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Double Heck Route to a Dibenzoxepine and Convergent Suzuki Cross-Coupling Strategy for Synthesis of an MR Antagonist

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Small Molecule Design and Development, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285

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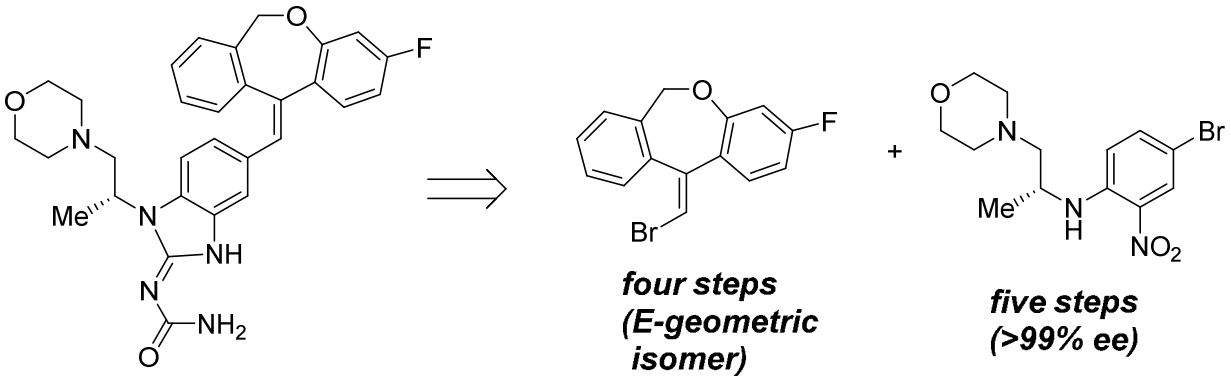


MR antagonist LY2623091

four steps (E-geometric isomer)

five steps (>99% ee)

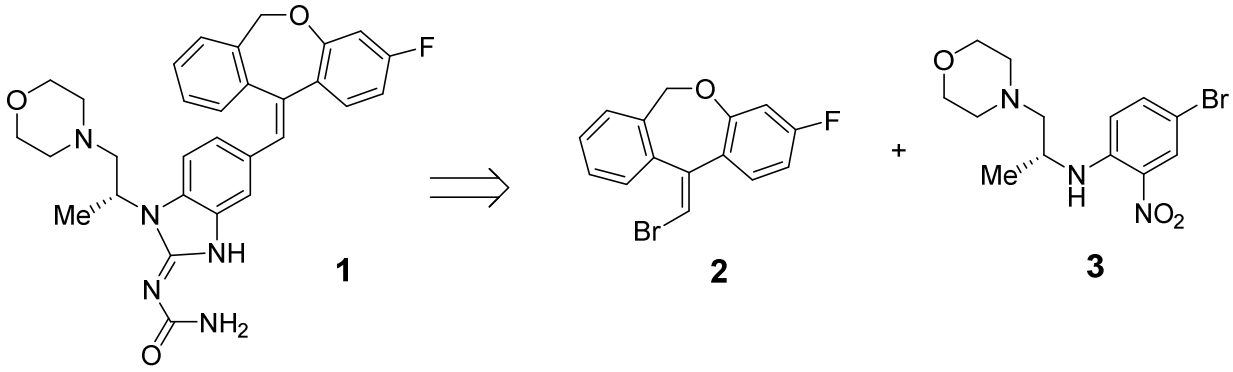
ABSTRACT: A practical pilot plant convergent synthesis of MR antagonist LY2623091 was established. For synthesis convergence, a vinyl bromide geometric isomer and chiral alaninol derivative were required building blocks. Key to the synthesis route development is a stereoselective synthesis of the *E*-vinyl bromide via a sequential double Heck reaction; Suzuki-Miyaura cross-coupling of the vinyl bromide; a selective nitro reduction and a highly sensitive cyanamide hydrolysis to the urea. Improvements in yield and processing were accomplished by two sets of telescoping methods which decreased manufacturing time and provided purity enhancements.

Keywords: MR antagonist LY2623091, Heck reaction, vinyl bromide, alaninol, Suzuki-Miyaura cross-coupling, cyanamide hydrolysis.

INTRODUCTION

Mineralocorticoid receptor (MR) antagonists have been evaluated as treatment for hypertension, congestive heart failures and chronic kidney disease including diabetic nephropathy.[1] Marketed MR antagonists include eplerenone, spironolactone and nifedipine to name a few.[2] More recently, LY2623091 (**1**, Figure 1), an MR antagonist, was evaluated as therapy for resistant hypertension with an effective amount of tadalafil.[3] In an effort to prepare active pharmaceutical ingredient (API) for clinical evaluation, a multi-kilogram synthesis was developed which was based on a cross-coupling retrosynthesis of vinyl bromide **2** and arylbromide **3** (Figure 1). This article describes the development of a practical means for preparing **1** on pilot plant scale.

Figure 1. Retrosynthesis of 1.

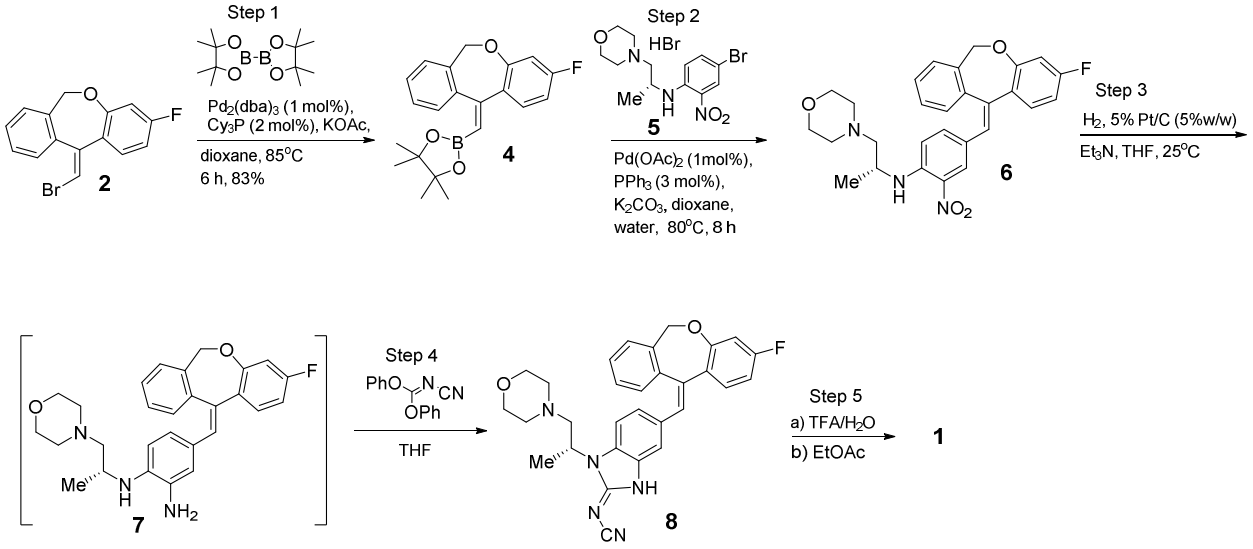


The first generation synthesis of **1** is presented in Scheme 1. The process was efficient such that it afforded multiple kilogram quantities of API for early animal toxicology and clinical evaluation. Vinyl bromide **2** was available as a building block from related drug discovery programs in our laboratories.[4] In addition, multiple means for its preparation were attainable. A Miyaura borylation[5] provided vinylboronate **4** which served as a coupling partner for aryl

bromide **5**. The Suzuki-Miyaura cross-coupling[6] gave the single *E*-geometric isomer **6**. Reduction of the nitro group and reaction of the resulting aniline **7** in solution with a carbonimidate resulted in the cyanoguanidine **8**. Hydrolysis of cyanamide functionality of **8** as the final step gave compound **1** which was further purified by crystallization to afford the API.

For synthesis route design, the first generation route was selected for optimization. Advantages of this approach included the following: a) the route was highly convergent as it dissected the target into two approximately equal parts; b) we had multiple experiences preparing analogs of vinyl bromide **2**; c) there was no need to install the chiral methyl center as the moiety was available as an alpha raw material from alaninol; and d) the cross-coupling of vinyl boronate **4** and aryl bromide **3** established and retained the required *E*-geometric isomer. Our work plan also involved stream lining the first three steps as they were all metal catalyzed processes. The hydrobromide salt of **3** (compound **5**) was corrosive to plant equipment as well as being an irritant due to the salt form. Therefore, optimizing the synthesis also included the search for an alternate salt form. The remaining development plan included impurity rejection in crystallization of **1** as well as overall step reduction and waste minimization.

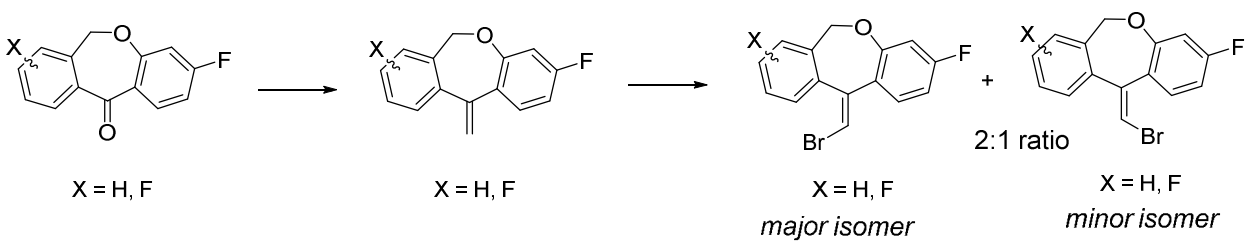
Scheme 1. First Generation Synthesis Route



RESULTS and DISCUSSION

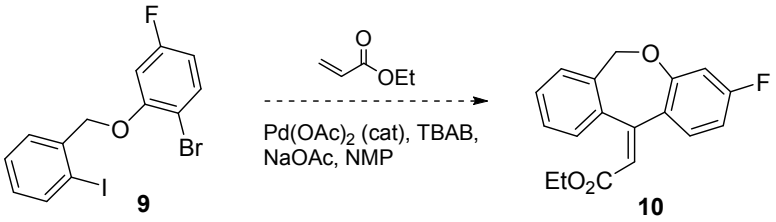
1. Synthesis of vinyl bromide 2 via a sequential double Heck reaction. Preparation of vinyl bromide **2** focused on a requirement to selectively prepare the *E*-geometric isomer. In the initial drug discovery route, this was achieved with low stereocontrol (2:1) by bromination of the alkene as shown in Scheme 2.[4a,b] Several different fluoro substitution patterns on the dibenzoxapine ring system were required for the discovery structure- activity relationship (SAR) efforts. The data from preparing these analogs were utilized in the development evaluation process.

Scheme 2. Discovery Route to Vinyl Bromide 2

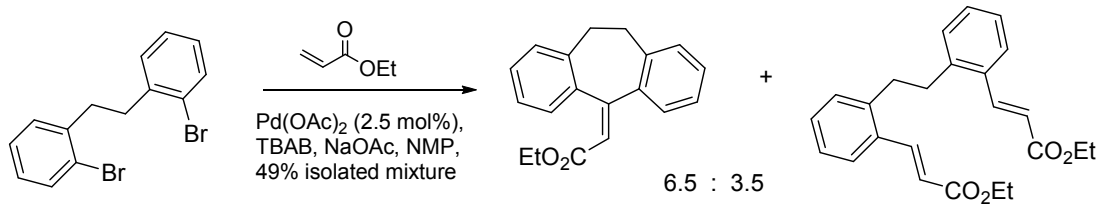


It was envisioned that a double Heck reaction[7] disconnection as shown in Scheme 3 might provide an expeditious and stereoselective synthesis of the dibenzoxepine ring system from **9** to **10**. The literature has an example of a similar double Heck disconnection for preparation of 6-membered rings, and includes one example of a 7-membered ring, lacking the oxygen in the bridge, as shown in Scheme 3.[8] The literature example showed that formation of the 7-membered ring was more difficult than the 6-membered ring, as evidenced by formation of the double intermolecular Heck product, and did not address the stereochemistry question. However, the rapid assembly of two bonds in a single step made this disconnection a top priority for further evaluation.

Scheme 3. Proposed Double Heck Route to Dibenzoxepine Ring System

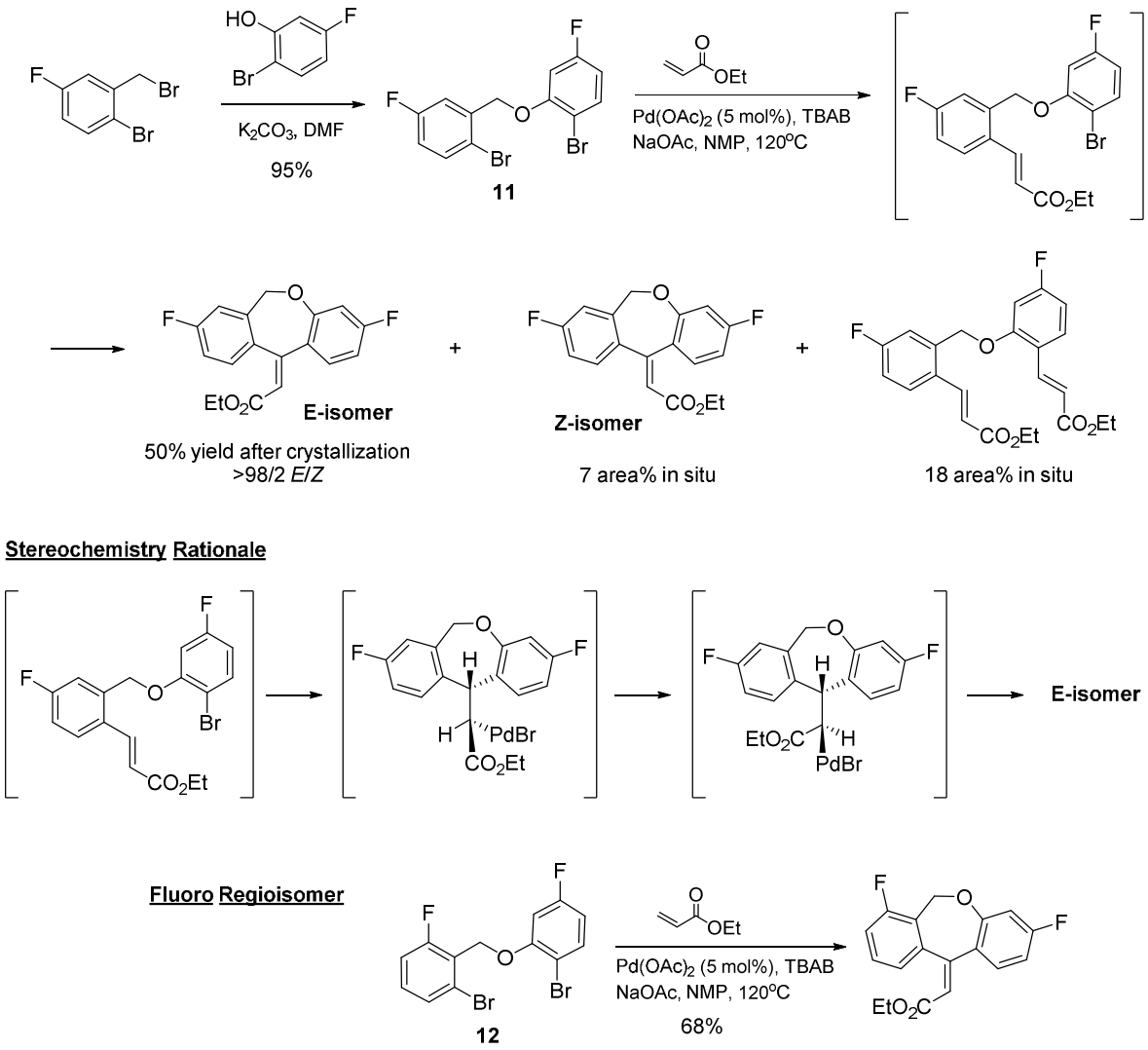


Literature Precedent



The fluorinated biaryl ethers **11** and **12** were explored first, utilizing the more readily attainable dibromo ether precursors (Scheme 4). The double Heck reaction with **11** proceeded to afford a 7:1 mixture of the desired *E*-isomer relative the *Z*-isomer along with 18% of the double intermolecular Heck byproduct that was also observed in the literature example above. Efforts to suppress the intermolecular Heck byproduct through reaction dilution or control of the ethyl acrylate stoichiometry were not successful. The stereocontrol can be explained by the mechanistic work of Heck,[7b] assuming that the more electron deficient aryl bromide reacts first, followed by cis addition in the second Heck reaction, then rotation and cis elimination (Scheme 4). Despite formation of the double intermolecular Heck byproduct, the rapid assembly of the dibenzoxepine ring in one step with acceptable stereocontrol was gratifying, and crystallization afforded purified product in 50% yield. Applying the same double Heck reaction to the regioisomeric biaryl ether **12** gave a higher yield (68%) as shown in Scheme 4. The lower level of impurities formed in this case may be related to the more electon deficient aryl bromide in the left hand ring, due to inductive withdrawl from the meta-F group, without any donation from the fluorine lone pair of electrons.[9]

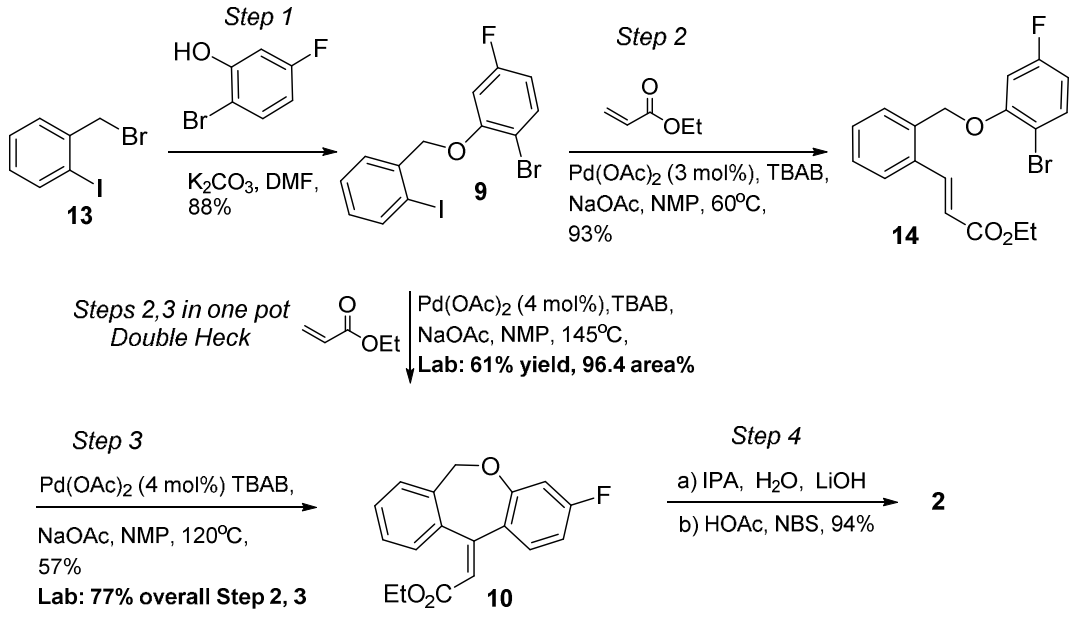
Scheme 4. Double Heck Reactions of Fluorinated Dibromo Ether Substrates



With this strong precedent provided by two successful double Heck reactions in the difluoro ether series, the same strategy was applied to the monofluoro analog in Scheme 5. Iodo bromo substrate **9** was prepared, as the left hand aromatic ring lacks a fluoro electron withdrawing group to help direct the regiochemistry of the initial Heck reaction. It was hoped that the iodo bromo substrate would give the highest possible stereocontrol, by virtue of a regiocontrolled initial intermolecular Heck reaction. Surprisingly, the one pot double Heck

reaction required higher temperature (145ºC) than the dibromo analogs **11** and **12**. Further study showed that the first Heck reaction proceeded at only 60ºC due to the more reactive aryl iodide **9**, and the second step (intramolecular rection) was the slow step. If the initial Heck product **14** was isolated, and then resubjected to Heck conditions in a separate step, the second Heck reaction proceeded at 120ºC in higher overall yield (77 versus 61% during development), and provided acrylate **10** in higher purity (99.2 versus 96.4 area%). Spiking studies showed that iodide was a catalyst poison for the second Heck reaction, and this explains the higher temperature required for the one pot process. The sequential double Heck approach provided good control of the alkene stereochemistry and delivered dibenzoxepine **10** as shown in Scheme 5 during laboratory development.

Scheme 5. Preparation of 2 by Sequential and Double Heck Reactions[a]



a) All yields are pilot plant isolated transformations except as noted.

Details for the overall optimization and plant scale production of **2** for each step in Scheme 5 are as follows. Plant scale alkylation to provide ether **9** involved the use of aqueous K_2CO_3 (0.7 g/1 mL) rather than the solid reagent in order to control a mild exotherm. The aqueous K_2CO_3 solution was added drop-wise to initiate the reaction. After reaction completion, the reaction was quenched by charging water directly to the reaction mixture. This approach for preparing **9** provided 88.2% yield after isolation by filtration and drying.

Based on laboratory development, the sequential two step Heck reaction was selected for pilot plant processing due to higher overall yield and catalyst performance. The conditions for the intermolecular Heck reaction of **9** with ethyl acrylate proved sensitive to oxygen on gram scale. The quality of catalyst also played an important role in the reaction performance. The catalyst loading amount was screened, 1.5% w/w was enough for the reaction completion at 65-70^{o}C after 5 h. During lab trials of pilot plant materials, two separate reactions failed to reach completion. In one case only 59% of **14** was observed after 2 h. An additional catalyst charged only increased the in-process yield to 63%. When a similar pattern was observed for a second reaction, the temperature was increased to 100ºC. Although an 82% yield of **14** was observed, 12% of compound **10** was also detected. The increased reaction temperature may have contributed to formation of compound **10**. After investigating the reaction parameters, two different lots of $Pd(OAc)_2$ catalyst performed without any of the problems observed previously. It was concluded that catalyst lot variability was the problem. Interestingly, up to 20% water content (based on w/w of **9**) did not negatively impact the reaction performance. Compound **14** was consistently obtained in 93% yield with satisfactory $Pd(OAc)_2$ catalyst. With isolated compound **14** free from residual iodide or ethyl acrylate, the second sequential Heck reaction (intramolecular) proceeded smoothly to afford cyclized acrylate **10**. The plant scale conversion

of iodo bromo ether **14** to ester **10** proceeded in only 53% overall yield, but afforded **10** with high purity (99.7 area %) after crystallization. Further development is needed to understand the lower plant yield relative to higher yields (77%) observed during development of the reaction.

Initially ester **10** was hydrolyzed to the acrylic acid, which was isolated and treated with NBS and catalytic LiOAc per the procedure developed by Roy and coworkers.[10] Although this provided the vinyl bromide **2** in high yield and with retention of stereochemistry, isolation of the acrylic acid proved unnecessary. Ester hydrolysis with excess LiOH (Li^+ carboxylates react more rapidly with NBS than Na^+ carboxylates per Roy[10]) and adjustment of the pH with HOAc gave the Li carboxylate in situ, and this reacted cleanly to afford **2** in a one-pot process. If the pH was not adjusted with HOAc, the NBS was decomposed by excess LiOH and lower conversion resulted.

2. Synthesis of aryl bromide 3 salt. Arylbromide **3** was prepared by a five steps process starting with the Boc protected, chiral *R*-(-) alaninol (Scheme 6). The alcohol was converted to mesylate **15**. Reacting **15** with morpholine gave compound **16** which was deprotected and an ammonium dihydrochloride salt **17** was isolated. During laboratory development, all three steps were telescoped due to weak UV adsorption of the intermediates which caused a challenge for in process analytical monitoring. For example, HPLC, TLC and ^{1}H NMR monitoring all provided inconsistencies for the reaction end point. In the formation of **15**, HPLC indicated an incomplete reaction compared to ^{1}H NMR. Focusing on the methyl doublet shift, ^{1}H NMR was utilized for reaction monitoring. A brief solvent survey indicated that EtOAc was best for all three reactions. Some decomposition of the intermediates was noted with CH_2Cl_2 solutions. In 2-MeTHF, a challenging emulsification was observed during aqueous extraction. Phase separation at times took several hours. Neither decomposition nor emulsification was observed with EtOAc.

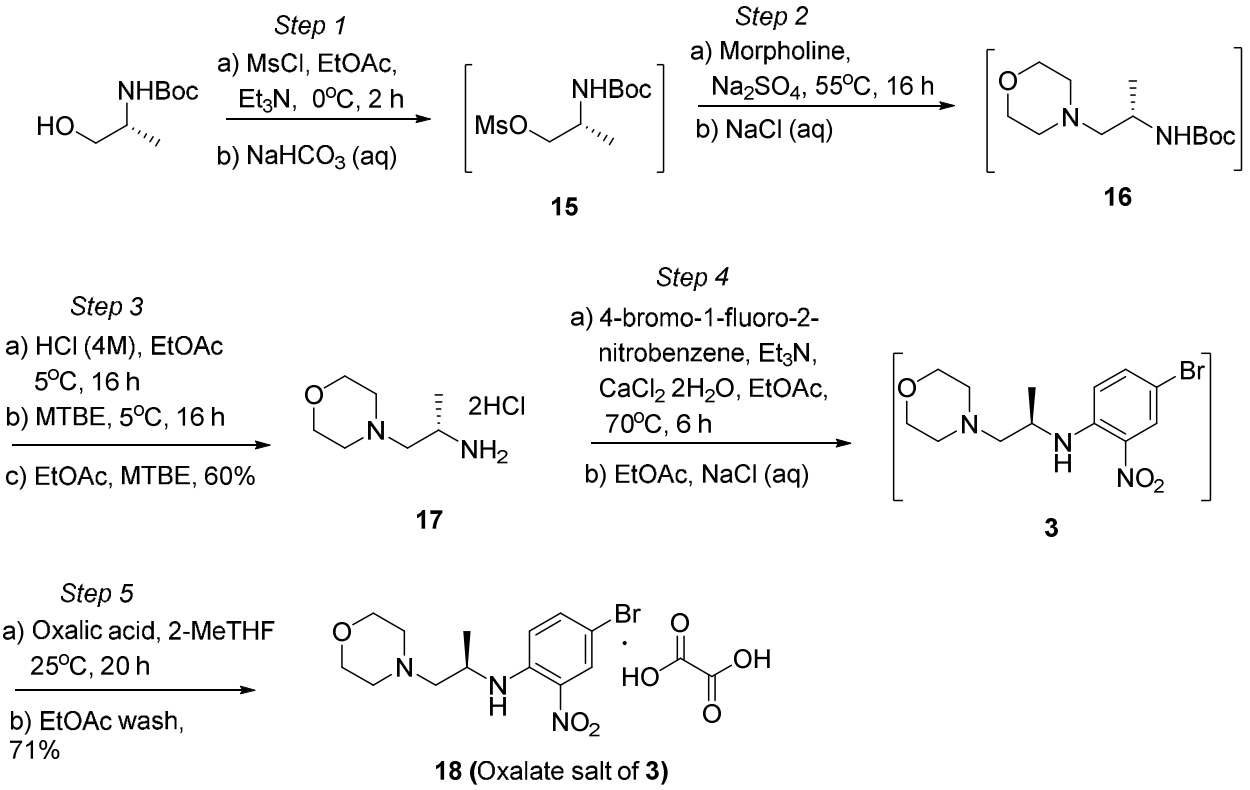
However, preparation of the hydrochloride salt after removal of Boc protecting group indicated that EtOAc was not the best solvent for preparing **17**. Only a 42% overall yield of the three-steptransformation was obtained when EtOAc was utilized as solvent. During salt formation in EtOAc, some loss of **17** was observed in the filtrate. Addition of two volumes of MTBE avoided product filtration lost The three step telescoped transformations: mesylate formation, amination of morpholine and Boc deprotection were robust providing di-HCl salt **17** in 60% overall yield.

The S_NAr reaction of **17** and 4-bromo-1-fluoro-2-nitrobenzene in EtOAc and Et_3N was robust providing freebase **3** in very good yield (93%). $CaCl_2$ dihydrate was used as a fluoride trapping agent. Performing the reaction in other solvents provided lower yields. For example 2-MeTHF under the same conditions as EtOAc provided <88% yield. For the Step 4 S_NAr reaction, it was important to minimize the levels of other nucleophilic amines (e.g. alaninol, from BOC cleavage in Step 1, and morpholine, from Step 2), as these could compete with amine **17** in Step 4. The levels of these other amines were minimized by careful monitoring and control in the steps preceding Step 4.

Compound **3** as a free base is not a solid. Therefore, the first generation synthesis utilized a crystalline HBr salt. However, forming the HBr salt using a solution of HBr in acetic acid was corrosive to plant equipment. Evaluation of possible acid salts of **3** that were crystalline involved oxalic acid, tartaric acid and fumaric acid. Among these salts, the oxalate salt **18** (oxalate salt of **3**)gave the best purity, and minimized product loss during isolation. The formation of **18** was also conducive to EtOAc as solvent. A 2-MeTHF solution of oxalic acid was added to the EtOAc solution of free base of compound **3**. Therefore, the salt formation was conducted in a mixture of 2-MeTHF and EtOAc. EtOAc was utilized as a final rinse of the salt.

Since the oxalate salt provided similar quality (99.7% purity) to the hydrobromide salt but was not corrosive to plant equipment, it was the salt of choice for future large scale processing.

Scheme 6. Preparation of Aryl Bromide 3 Oxalate Salt (18)[a]



a) all yields are isolated pilot plant transformations.

3. Second generation synthesis of 1. Having a robust pilot plant syntheses of key intermediates **2** and **3** (as the oxalate salt **18**), we turned our attention to the final API sequence (Scheme 7). In the first generation synthesis, the organometallic transformations of Steps 1 and Steps 2 were performed in dioxane with catalytic palladium at 80-85°C. Each reaction required a different catalyst system. Our strategy was to perform a single work-up. For optimization, the two reactions were streamlined in dioxane such that isolation and a separate work-up for each step would be avoided.

Vinyl bromide **2** was converted to a vinyl boronate ester **4** by a Miyaura borylation reaction. It was found that addition of trace H_2O (approximately 1 w/w % relative to KOAc) was important for reproducible reaction rates, especially on larger scale. It is believed that on lab scale adequate H_2O is present to provide enhanced KOAc solubility, but on larger scale where less adventitious moisture is present, a spike of H_2O is necessary to aid in solubilization of KOAc. Filtration of the reaction mixture to remove solids was the only purification undertaken before a Suzuki cross-coupling with aryl bromide **18,** catalytic $Pd(OAc)_2$, PPh_3, one equivalent of K_2CO_3, water and no additional solvent. Compound **6** was isolated by an EtOAc/water extractive work up. A crystallization with MTBE and drying provided **6** in 56 % yield over two steps.

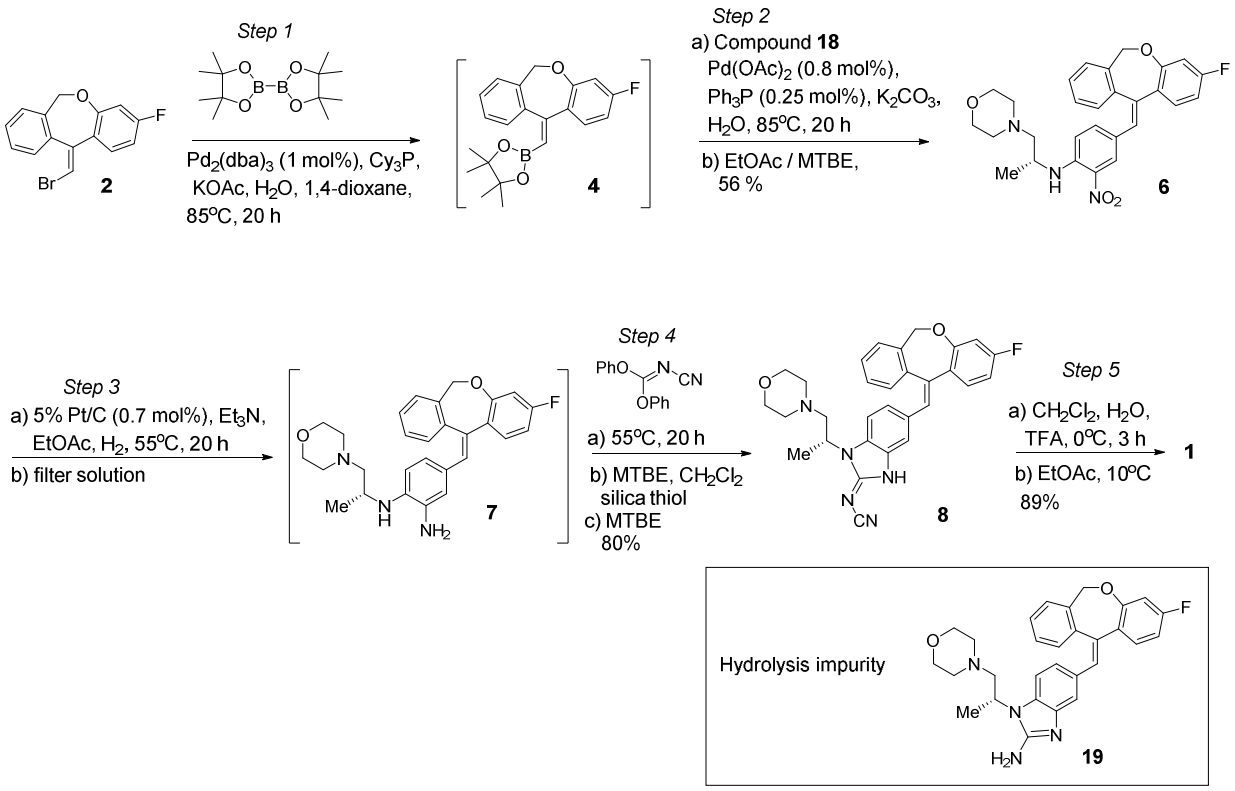
The nitro reduction of **6** utilized 5% Pt-C, EtOAc as solvent, Et_3N as an additive and 50 psi H_2atmosphere at 30-40^{o}C. Although there is no rationale for Et_3N impacting the reaction, there is a reaction rate association. For example, performing the nitro reduction with 0.1 equivalents of Et_3N the reaction is completed in 20 h. Under the same reaction conditions except without Et_3N, 10 % of the unreduced nitro group was observed. A total of 48 h was required for reaction completion. As the subsequent guanidine ring forming step for **7** was performed in EtOAc, the completed hydrogenation reaction solution was filtered and used directly in the next step.

Commerically available diphenyl cyanocarbonimidate[11] was reacted with diamine **7** in EtOAc solution from the previous reaction at reflux (75-80^{o}C) for 20 h. After completion of the reaction, the mixture was concentrated, crystallized from MTBE and dried to provide cyanoguanidine **8** as a crude intermediate. At this stage, a metal scavenger was utilized to remove any residual metal since the three prior steps had utilized Pd or Pt metals. Silica thiol

was selected as the metal scavenger of choice. However, **8** was not readily soluble in EtOAc. The solubility of **8** in EtOAc at ambient temperature was only 15 g/L. A solvent screen indicated that CH_2Cl_2 provided enhanced solubility at 100 g/L. Therefore, **8** was dissolved in CH_2Cl_2 and treated with silica thiol (5% w/w) for residual metal removal. The resulting residual Pd was 26 ppm while residual Pt was <10 ppm. After residual metal removal, **8** was recrystallized from MTBE to provide an 80% isolated yield.

The final transformation in the second generation synthesis involved hydrolysis of the cyanamide functionality of **8** to the indazole urea **1**. A major development challenge was circumventing complete hydrolysis to guanidine **19**. The original hydrolysis procedure involved addition of **8** as a solid to a CH_2Cl_2/ TFA/water mixture at 0-25^oC for 3 h. In an effort to improve the process, a solution of **8** during addition to the reactor was preferred. A solubility screen consisting of THF, AcOH and CH_2Cl_2 indicated that CH_2Cl_2 or THF provided increased solubility of **8**. Upon further development, the rate of hydrolysis in THF as solvent was much slower when compared to CH_2Cl_2. The reaction time was 10 h in THF vs 3 h in CH_2Cl_2. Due to concern that longer reaction time may lead to increased hydrolyzed by-products, CH_2Cl_2 was selected as solvent. The optimized reaction involved forming an aqueous CH_2Cl_2 mixture of **8** to which TFA was added at 0^oC and the hydrolysis reaction was allowed to proceed for 3 h, at ambient temperature. Extractive work up and crystallization with EtOAc followed by drying resulted in 89 % yield of **1**.

Scheme 7. Second Generation Synthesis Route[a]



a) all yields are pilot plant isolated transformations.

CONCLUSION

A highly convergent pilot plant synthesis for MR antagonist LY2623091 (1) was developed. The synthesis is based on both the first generation synthesis approach and preparation of related MR analogs. However, the first generation synthesis did not posess complete stereocontrol of the tri-substituted olefin. Incorporating and developing a double Heck reaction for geometric control of the *E*-olefin isomer was key to the synthesis success. Execution of the sequential Heck reaction on a pilot plant scale provided complete control of the stereoisomer in moderate yield.

In addition to the geometric isomer control, a chiral alaninol derivative as a building block was prepared. An important HBr to oxalate salt switch was required to avoid plant equipment corrosion from the HBr salt. Other methodologies developed for synthesis success include Suzuki cross-coupling, amination, nitro reduction, indazole formation and hydrolysis of a challenging cyanamide. Overall, multi-kilogram quantities of API were obtained to support clinical trials.

EXPERIMENTAL SECTION

General. All commercial reagents were used as received without further purification. Known compounds were prepared according to reported procedures or were purchased from commercial sources. Melting points were determined by DSC using TA Instruments Discovery Series SA+ Differential Scanning Calorimeter, running the latest version of TRIOS software. IR spectra were recorded with Nicolet 6700 FT-IR with Smart OMNI sampler. All NMR data were collected with a 400 MHz Varian Spectrometer ATB probe. HRMS analyses were performed with a Thermo LTQ Orbitrap Discovery, using Electrospray ionization (ESI) technique, in the positive ion mode. Analytical methods for purity (wt% and area% impurities) was developed utilizing an HPLC (Shimadzu LC-20A HPLC with PDA detector or equivalent) and measured against an authentic external standard. Assay: Shimadzu LC-20A HPLC with PDA detector or equivalent, Waters XBridge Phenyl, 4.6x150 mm, 3.5 um, 40ºC, 1.5 mL/min; 240 nm; 5 uL injection; A:0.2% Perchloric acid in 95 : 5 MilliQ water : MeCN; B: MeCN; gradient: 0% B to 74% B in 20 mins; to 100% B in 1 min; hold at 100% B for 3 mins; Diluent: MeCN.

1-Bromo-4-fluoro-2-((2-iodobenzyl)oxy)benzene (9). DMF (320 L), 2-bromo-5-fluorophenol, 39.4 kg, 206 mol), and 2-iodobenzyl bromide, (60.0 kg, 202 mol) were combined at 15ºC to 25ºC under an inert atmosphere. K_2CO_3 (44.4 kg, 321 mol) was dissolved in water

(60 L) and added to the DMF mixture at 15ºC to 30ºC over 1.5 h. After stirring for 12.5 h, assay showed no 2-iodobenzyl bromide. Water (603 L) was added over 2 h, and the mixture stirred for another 2 h. The slurry was filtered and washed with water, before the wet cake was dried, resulting in **9** (73.6 kg, 98.6 wt%, 178 mol, 88.2% yield). Mp 89.8-92.3 ºC. IR (neat, ATR): 3072 (w), 1482 (s), 1451 (s), 1294 (s), 1294 (s) cm-1. ^{1}H NMR (399 MHz, DMSO-d_6) δ 5.12 (s, 2H), 6.81 (td, J = 8.49, 2.77 Hz, 1H), 7.14 (td, J = 7.64, 1.65 Hz, 1H), 7.18 (dd, J = 10.90, 2.82 Hz, 1H), 7.46 (td, J = 7.52, 0.92 Hz, 1H), 7.60 (dd, J = 7.64, 1.41 Hz, 1H), 7.62 (dd, J = 8.66, 6.23 Hz, 1H), 7.92 (dd, J = 7.83, 0.83 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 74.5, 99.2, 102.4 (d, J = 27.1 Hz), 105.8 (d, J = 3.4 Hz), 108.9 (d, J = 22.5 Hz), 128.5, 129.8, 130.3, 133.6 (d, J = 9.9 Hz), 138.0, 139.2, 155.4 (d, J = 10.7 Hz), 162.2 (d, J = 244.3 Hz). GCMS: m/z [M]+ calcd for $C_{13}H_9BrFIO$: 405.88600; found: 405.88620.

Ethyl (*E*)-3-(2-((2-bromo-5-fluorophenoxy)methyl)phenyl)acrylate (14). *N*-methyl-2-pyrrolidone (778 L), compound **9** (73.4 kg, 177 mol), NaOAc (23.0 kg, 280 mol), and TBAB (59.0 kg, 183 mol) were combined. The mixture was degassed by sparging N_2 gas through the mixture for 1 h. $Pd(OAc)_2$ (1.17 kg, 5 mol) was placed in a charge box, degassed with N_2 gas three times, before adding it, and heating the mixture to 60ºC to 65ºC. Separately, N-methyl-2-pyrrolidone (14.7 L) was combined with ethyl acrylate (19.9 kg, 199 mol) and added to the mixture at 60ºC to 65ºC over 1.25 h. The combined mixture was then heated to 70ºC to 75ºC for 5 h. Assay showed non-detect level of **9**. The mixture was cooled to 0ºC to 5ºC before adding this mixture to another vessel containing water (1854 L) at 0ºC to 10ºC over 13.5 h. The combined mixture was adjusted to 20ºC to 30ºC and stirred for 2.5 h. The slurry was filtered in three sections, washing each section with water (50 – 60 L). The reactor was rinsed with water (90 L) to completely transfer the product. The combined wet cake (203 kg) was returned to the

reactor and slurried in water (750 L) for 1 h, before filtering, washing with water, and drying at 50ºC to 55ºC for 58 h. This resulted in **14** (70.2 kg, 89.3 wt%, 165 mol, 93.0 % yield). Mp 84.9-89.4 ºC. IR (neat, ATR): 2979 (w), 1711 (vs), 1314 (vs), 1296 (vs), 1290 (s), 1184 (vs), 1167 (s) cm-1. ^{1}H NMR (399 MHz, DMSO-d_6) δ 1.20 (t, J = 7.10 Hz, 3H), 4.15 (q, J = 7.10 Hz, 2H), 5.35 (s, 2H), 6.55 (d, J = 15.86 Hz, 1H), 6.80 (td, J = 8.47, 2.82 Hz, 1H), 7.30 (dd, J= 11.00, 2.72 Hz, 1H), 7.44 (quind, J = 7.25, 1.46 Hz, 2H), 7.60 (t, J = 6.62 Hz, 1H), 7.61 (d, J = 6.42 Hz, 1H), 7.84 (dd, J = 7.35, 1.41 Hz, 1H), 7.94 (d, J = 15.86 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.1, 60.0, 68.9, 102.8 (d, J = 27.3 Hz), 105.9 (d, J = 3.4 Hz), 108.9 (d, J = 22.5 Hz), 120.2, 127.1, 129.0, 129.8, 130.1, 133.5 (br d, J = 9.7 Hz), 133.5, 134.8, 141.0, 155.3 (d, J = 10.9 Hz), 162.1 (d, J = 244.1 Hz), 165.9. HRMS: m/z [M+H]+ calcd for $C_{18}H_{17}BrFO_3$: 379.03396; found: 379.03436.

Ethyl (*E*)-2-(3-fluorodibenzo[b,e]oxepin-11(6H)-ylidene)acetate (10). *N*-methyl-2-pyrrolidone (723 L), compound **14** (67.5 kg, 159 mol), NaOAc (22.0 kg, 268 mol), and TBAB (58.0 kg, 180 mol) were combined in a pre-treated reactor and degassed by bubbling with N_2 gas for 1 h. $Pd(OAc)_2$ (1.45 kg, 6.47 mol) was added. The atmosphere was exchanged with N_2gas three times before heating the mixture to 115ºC to 125ºC for 5 h. Assay showed 0.5% **14**. The mixture was adjusted to 20ºC to 30ºC. In a separate tank was added water (829 L), adjusted to 20ºC to 30ºC. The reaction mixture was added to the water over 0.75 h. EtOAc (783 L) was added to the mixture. After stirring for 0.75 h, the phases were separated. The aq phase was back extracted with EtOAc two times (610 L, followed by 636 L). The combined organic extracts were washed with brine (457 L). Activated charcoal (16.5 kg) in EtOAc (31 L) was added, and the mixture was stirred at 20ºC to 30ºC for 4 h, before filtering over diatomaceous earth (12.3 kg) and rinsing with EtOAc (110 L). The filtrate was concentrated under reduced

pressure at < 35ºC (to 110 L) before methanol (446 L) was added. This mixture was then concentrated under reduced pressure at < 35ºC (to 213 L). Assay showed 0.1% EtOAc. The mixture was heated to 60ºC to 70ºC and held for 1 h to ensure dissolution of the solids. N-heptane (801 L) was added over 7 h to the mixture at 60ºC to 70ºC. After stirring for 1 h at this temperature, the slurry was cooled to 25ºC to 30ºC over 4 h, cooled to -10ºC to -5ºC over 3 h, and held at this temperature for 14 h. The slurry was filtered, washing the wet cake with n-heptane (133 L). The wet cake was dried under vacuum at 35ºC to 40ºC for 36 h. This resulted in **10** (27.9 kg, 97.5 wt%, 99.7 area%, 91 mol, 57.4% yield). Mp 104.5-105.4 ºC. IR (neat, ATR): 2989 (vw), 1716 (vs), 1287 (vs), 1173 (vs), 1165 (vs) cm-1. ^{1}H NMR (399 MHz, DMSO-d_6) δ 1.04 (t, J = 7.10 Hz, 3H), 3.97 (q, J = 7.10 Hz, 2H), 5.20 (br s, 2H), 6.36 (s, 1H), 6.66 (dd, J = 10.51, 2.63 Hz, 1H), 6.80 (td, J = 8.37, 2.63 Hz, 1H), 7.22 (dd, J = 7.44, 0.92 Hz, 1H), 7.34 (td, J = 7.44, 1.36 Hz, 1H), 7.39 (td, J = 7.37, 1.31 Hz, 1H), 7.45 (dd, J = 8.81, 6.86 Hz, 1H), 7.49 (dd, J = 7.30, 1.07 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.8, 59.7, 69.5, 105.9 (d, J = 24.4 Hz), 108.5 (d, J = 21.6 Hz), 120.1, 121.6 (d, J = 3.1 Hz), 127.5, 128.0, 128.5, 128.8, 131.6 (d, J = 9.9 Hz), 131.8, 140.0, 152.7, 156.7 (d, J = 12.4 Hz), 163.4 (d, J = 246.4 Hz), 164.7. HRMS: m/z [M+H]+ calcd for $C_{18}H_{16}FO_3$: 299.10780; found: 299.10798.

(*E*)-11-(Bromomethylene)-3-fluoro-6,11-dihydrodibenzo[b,e]oxepine (2). Isopropanol (284 L), water (110 L), **11** (27.9 kg, 97.5 wt%, 91 mol), and $LiOH.H_2O$ (8.0 kg, 190 mol) were combined and heated to 80ºC to 85ºC for 2 h. Assay showed non detect levels of **11**. While at 40ºC to 45ºC, acetic acid (11.2 kg, 186 mol) was added over 0.7 h, rinsing with isopropanol (7.6 L). The mixture was stirred for 1 h at 40ºC to 45ºC before *N*-bromosuccinimide (17.7 kg, 99 mol) was added in portions over 1.5 h to maintain 40ºC to 45ºC. After cooling to 20ºC to 30ºC, the mixture was stirred for 7.5 h. 4% aq $NaHSO_3$ (73 L, 28 mol) was added to quench the

reaction over 0.75 h and stirred for another 1 h at 20ºC to 30ºC. 7% aq $NaHCO_3$ (70 L, 61.6 mol) was added over 0.5 h and stirred for another 1 h at 20ºC to 30ºC. Water (261 L) was added over 0.5 h and the mixture was stirred for another 1 h at 20ºC to 30ºC. The slurry was filtered, washing the wet cake with aq isopropanol (29 L). The wet cake was dried at 35ºC to 40ºC for 29 h. This resulted in **2** (27.2 kg, 96.4 wt%, 98.4 area%, 85 mol, 94.0% yield) as a white powder. Mp 115.8-116.8 ºC. IR (neat, ATR): 3060 (vw), 1492 (vs), 1462 (s), 1249 (vs), 1160 (s), 1145 (s), 1025 (s), 817 (vs), 791 (s) cm-1. ^{1}H NMR (399 MHz, DMSO-d_6) δ 5.03 (br s, 1H), 5.33 (br s, 1H), 6.64 (dd, J = 10.61, 2.63 Hz, 1H), 6.78 (td, J = 8.37, 2.63 Hz, 1H), 7.13 (s, 1H), 7.36 (dd, J = 8.66, 6.91 Hz, 1H), 7.38 (dd, J = 7.01, 1.95 Hz, 1H), 7.39-7.42 (m, 1H), 7.44 (br td, J = 7.40, 1.40 Hz, 1H), 7.53 (dd, J = 6.76, 1.31 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 69.7, 106.2 (d, J = 24.4 Hz), 107.8, 108.7 (d, J = 21.4 Hz), 121.5 (d, J = 3.1 Hz), 128.4, 129.0, 129.2, 129.2, 132.2 (d, J = 9.9 Hz), 133.5, 140.4, 142.4, 156.2 (d, J = 12.4 Hz), 163.3 (d, J = 245.3 Hz). HRMS: m/z [M+H]+ calcd for $C_{15}H_{11}BrFO$: 304.99718; found: 304.99730.

(*R*)-2-((*tert*-Butoxycarbonyl)amino)propyl methanesulfonate (15). *tert*-butyl (R)-(1-hydroxypropan-2-yl)carbamate, Boc-alaninol, (38.4 kg, 219 mol) was combined with EtOAc (123 L) and Et_3N (44.4 kg, 439 mol), forming a solution. This solution was cooled to 0ºC before methanesulfonyl chloride (30.3 kg, 264 mol) in EtOAc (38 L) was added over 6 h, maintaining -5ºC to +5ºC. After the addition was complete, the mixture was stirred for 2 h. Assay showed 0.04% Boc-alaninol remaining. The mixture was adjusted to 15ºC before the reaction was quenched with 7% aq $NaHCO_3$ (115 L). While maintaining 5ºC to 15ºC, the phases were separated, and the organic phase was washed twice with brine (154 L). The organic phase was kept < 10ºC, dried over Na_2SO_4 (50 kg) and filtered, rinsing with EtOAc (38 L).

***tert*-Butyl (*R*)-(1-morpholinopropan-2-yl)carbamate (16).** To the solution of **15** was added morpholine (116 kg, 1330 mol). This solution was heated to 52ºC to 55ºC for 16 h. Assay showed no **15** remaining. The solution was cooled to 20ºC to 25ºC, before it was washed twice with 10% brine (154 L). The organic phase was concentrated (77 L – 115 L) at < 30ºC and utilized as a solution in the next step.

(*R*)-1-Morpholinopropan-2-amine dihydrochloride (17). The solution of **16** was cooled to 0ºC to 5ºC before HCl in EtOAc (41 kg) was added over 4 h, maintaining 0ºC to 5ºC. After stirring for 20 h at 0ºC to 5ºC, assay showed 0.4% **16**. MTBE (162 L) was added over 3.5 h. While at 0ºC to 3ºC, the slurry was stirred for 5 h, before it was filtered, washed with MTBE (39 L), and dried at 50ºC to 55ºC, resulting in **17** (28.6 kg, 132 mol, 60.2% yield over the three steps). ^{1}H NMR (399 MHz, acetonitrile-d_3) δ 1.39 (d, J = 6.71 Hz, 3H), 3.12-3.18 (m, 2H), 3.28 (br dd, J = 14.60, 3.70 Hz, 3H), 3.49 (dd, J = 14.45, 8.51 Hz, 1H), 3.81-3.86 (m, 1H), 3.87-3.94 (m, 2H). ^{13}C NMR (100 MHz, acetonitrile-d_3) δ 17.7, 43.5, 44.2, 53.9, 60.7, 64.5, 64.6. HRMS: m/z [M+H]+ calcd for $C_7H_{17}N_2O$: 145.13354; found: 145.13335.

(*R*)-4-Bromo-N-(1-morpholinopropan-2-yl)-2-nitroaniline oxalate (18). Compound **17** (18.3 kg, 84 mol), calcium chloride (8.9 kg, 80 mol), 5-bromo-2-fluoronitrobenze, 18.8 kg, 85 mol), EtOAc (182 L), and Et_3N (34.4 kg, 340 mol) were combined and heated to 72ºC for 26 h. Assay showed 0.1% **17** remaining. The mixture was cooled to 20ºC to 25ºC and filtered. The filtrate was washed with 20% aq NH_4Cl (73 L) four times. Oxalic acid (8.5 kg, 94 mol) was dissolved in 2-methyltetrahydrofuran (38 L) and added over 0.7 h to the product solution at 20ºC. This slurry was stirred at 20ºC for 20 h, before it was filtered. The wet cake was dried at 40ºC to 45ºC for 16 h, resulting in **18** (27.6 kg, 94.7 wt%, 60 mol, 71.2% yield). Mp 191.7-192.2 ºC. IR (neat, ATR): 3363 (w), 1617 (s), 1518 (s), 1280 (s), 1176 (s), 1154 (s), 1133 (s) cm-1. ^{1}H

NMR (399 MHz, DMSO-d_6) δ 1.20 (t, J = 7.10 Hz, 3H), 4.15 (q, J = 7.10 Hz, 2H), 5.35 (s, 2H), 6.55 (d, J = 15.86 Hz, 1H), 6.80 (td, J = 8.47, 2.82 Hz, 1H), 7.30 (dd, J = 11.00, 2.72 Hz, 1H), 7.44 (quind, J = 7.25, 1.46 Hz, 2H), 7.60 (t, J = 6.62 Hz, 1H), 7.61 (d, J = 6.42 Hz, 1H), 7.84 (dd, J = 7.35, 1.41 Hz, 1H), 7.94 (d, J = 15.86 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d6) δ 18.7, 44.9, 53.0, 61.9, 65.3, 105.4, 117.5, 128.0, 131.8, 138.8, 143.5, 162.1. HRMS: m/z [M+H]+ calcd for $C_{13}H_{19}BrN_3O_3$: 344.06043; found: 344.06041.

(*E*)-2-((3-Fluorodibenzo[b,e]oxepin-11(6H)-ylidene)methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4). Compound **2** (33.0 kg, 96.4 wt%, 104 mol), bis(pinacolato)diboron (30.5 kg, 120 mol), and dioxane (279 L) were combined and stirred until all the solids dissolved. Tricyclohexylphosphine (1.9 kg, 6 mol), KOAc (11.7 kg, 119 mol), $Pd_2(dba)_3$ (1 kg, 1.0 mol), and water (0.16 kg, 8.8 mol) were added. The mixture was heated at 80ºC to 85ºC for 27 h, resulting in 8% residual **2**. The mixture was cooled to 20ºC to 30ºC, filtered, washing the wet cake with dioxane (59 L). Assay of the filtrate showed that it contained **4** (30.4 kg, 86 mol, 83% yield).

(*R*,*E*)-4-((3-Fluorodibenzo[b,e]oxepin-11(6H)-ylidene)methyl)-*N*-(1-morpholinopropan-2-yl)-2-nitroaniline (6). To the solution of compound **4** was added K_2CO_3 (39.4 kg, 285 mol), water (140 L), and **18** (43.1 kg, 94.7 wt%, 94 mol). The mixture was stirred for 0.5 h before PPh_3 (0.07 kg, 0.27 mol) and $Pd(OAc)_2$ (0.195 kg, 0.87 mol) were added. The mixture was heated at 80ºC to 85ºC for 24 h. Assay showed 0.05% **4** remaining. After cooling to 20ºC to 30ºC, the mixture was diluted with EtOAc (334 L) and brine (92 L). After stirring for 1 h, the mixture was filtered, washing the wet cake with EtOAc (50 L). The organic phase was separated. The aqueous phase was extracted with EtOAc (60 L). The organic phases were combined and concentrated. MTBE (176 L) was added, and the mixture concentrated . This

was repeated with additional MTBE (136 L) and concentrating. MTBE (312 L) was added. Assay showed 4.5% dioxane remaining in the organic phase. The mixture was stirred for 8 h at 20ºC to 30ºC, before the mixture was filtered, washing the wet cake with MTBE (48 L). The wet cake was dried at 45ºC to 50ºC for 16 h, resulting in **6** (30.2 kg, 94.9 wt%, 98.4 area%, 58 mol, 56.2 % yield across the two steps) as a brown solid. ^{1}H NMR (399 MHz, DMSO-d_6) δ 1.15 (d, J = 6.13 Hz, 3H), 2.38 (br t, J = 3.94 Hz, 4H), 2.40-2.47 (m, 2H), 3.50 (br t, J = 4.38 Hz, 4H), 3.90 (quin, J = 6.54 Hz, 1H), 4.93-5.15 (m, 1H), 5.50-5.70 (m, 1H), 6.61 (dd, J = 10.61, 2.63 Hz, 1H), 6.80 (td, J = 8.37, 2.72 Hz, 1H), 6.89 (d, J = 9.24 Hz, 1H), 6.93 (s, 1H), 7.02-7.09 (m, 2H), 7.28 (td, J = 7.54, 1.07 Hz, 1H), 7.35-7.42 (m, 1H), 7.57-7.63 (m, 2H), 7.86 (d, J = 1.95 Hz, 1H), 8.18 (br d, J = 6.62 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 18.8 (s), 45.2 (s), 53.6 (s), 63.0 (s), 66.2 (s), 69.6 (s), 105.5 (br d, J=24.4 Hz), 108.1 (br d, J=21.4 Hz), 114.7 (br s), 123.5 (s), 123.7 (d, J = 3.1 Hz), 126.8 (s), 127.4 (s), 128.1 (s), 128.4 (s), 128.9 (s), 129.4 (s), 130.5 (s), 131.1 (br d, J = 9.2 Hz), 133.7 (s), 136.3 (s), 136.8 (br s), 141.1 (s), 143.6 (s), 156.0 (d, J = 12.2 Hz), 162.3 (d, J = 243.8 Hz). HRMS: m/z [M+H]+ calcd for $C_{28}H_{29}FN_3O4$: 490.21366; found: 490.21238.

(*R,E*)-4-((3-Fluorodibenzo[b,e]oxepin-11(6H)-ylidene)methyl)-N1-(1-morpholinopropan-2-yl)benzene-1,2-diamine (7). Compound **6** (29.5 kg, 94.9 wt%, 57 mol), EtOAc (297 L), Et_3N (0.6 kg, 5 mol) and 5% Pt-C (1.5 kg, 0.4 mol) were combined, degassed twice with N_2 and once with H_2, before being placed under 50 – 55 psi H_2 and heating to 40ºC to 45ºC for 20 h. Assay showed no **6** remaining. The mixture was cooled to 20ºC to 30ºC before the mixture was filtered, rinsing the wet cake with EtOAc (74 L). Assay of the filtrate showed that it contained **7** (26.0 kg, 56 mol, 99% yield). IR (neat, ATR): 3302 (w br), 1516 (s), 1493 (s), 1299 (s), 1140 (s), 1116 (s), 1069 (s) cm-1. ^{1}H NMR (399 MHz, DMSO-d_6) δ 1.07 (d, J = 6.13 Hz, 3H), 1.16 (t,

J = 7.10 Hz, 1H), 1.98 (s, 1H), 2.19 (br dd, *J* = 12.12, 7.15 Hz, 1H), 2.25-2.46 (m, 5H), 3.44-3.57 (m, 1H), 3.52 (t, *J* = 4.57 Hz, 3H), 4.02 (q, *J* = 7.10 Hz, 1H), 4.32 (s, 1H), 4.34 (br d, *J* = 6.62 Hz, 1H), 4.99 (br s, 1H), 5.53 (br s, 1H), 6.17 (dd, *J* = 8.37, 1.65 Hz, 1H), 6.23 (d, *J* = 8.47 Hz, 1H), 6.32 (d, *J* = 1.75 Hz, 1H), 6.56 (dd, *J* = 10.61, 2.63 Hz, 1H), 6.67 (s, 1H), 6.75 (td, *J* = 8.34, 2.68 Hz, 1H), 7.10 (d, *J* = 6.91 Hz, 1H), 7.26 (td, *J* = 7.52, 1.12 Hz, 1H), 7.33 (td, *J* = 7.42, 1.12 Hz, 1H), 7.46 (dd, *J* = 8.66, 7.01 Hz, 1H), 7.54 (d, *J* = 7.30 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.1 (s), 19.3 (s), 20.7 (s), 44.8 (s), 53.6 (s), 59.7 (s), 63.9 (s), 66.2 (s), 69.5 (s), 105.3 (d, *J* = 24.0 Hz), 107.9 (d, *J* = 21.0 Hz), 109.6 (s), 115.6 (s), 119.5 (s), 124.6 (s), 124.9 (d, *J* = 3.1 Hz), 127.7 (d, *J* = 5.0 Hz), 128.6 (s), 129.0 (s), 130.8 (d, *J* = 9.5 Hz), 131.3 (s), 132.4 (s), 133.3 (s), 134.7 (s), 134.9 (s), 142.3 (s), 155.7 (d, *J* = 11.8 Hz), 161.9 (d, *J* = 243.4 Hz. HRMS: m/z [M+H]+ calcd for $C_{28}H_{31}FN_3O_2$: 460.23948; found: 460.23868.

***N*-((*E*)-5-((*E*)-(3-Fluorodibenzo[b,e]oxepin-11(6H)-ylidene)methyl)-1-((*R*)-1-morpholinopropan-2-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-ylidene)cyanamide (8).** To the filtrate of **7** was added diphenyl *N*-cyanocarbonimidate (14.5 kg, 60 mol). The mixture was heated at reflux (76ºC) for 18 h. Assay showed 0.3% **7** remaining. The mixture was cooled to 20ºC to 30ºC and concentrated. MTBE (159 L) was added, and the mixture concentrated again. MTBE (562 L) was added. Assay showed 1.5% EtOAc remaining. The mixture was stirred for 8 h, before the slurry was filtered, washing the wet cake with MTBE (43 L). The wet cake (25.75 kg) was combined with CH_2Cl_2 (426 L) and stirred until a solution resulted. Silica thiol (1.51 kg, 0.058 g / g **7**) was added. The mixture was heated to 40ºC to 45ºC for 5 h, before the mixture was cooled to 20ºC to 30ºC and filtered, washing the wet cake with CH_2Cl_2 (30 L). The filtrate was concentrated MTBE (150 L) was added. This mixture was concentrated before MTBE (566 L) was added. Assay showed 2.4% CH_2Cl_2. The slurry was stirred at 20ºC to 30ºC

for 10 h and filtered, washing the wet cake with MTBE (81 L). The wet cake was dried at 45ºC to 50ºC for 14 h, resulting in **8** (23.4 kg, 99.4 wt%, 45 mol, 79.6% yield across the two steps) as an off-white solid. Mp 227.8-231.5 ºC. IR (neat, ATR): 2182 (s), 1637 (s), 1615 (s) cm-1. ^{1}H NMR (399 MHz, DMSO-d_6) δ 1.38 (d, J = 6.91 Hz, 3H), 2.12-2.23 (m, 2H), 2.40-2.47 (m, 2H), 2.93 (br dd, *J* = 12.80, 10.07 Hz, 1H), 3.31 (s, 2H), 3.33-3.39 (m, 4H), 4.58-4.75 (m, 1H), 5.06 (br s, 1H), 5.60 (br s, 1H), 6.62 (dd, *J* = 10.51, 2.63 Hz, 1H), 6.80 (td, *J* = 8.37, 2.63 Hz, 1H), 6.84-6.93 (m, 2H), 7.00 (d, *J* = 7.40 Hz, 1H), 7.02 (s, 1H), 7.25 (td, *J* = 7.54, 0.97 Hz, 1H), 7.34 (d, *J* = 8.47 Hz, 1H), 7.39 (td, *J* = 7.52, 1.02 Hz, 1H), 7.56-7.66 (m, 2H), 7.56-7.66 (m, 2H), 12.51 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 15.9, 47.2, 53.2, 59.9, 66.1, 69.5, 105.5 (br d, *J* = 24.0 Hz), 108.1 (br d, *J* = 21.2 Hz), 110.2, 110.7, 117.5, 123.9 (d, *J* = 2.9 Hz), 124.2, 127.4, 128.4, 128.8, 129.3, 129.8, 130.7, 131.2 (br d, *J* = 9.7 Hz), 133.5, 136.9, 141.2, 154.1, 156.0 (d, *J* = 12.0 Hz), 162.3 (d, *J* = 244.1 Hz). HRMS: m/z [M+H]+ calcd for $C_{30}H_{29}FN_5O_2$: 510.22998; found: 510.22876.

1-((*E*)-5-((*E*)-(3-Fluorodibenzo[b,e]oxepin-11(6H)-ylidene)methyl)-1-((*R*)-1-morpholinopropan-2-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-ylidene)urea (1). Compound **8** (23.0 kg, 99.4 wt%, 44 mol) was combined with CH_2Cl_2 (68 L), resulting in a slurry. Water (19 L) was added, and the slurry cooled to 0ºC to 5ºC. Trifluoroacetic acid (107 kg, 938 mol) was added over 2.5 h, maintaining 0ºC to 5ºC. The mixture was warmed to 20ºC to 25ºC and stirred for 4 h. Assay showed no compound **8** remaining. CH_2Cl_2 (229 L) was added, and the mixture cooled to 0ºC to 10ºC. While maintaining this temperature, 5 N aq NaOH (172 kg, 141 L, 705 mol) was added, adjusting the pH to 8 to 9, resulting in an emulsion. The mixture was warmed to 20ºC and brine (100 L) was added, removing the emulsion. The organic phase was separated. The aq phase was extracted with CH_2Cl_2 (96 L). The organic phases were combined, washed

with brine (100 L), and dried over Na_2SO_4 (46 kg, 2 g / g, **8**) by stirring for 4 h, resulting in a K.F. of 0.08%. The mixture was filtered, washing the wet cake with CH_2Cl_2 (27 L). While maintaining < 35ºC, the mixture was concentrated. EtOAc (124 L) was added, and the mixture concentrated. More EtOAc (127 L) was added, and the mixture was concentrated. EtOAc (110 L) was added to adjust to the total volume. Assay showed 400 ppm CH_2Cl_2. Therefore, the mixture was concentrated before EtOAc (106 L) was added to adjust the total volume. Assay now showed 30 ppm CH_2Cl_2. The mixture was adjusted to 0ºC to 10ºC and stirred for 2 h. Seed (200 g, 0.9 wt% seed) was added, and the mixture stirred at 0ºC to 10ºC for 12 h. The mixture was concentrated and stirred for 2 – 3 h at 0 – 10ºC, and filtered, washing the wet cake with EtOAc (39 L). The wet cake was dried at 45ºC to 50ºC for 37 h, resulting in **1** (21.2 kg, 99 wt%, 99.5 area%, 1.04% EtOAc, 39 mol, 88.6% yield) as an off-white solid. Mp 200.8-207.8 ºC. IR (neat, ATR): 3468 (vw br), 1697 (vs), 1581 (vs), 1491 (vs), 1437 (s) cm-1. ^{1}H NMR (399 MHz, DMSO-d_6) δ 1.38 (br d, J = 6.91 Hz, 1H), 1.43 (d, J = 6.81 Hz, 2H), 2.17-2.29 (m, 2H), 2.36-2.47 (m, 1H), 2.62 (dd, J = 13.38, 5.01 Hz, 1H), 2.78 (dd, J = 13.33, 7.88 Hz, 1H), 3.34-3.40 (m, 1H), 3.41-3.50 (m, 3H), 4.72-4.85 (m, 1H), 4.86-4.97 (m, 1H), 4.99-5.17 (m, 1H), 5.48-5.72 (m, 1H), 5.87-6.10 (m, 1H), 6.61 (dd, J = 10.51, 2.63 Hz, 1H), 6.80 (td, J = 8.30, 2.68 Hz, 2H), 6.94-7.09 (m, 3H), 7.23 (br t, J = 7.54 Hz, 1H), 7.30-7.41 (m, 2H), 7.54-7.62 (m, 2H), 9.93 (s, 1H), 11.72 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 16.7, 17.3, 49.2, 53.8, 54.1, 61.3, 66.4, 66.6, 70.1, 105.9 (d, J = 24.4 Hz), 108.5 (d, J = 21.0 Hz), 111.0, 118.0, 124.7 (d, J = 2.6 Hz), 128.0, 128.6, 129.3, 129.7, 130.1, 131.3, 131.5 (br d, J = 9.5 Hz), 131.6, 134.0, 136.1, 136.6, 140.9, 142.2, 149.6, 155.2, 156.4 (d, J = 11.8 Hz), 162.7 (br d, J = 243.8 Hz), 165.1. HRMS: m/z [M+H]+ calcd for $C_{30}H_{31}FN_5O_3$: 528.24054; found: 528.23986.

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SUPPORTING INFORMATION

Supplementing information include a general preparative experimental conditions, ^{1}NMR and ^{13}NMR for compounds **1**, **2**, **6**, **7**, **8**, **9**, **10**, **14**, **17**, and **18**. IR spectrum for compounds **1**, **2**, **7**, **8**, **9**, **10**, **14**, and **18** are also included as supplementing information.

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