1, 51.4, 36.8; HRMS (ESI+) calcd for $C_{20}H_{21}N_3O_5SCl$ 450.0890, found 450.0897; Anal. Calcd for $C_{20}H_{21}N_3O_5SCl$: C, 53.39; H, 4.48; N, 9.34. Found: C, 53.33; H, 4.39; N, 9.29.

4-Bromo-1-methyl-1H-pyrazole (23). A stirred solution of 1-methyl-1*H*-pyrazole (**24**, 6.6 kg, 80.4 mol) in dichloromethane (105.3 kg) was cooled to 10 °C under an atmosphere of nitrogen. Bromine (19.3 kg, 120.8 mol) was then added over a period of 40 min, whilst maintaining the internal reaction temperature below 28 °C. The addition line was rinsed through with dichloromethane (5 kg) into the batch. The resulting reaction mixture was aged at 20−25 °C for 1.5 h. The reaction was then carefully quenched by addition of aqueous sodium sulfite (5 kg Na_2SO_3 in 20 kg water) over a period of 20 min, whilst maintaining the internal temperature below 25 °C. Once the addition was complete, the batch was aged for a further 45 min. Brine (5 kg NaCl in 25 kg water) was then added, the biphasic mixture was stirred for 5 min, and the two layers were separated. The aqueous layer was extracted twice with dichloromethane (2 × 43.9 kg), and the combined organic layers were then washed with half-saturated brine (2.5 kg NaCl in 25 kg water). The resulting dichloromethane solution was concentrated to minimum stirred volume by distillation under partial vacuum (>500 mbar) at <35 °C. THF (44 kg) was added and the solution was reconcentrated to minimum stirred volume, as described above. A second charge of THF (44 kg) was then added and the solution was concentrated to a volume of ~20 L. The

resulting THF solution (24.7 kg) of bromopyrazole **23** (11.6 kg by assay, 90% assay yield) was transferred to a 25 L container, and stored under nitrogen at 5 °C.

1-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole Lithium Hydroxy-ate Complex (28). The THF solution of 4-bromo-1-methyl-*1H*-pyrazole (**23**) (24.3 kg total, 11.4 kg of **23** by assay, 70.8 mol) prepared above was diluted with THF (47.3 kg) and toluene (56.9 kg), and then put under a nitrogen atmosphere. Triisopropylborate (16.6 kg, 88.2 mol) was added, rinsing the addition line into the batch with toluene (2 kg), and the resulting stirred reaction mixture was cooled to −70 °C. Hexyllithium (33 wt % in hexane, 30.0 kg, 108 mol) was then slowly added whilst maintaining the internal reaction temperature below −63 °C and, once the addition was complete, the batch was aged for 30 min at this temperature. Pinacol (12.0 kg, 101 mol) was then added, and the resulting reaction mixture was warmed to 25 °C over 40 min. After aging at this temperature for 1 h, water (6.1 kg) was added over a period of 10 min. The slurry obtained was aged for ∼2.5 h and then filtered, washing the wet-cake with MTBE (20.9 kg). The resulting filter-cake was dried on the filter for 20 min, and then under vacuum at 35 °C for >12 h, to afford lithium -ate complex **28** (16.56 kg, 78 wt %, 79% corrected yield) as a white solid. Mp 136−139 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.90 (6 H, m), 1.05 (6 H, m), 1.46 (1 H, s, br), 3.68 (3 H, s), 7.00 (1 H, s), 7.05 (1 H s); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 143.1, 132.7, 77.5, 76.5, 74.0, 37.9, 26.7, 26.5, 26.0, 25.6; HRMS (ESI+) calcd for $C_{10}H_{18}N_2O_2B$ (- LiO) 209.1461, found 209.1456.

***N*-[(2*R*)-1,4-Dioxan-2-ylmethyl]-*N*-methyl-N′-[3-(1-methyl-1H-pyrazol-4-yl)-5-oxo-5H-benzo[4,5]cyclohepta[1,2-b]pyridin-7-yl]sulfamide (1).** Penultimate **22** (3.2 kg, 7.1 mol), pyrazole -ate complex **28** (2.7 kg, 11.7 mol) and Pd(P^tBu_3)$_2$ (21.8 g, 0.04 mol) were charged to a vessel. DMF (27 L) was added, and the mixture was degassed by vacuum/nitrogen purge cycles followed by subsurface degassing. The reaction mixture was then heated to 100 °C and left to age at this temperature for 1 h. The resulting batch was cooled to 25 °C and 2 M aqueous NaOH (14 L) was then added, whilst maintaining the internal temperature below 27 °C. Ecosorb C-941 (350 g) was added and the batch was aged at 22 °C for 1.5 h before filtering through a pad of Solka-Floc (3.0 kg). The filter pad was washed with 1:1 DMF/2 M $NaOH_{(aq)}$ (3 L) followed by 1:1 DMF/water (6 L), and the combined filtrate and washes were returned to the (cleaned) vessel. Five M Hydrochloric acid (4.8 L) was then added, which led to the product crystallizing from solution. The resulting slurry was heated to 30 °C, cooled to 20 °C, reheated to 30 °C, and then left to age overnight. After the overnight age, water (4 L) was added. The slurry was then filtered, washing the wet-cake with 2:1 water/DMF (3 L). The resulting filter-cake was dried under vacuum at 50 °C to afford **1** (2.81 kg, 100 LCWP relative to standard, 99.4 LCAP, 80% corrected yield) as a yellow solid. Mp 192−193 °C; $[\alpha]_D$ +18.3 (c = 0.04, DMF); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.81 (3 H, s), 3.16 (3 H, m), 3.42 (2 H, m), 3.60 (4 H, m), 3.91 (3 H, s), 7.25 (1 H, d, J = 12.5 Hz), 7.35 (1 H, d, J = 12.5 Hz), 7.57 (1 H, m), 7.77 (1 H, d, J = 8.6 Hz), 7.99 (1 H, m), 8.15 (1 H, s), 8.48 (1 H, s), 8.58 (1 H, m), 9.21 (1 H, m), 10.55 (1 H, s); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 190.2, 150.6, 149.7, 140.3, 138.8, 137.2, 134.0, 133.3, 133.2, 133.0, 131.6, 130.3, 129.5, 128.8, 123.4, 118.7, 118.1, 73.5, 68.7, 66.2, 66.1, 51.4, 39.3, 36.8; HRMS (ESI+) calcd for $C_{24}H_{26}N_5O_5S$ 496.1655, found 496.1666. Anal. Calcd for $C_{24}H_{26}N_5O_5S$: C, 58.17; H, 5.08; N, 14.13. Found: C, 57.98; H, 5.06; N, 14.25.

Reduction of Palladium Level in 1. 1 (2.8 kg, 5.7 mol) and DMF (28 L) were charged to a vessel, under a nitrogen atmosphere. The contents were then warmed to 40 °C and stirred at this temperature until solid had fully dissolved. The resulting solution was cooled to 20 °C, the MP-TMT resin (480 g) was added, and the mixture was then left to stir at ambient temperature overnight. After this age, the batch was filtered through a pad of Solka-Floc (2.0 kg), washing the pad twice with DMF (2 × 2.8 L). The combined filtrate and washes were charged to a second vessel. Water (11 L) was added and the batch was then seeded (3 g of **1**). After stirring for 1 h, in order to form a seed-bed, a second portion of water (22 L) was slowly added over a period of 1 h. Once this addition was complete, the slurry was aged for 2 h at ambient temperature and then filtered, washing the wet-cake with 1:1 DMF/water (10 L) followed by water (10 L). The resulting filter-cake was dried under vacuum at 60 °C to afford **1** (2.71 kg, 7 ppm Pd, >100 LCWP relative to standard, 99.7 LCAP, 97% recovery) as a yellow solid.

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