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Process Development of a Potent Bradykinin 1 Antagonist

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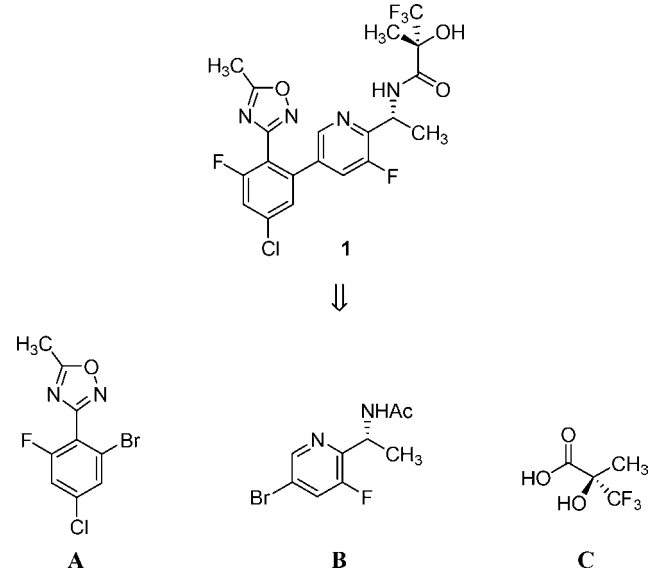
Abstract:

As part of Merck's continued research effort on inflammation and pain, a safe synthesis of an orally bioavailable and CNS penetrant bradykinin 1 antagonist was developed and demonstrated on kilogram scale. The key step included a novel regioselective metal−halogen exchange reaction on 1,2-dibromo-5-chloro-3-fluorobenzene using isopropyl magnesium chloride to install the 1,2,4-oxadiazole ring structure. Suzuki cross-coupling reaction between a highly functionalized and sterically hindered electrophile and boronic ester generated the biaryl ring system, which was converted to the target molecule (1) using standard chemistry. The safe installation of a 1,2,4-oxadiazole ring proved to be challenging since the original synthetic route relied on the preparation of a highly functionalized benzonitrile using potassium cyanide and resulted in low yields and large amounts of potentially hazardous waste. Overall, a safe and robust synthesis was developed, which occurred in eight linear steps with an overall yield of 28%.

Introduction

Kinins play an important role in the pathophysiological processes of pain and inflammation.[1] Bradykinin and kallidin, two peptide agonists, are known to interact selectively with the kinin receptor B2, while desArgBradikinin and desArgKallidin act on kinin receptor B1. Many study results indicate that the B1 receptor is involved in inflammatory pain and neutrophil infiltration through activation of a cytokine network.[2−4] A highly selective and potent B1 receptor antagonist could block hyperalgesia as shown in animal models. A series of biphenylaminocyclopropane carboamide bradykinin B1 receptor antagonists were discovered and evaluated.[5] The structurally related phenylpyridine (**1**)[6]was recently targeted for clinical development and required the preparation of multikilogram quantities. Faced with a short development timeline, it was important to quickly identify a robust synthetic route which provided multikilogram quantities.

Scheme 1. **Retrosynthetic analysis of target molecule (1)**



Envisioning a convergent route to the target, **1** could be synthesized from three fragments (**A**−**C**) as depicted in Scheme 1. Our process research efforts focused on the development of an efficient, safe, and robust synthetic route for the synthesis of fragment **A** and the coupling reactions between fragments **A**−**C**. The union of **A** and **B** could be envisioned by a transition metal-catalyzed cross-coupling reaction, followed by a typical amide bond formation with fragment **C**. The convergent coupling strategy minimized the consumption of the enantiomeric enriched fragments **B** and **C** and avoided a transition metal-catalyzed reaction in the last step of the synthesis.

Results and Discussion

Synthesis of Oxadiazole Fragment A. We faced the challenge to regioselectively install a [1,2,4]-oxadiazole ring system on a highly functionalized halogenated benzene ring. After an extensive literature search and bearing the coupling

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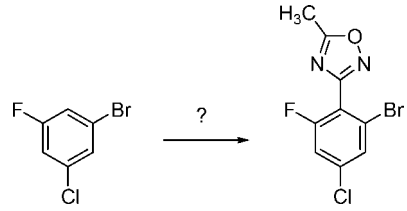
Scheme 2. **Regioselective functionalization of 5-bromo-3-chloro-1-fluorobenzene (2)**



2 **A**

strategy in mind, we realized that an efficient synthesis could be derived by the regioselective functionalization of the halogenated compound (**2**, Scheme 2) and the sequential preparation of the 1,2,4-oxadiazole moiety.

Nitrile Route. First we envisioned that the inexpensive and readily available aniline (**3**) could be converted to nitrile (**4**) by a Sandmeyer reaction as depicted in Scheme 3. In the presence of $NOBF_4$, 2-bromo-4-chloro-6-fluoroaniline (**3**) was converted to the diazonium ion which resulted in the formation of the benzonitrile (**4**) in 45−70% yield upon the addition of CuCN and $Cu(BF_4)_2$ in dichloromethane. After an extractive workup and concentration, the residue was purified by distillation at 120 °C @ 9 Torr to afford a pale-yellow solid. After dissolving the solid in butanol, the nucleophilic attack of hydroxylamine at the nitrile carbon atom led to a 9:1 mixture of amidoxime (**5**) and amide (**6**). All attempts failed to improve the product ratio, and extensive investigations of the experimental conditions revealed that the amidoxime/amide ratio strongly depended on the chemical purity, metal content of the starting nitrile (**4**), and the choice of solvent. Finally, the amidoxime (**5**) was condensed to the 1,2,4-oxadiazole derivative (**A**) by using dimethylacetamide dimethylacetal (DMADMA) at 22 °C in 20−30% overall yield starting from the aniline (**3**).

Our investigations of this synthetic route disclosed several major challenges for large-scale production, which included: (I) the evolution of large quantities of nitrogen, (II) evolution of HCN under pH 1 reaction conditions, (III) evolution of NO_x off-gases, (IV) low yield of nitrile (**4**), which strongly depended on the rate of copper tetrafluoroborate addition, (V) distillation of the nitrile on scale was not practical, and (VI) amidoxime/amide ratio was highly dependent on the chemical purity and residual metal level of the nitrile (**4**) and was in favor of the undesired amide (**6**) on multigram scale. In this light an alternative and less hazardous route was developed for scale.

Regioselective Halogen−Metal Exchange Route. A major challenge in the synthesis of **A** is the regioselective synthesis of the tetrasubstituted benzene ring. Instead of developing an electrophilic aromatic substitution, an alternative approach was explored: a previously reported regioselective halogen−metal exchange of 1,2-dibromobenzene derivatives[7−9] was investigated by trapping the metalated benzene derivative with a carbonyl compound such as dimethylformamide as outlined in Scheme 4. This synthetic route was evaluated and found to be more efficient and safer with respect to large-scale operations compared to the route shown in Scheme 3.

Following a modified procedure for the Sandmeyer reaction,[10] aniline (**3**) was converted to the 1,2-dibromobenzene derivative (**7**) in the presence of $NOBF_4$ and $CuBr_2$ in a 91% assay yield.[11] The regioselective metal−halogen exchange on **7** was optimized for iPrMgCl (1.2 equiv) in tetrahydrofuran at −40 °C followed by the addition of dimethylformamide. Upon aqueous workup at pH 1, benzaldehydes (**8** and **9**) could be obtained in 95% assay yield[9] as a 97:3 mixture in methyl *tert*-butyl ether.[12] In agreement with the literature, the bromide at C-1 of compound **7** was preferentially exchanged due to the position of the electron-withdrawing fluoride in the ring.

After a solvent switch to 2-propanol for the subsequent step, benzaldehydes (**8** and **9**) were treated with an aqueous solution of hydroxylamine (50%, 1.1 equiv) at 40 °C.[13] The expected benzaldehyde oxime (**10**) crystallized upon the addition of water and afforded an off-white crystalline material (98.8 area %) in 75% overall yield from (**3**). We were pleased to observe that the undesired regioisomeric oxime, which was formed from **9**, was rejected in that crystallization step. Oxime (**10**) was converted to the amidoxime (**5**) in a two-step process. To this end, a solution of **10** in dimethylformamide was treated with a solution of *N*-chlorosuccinimide (1.05 equiv) in dimethylformamide at 50 °C to afford the imidoyl chloride derivative.[13] The resultant dimethylformamide solution of imidoyl chloride was transferred into a cooled aqueous solution of ammonium hydroxide (30%, 3.0 equiv) to provide amidoxime (**5**) in 90% assay yield.[11] Follow-up experiments suggested that, during the temperature controlled addition of the imidoyl chloride to the aqueous ammonium hydroxide solution, a succinimide adduct was formed as the major side product up to 5%.[14] We were pleased to find that this side product could be completely removed during the isolation of fragment **A**. After aqueous workup and solvent switch to 2-propanol, amidoxime (**5**) was treated with DMADMA at 20 °C for 90 min to afford fragment **A** in 89% assay yield,[15,16] which crystallized out of a 2-propanol solution by the addition of water. Upon a final 2-propanol/water ratio of 1:1.75, an optimized balance between rejected color and mother liquor losses was obtained. After filtration and drying, fragment **A** was afforded as an off-white solid (45% isolated yield over six steps; LCAP:[17] 99.0%, LCWP:[17] 99.8%; K_f = 229 ppm; ^{1}H NMR: traces of IPA; DSC: 83.2 °C, TGA: 0.2% losses).

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(10) de Lang, R.-J.; van Hooijdonk, M. J. C. M.; Brandsma, L.; Kramer, H.; Seinen, W. *Tetrahedron* **1998**, *54*, 2953.
(11) As determined by HPLC versus a standard isolated, purified, and characterized by ^{1}H- and ^{13}C NMR.
(12) Interestingly, in contrast to Burton's observation, in which a rearrangement reaction of a lithiated anion in the 3-position of 1,2,4-trichlorobenzene occured after trapping and aging the reaction mixture in the presence of DMF, a similar observation with the Grignard reagent was not observed. Burton, A. J.; Cardwell, K. S.; Fuchter, M. J.; Lindvall, M. K.; Patel, R.; Packham, T. W.; Prodger, J. C.; Schilling, M. B.; Walker, M. D. *Tetrahedron Lett.* **2003**, 5653.
(13) Liu, K.-C.; Shelton, B. R.; Howe, R. K. *J. Org. Chem.* **1980**, 3916.
(14) Succinimide side product of **10** was proposed by mass spectrometric analysis and is believed to be 1-((2-bromo-4-chloro-6-fluoro-phenyl)-[(*E*)-hydroxyimino]methyl)pyrrolidine-2,5-dione.
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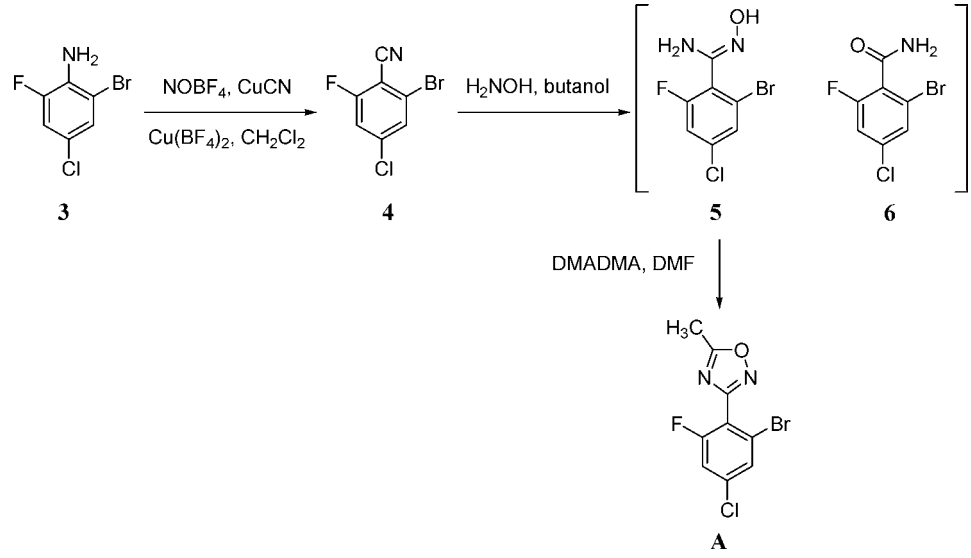
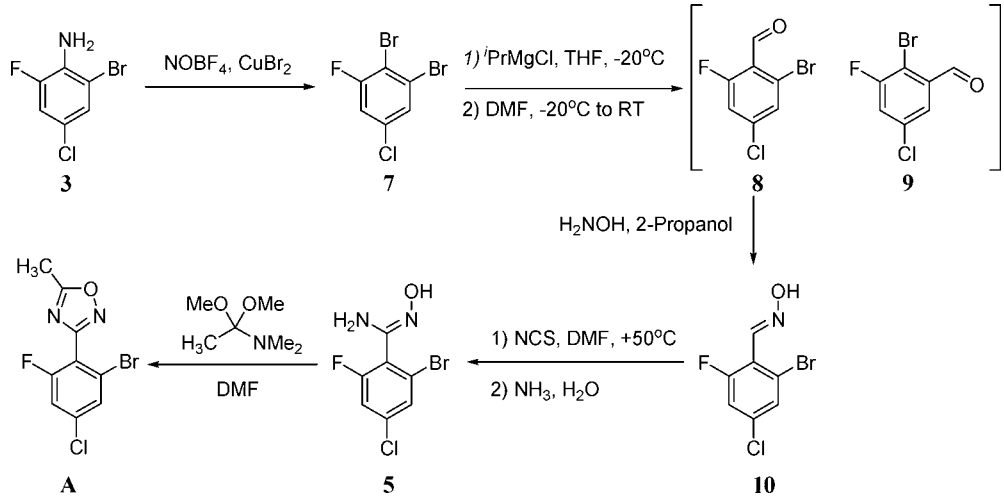
(16) Botta, A. *Justus Liebigs Ann. Chem.* **1978**, 306.
(17) LCAP: HPLC area percent; LCWP: HPLC weight percent.

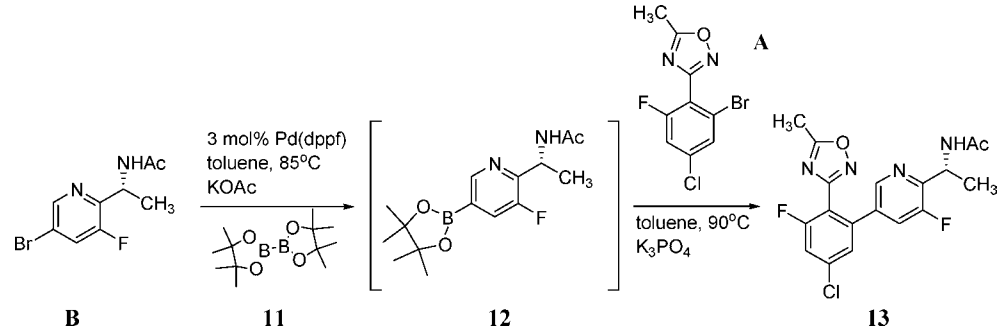
Scheme 3. **Original synthetic route for the preparation of fragment A**



Scheme 4. **Final synthetic route for the preparation of fragment A via regioselective halogen−metal exchange**



Scheme 5. **Cross-coupling reaction between fragment A and B**



Cross-Coupling Reaction between Fragments A and B. The synthesis of the chiral pyridine fragment **B** has been recently reported[18,19] and was available on multikilogram quantities. As outlined in Scheme 5, our strategy involved the cross-coupling between fragments **A** and **B**. A robust palladium-mediated cross-coupling reaction to form the biaryl system had to be developed. We explored a variety of reaction conditions for the conversion of fragment **B** into a nucleophilic coupling partner, including a potassium trifluoroboronate salt and subsequent cross-coupling reaction under standard reaction conditions.[20] However, due to the liberation of HF which caused corrosion of stainless steel and glassware, this method was not further pursued, although it provided a reliable process for the formation of a single boron species. A robust process suitable

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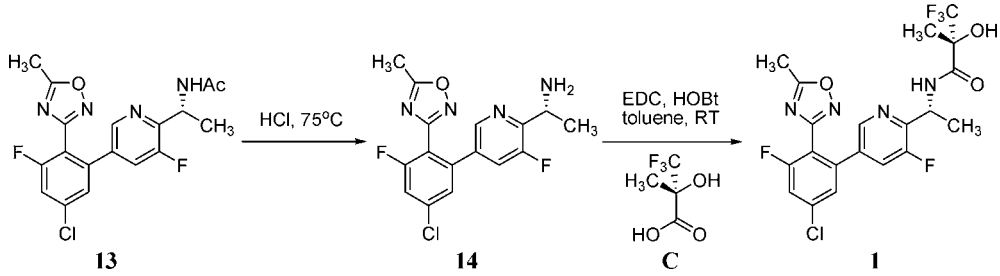
Scheme 6. **API formation**



for scale-up was then discovered by converting the pyridine into a boronic ester via a palladium-mediated cross-coupling reaction using bis-pinacol diboron (**11**).[21] The catalyst, ligand, additives, solvents, and temperature had been optimized to support a one-pot reaction between fragments **A** and **B**. The initial step required 3 equiv of anhydrous potassium acetate and 3 mol % of Pd(dppf) in toluene at 85 °C to form the boronic ester (**12**) quantitatively (based on assay yield) after 12 h. The cross-coupling reaction was completed by the addition of aqueous potassium phosphate (1 M; 2 equiv) and the oxadiazole fragment **A** (1.05 equiv) in toluene at 90 °C. After 16 h, an aqueous workup provided the crude biaryl derivative as a toluene stream in 87% assay yield. The toluene phase was passed through solka floc to remove black precipitation and was treated with 50 wt % Ecosorb C-941 for 15 h at room temperature to reduce color. After filtration, the crystallization of **13** was initiated by the addition of heptane. A final 2:1 mixture of toluene to heptane minimized the losses to the mother liquor and afforded **13** in 78% isolated yield.

Formation of Penultimate Compound and API. Although the hydrolysis of acetamide **13** seemed to be straightforward, improvements in yield and impurity profile were highly desirable, since the original procedure provided **14** in low purity and 75% assay yield using 2 equiv of aqueous 1 M hydrochloric acid in tetrahydrofuran. In our efforts to identify suitable reaction conditions, 10 equiv of aqueous 2 M hydrochloric acid converted acetamide (**13**) in 9 h at 75 °C to the free amine (**14**) as depicted in Scheme 6 in high purity and yield. After aqueous workup, the amine was isolated in 85% yield as a toluene stream. Under standard amide bond-formation conditions, target molecule (**1**) was synthesized by suspending 1.5 equiv of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride in the toluene stream of amine **14** at room temperature. This suspension was charged with a solution of hydroxyl benzotriazole (0.25 equiv) and (*R*)-hydroxy acid **C**[22] (1.0 equiv) in tetrahydrofuran. It was necessary to follow this order of addition to avoid a self-coupling process of (*R*)-hydroxy acid (**C**), which would result in the formation of dimers and oligomers that could ultimately couple with the amine to form side products. An aqueous workup removed the coupling reagents, and the solvent was switched to toluene. The product crystallized from a toluene/heptane mixture of 1:1.5, which minimized the losses to the mother liquor to 3.5%. The final product was filtered and dried at room temperature, which afforded 2.98 kg of **1** as a white solid in an 89% yield.

Conclusion

The bradykinin antagonist **1** was synthesized in multikilogram quantities by a convergent route from readily available starting materials. The synthesis of fragment **A** was achieved by a regioselective halogen−metal exchange reaction of 1,2-dibromobenzene, **7**. The subsequent coupling sequence involved three steps with two isolations and 65% overall yield. Upon scale-up the synthesis was robust, safe, and efficient in producing **1** in high purity that could be used for clinical studies.

Experimental Section

Reactions were performed under N_2 atmosphere and monitored by HPLC. NMR spectra were obtained at 25 °C in $CDCl_3$, and the field strengths for the various nuclei were as follows: ^1H (700 and 300 MHz), ^{13}C (176 and 75 MHz). Achiral chromatography was conducted using a YMC-Pack Pro C18 HPLC column (4.6 mm ID × 250 mm, 5 μm). The mobile phase consisted of A: 1% perchloric acid in deionized water and B: acetonitrile. The analytes were eluted using a linear gradient from 10 to 90% B over 25 min at a flow rate of 1 mL/min at room temperature. The analytes were observed by UV absorption at 220 nm. Chiral chromatography was performed using a Chiralcel OD-H column (4.6 mm ID × 250 mm, 5 μm). The mobile phase consisted of A: isopropanol and B: hexane. The analyte was eluted using a linear gradient from 5−30% A over 30 min at a flow rate of 0.75 mL/min at room temperature. The analytes were observed by UV absorption at 220 nm.

1-(2-Bromo-4-chloro-6-fluorophenyl)-*N*-hydroxymethanimine (10) via 1,2-Dibromo-5-chloro-3-fluorobenzene[23] (7) and 2-Bromo-4-chloro-6-fluorobenzaldehyde (8). 2-Bromo-4-chloro-6-fluoro aniline (14.5 kg, 64.6 mol) was dissolved in acetonitrile (102.6 kg) at 20 °C. Nitrosonium tetrafluoroborate (9.81 kg, 84.0 mol) was added to the reactor in four equal portions at 0 °C, so that the temperature was maintained at 0 °C before the next portion was added. After the fourth addition, the reaction mixture was aged for 0.5 h at 0 °C. Acetonitrile (64.8 kg) and copper (II) bromide (15.9 kg, 71.2 mol) were combined and stirred for 20 min at 20 °C before the solution was transferred to the 2-bromo-4-chloro-6-fluoro aniline con-

(21) Selected references for the metal-mediated couplings of pyridine-containing structures: Hartung, C. G.; Fecher, A.; Chapell, B.; Snieckus, V. *Org. Lett.* **2003**, 1899. Spivey, A. C.; Zhu, F.; Mitchell, M. B.; Davey, S. G.; Jarvest, R. L. *J. Org. Chem.* **2003**, 7379.

(22) The acid **C** was commercially available on kilogram scale from Lonza. Shaw, N. M.; Naughton, A.; Robins, K.; Tinschert, A.; Schmid, E.; Hischier, M.-L.; Venetz, V.; Werlen, J.; Zimmermann, T.; Brieden, W.; Riedmatten, P.; de Roduit, J.-P.; Zimmermann, B.; Neumuller, R. *Org. Process Res. Dev.* **2002**, *6*, 497.

(23) 1-Chloro-3,4-dibromo-5-fluorobenzene is commercially available from Acros.

taining reaction mixture so that the batch temperature was maintained below 5 °C. After completed addition the reaction mixture was aged for one hour at 0 °C, before the reaction mixture was warmed to 20 °C and aged for another 4 h. Water (87 kg) and heptane (49.5 kg) were added sequentially to the slurry at 20 °C. The organic phase was collected, and the aqueous phase was extracted with heptane (49.5 kg). After separation of the aqueous phase, the combined organic phases were washed with aqueous 2 M hydrochloric acid solution (43.5 kg). The organic phase was concentrated by distillation to an approximated volume of 44 L (~16.0 kg of **7**, 91% assay yield; 97.5 LC area %, HPLC retention time: 20.3 min). ^{1}H NMR ($CDCl_3$, 700 MHz): δ 7.44 (dd, J = 2.38, 1.81 Hz, 1H); 7.10 (dd, J = 7.91, 2.40 Hz, 1H); ^{13}C NMR ($CDCl_3$, 176 MHz): δ 159.5 (d, J = 228.9 Hz, 1C), 134.4, 128.9, 126.6, 115.9, 111.8.

The heptane solution of **7** (44 L, 16.0 kg, 55.5 mol) was diluted with tetrahydrofuran (71.0 kg). After cooling the reaction mixture to −45 °C, isopropylmagnesium chloride solution (31.8 kg; 61.0 mol, 19.8% in tetrahydrofuran) was added over one hour to the reaction mixture so that the temperature was maintained between −45 to −40 °C. The batch was aged for 0.5 h at −40 °C before dimethylformamide (20.3 kg, 278 mol) was added to the reaction mixture over 0.5 h, while the batch temperature was maintained between −45 and −20 °C. The reaction mixture was aged for 0.25 h at −20 °C. Deionized water (187 kg), aqueous concentrated hydrochloric acid (21.1 kg), and methyl *tert*-butylether (106.6 kg) were combined. The mixture was cooled to 5 °C before the aldehyde-containing reaction mixture was added. The batch temperature was maintained below 5 °C during the addition and upon the completion was warmed to 20 °C. The organic phase was separated, and the aqueous phase was extracted two more times with methyl *tert*-butylether (106.6 kg) each. All combined organic phases were washed sequentially with aqueous 1 M hydrochloric acid (51.2 kg), aqueous 1 M sodium hydrogen carbonate (51.8 kg), and water (50 kg). After the last aqueous phase was separated, the organic phase was concentrated by distillation at reduced pressure to maintain the batch temperature below 40 °C. The product was obtained in 95% assay yield and 93 LC area % (HPLC retention time: 14.3 min). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.98 (s, 1 H), 7.53 (s, 1 H), 7.18−7.27 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.2, 159.7 (d, J = 255 Hz), 138.2, 130.3 (d, J = 7.5 Hz), 125.8, 123.5, 117.3 (d, J = 30 Hz).

A solution of 2-bromo-4-chloro-6-fluorobenzaldehyde (**8**) (13.2 kg, 55.5 mol) in methyl *tert*-butyl ether was charged with 2-propanol (79 kg) and concentrated under reduced pressure and at a batch temperature of below 40 °C. A second 2-propanol charge (48 kg) was added, so that the batch volume was around 96 L. The reaction mixture was charged with 50% aqueous hydroxylamine (4.0 kg) and warmed to 40 °C. After 2 h the batch was charged with water (48 kg) over a period of one hour and the slurry was aged for one hour at 20 °C. The solid was collected by filtration. The wet cake was washed with a mixture of water and 2-propanol (1:1.5; 17 kg, 26 kg, respectively) and dried in a tray dryer (40 °C, 50 Torr) to afford crude 2-bromo-4-chloro-6-fluorobenzaldehyde oxime (10.6 kg, 42.0 mol; 75%; 98.8 LC area %, HPLC retention time: 12.2 min). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.97 (s, 1 H), 8.14 (s, 1 H), 7.76 (s, 1 H), 7.62 (d, J = 10.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.7 (d, J = 255 Hz), 143.1, 134.8, 128.5, 123.8, 119.9 (d, J = 15 Hz), 116.2 (d, J = 23 Hz).

3-(2-Bromo-4-chloro-6-fluorophenyl)-5-methyl-1,2,4-oxadiazole (A) via 2-Bromo-4-chloro-6-fluoro-*N*′-hydroxybenzenecarboximidamide (5). The reaction mixture of **10** (8.5 kg, 33.7 mol) in *N*,*N*-dimethylformamide (16.0 L) was warmed to 50 °C. A solution of 4.72 kg of *N*-chlorosuccinimide (35.4 mol) in 16.1 L of *N*,*N*-dimethylformamide was added slowly to the oxime solution by maintaining the batch temperature between 50 and 60 °C. Upon completed addition, the reaction was monitored by HPLC and provided a typical assay yield of 95% of the imidoyl chloride. The reaction mixture was cooled to 3−5 °C and slowly transferred into 4.1 kg of an ammonium hydroxide solution (2.0 equivalent; 67.3 mol) cooled to 0 °C. The rate of addition was adjusted to maintain the batch temperature below +10 °C. After completed addition the batch temperature was maintained between 0 and 10 °C, and the reaction progress was monitored by HPLC providing an assay yield of 90%. Ethyl acetate (15 L) was added to the cooled reaction mixture, followed by 25 kg of 15 wt % brine. The reaction mixture was agitated vigorously for 10 min before the phases were allowed to settle, and the aqueous phase was separated, and the organic phases were collected. The aqueous layer was extracted with ethyl acetate (5 L × 2). A solvent switch of the combined organic layers to 2-propanol (50 L) was performed, and then the volume was reduced to 200 mg/mL. DMADMA (8.1 kg, 60.6 mol) was added to the 2-propanol reaction mixture, and within 15 min the reaction was deemed completed via HPLC analysis. An addition of 10 wt %/wt Darco 60 was made, and the reaction stirred for one hour before being filtered through a filter pot containing solka floc. The filter pot was washed with 5 L of IPA, and the combined organic layers were charged into a 100-L round-bottom flask. A mixture of water/IPA, 1:1, was added dropwise to the reaction stream to start crystallization. After reaching a ratio of water/organic solvents of 2:1 the white solid was collected by filtration and dried in a tray dryer under reduced pressure at 66 °C overnight. Mp: 81.5 °C, HPLC retention time: 15.3 min. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.55 (s, 1 H), 7.21−7.27 (m, 1 H), 2.71 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.4, 163.4, 161.0 (d, J = 255 Hz), 138.2 (d, J = 15 Hz), 129.3 (d, J = 3.8 Hz), 124.7 (d, J = 3.8 Hz), 117.2, 116.4 (d, J = 15 Hz), 12.7.

***N*-[(1*R*)-1-{5-[5-Chloro-3-fluoro-2-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-3-fluoropyridin-2-yl}ethyl]acetamide (13).** A flask was charged sequentially with *N*-[(1R)-1-(5-bromo-3-fluoropyridin-2-yl)ethyl]acetamide (**B**) (1.5 kg; 5.75 mol), 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi-1,3,2-dioxaborolane (1.75 kg; 6.9 mol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (3 mol %, 290 g; 0.35 mol) and potassium acetate (1.70 kg; 17.3 mol). After purging the flask with nitrogen gas for one hour, the reaction mixture was suspended in toluene (7.5 L) and degassed with nitrogen gas for 30 min. The reaction mixture was heated up to 85 °C and aged for 18 h. A sample analysis of the reaction mixture by HPLC determined the conversion to 96%, and the mixture was allowed to cool to 20 °C. A degassed solution of 3-(2-bromo-4-chloro-6-fluorophenyl)-5-methyl-1,2,4-oxadiazole (**A**) (1.76

kg, 6.04 mol) in toluene (4.4 L) was added to the reaction mixture, followed by a degassed aqueous potassium phosphate solution (2 M, 6 L). The batch was heated to 95 °C for 16 h. The reaction mixture was monitored by HPLC, and upon completion of the reaction, the mixture was cooled to 50 °C before water (15 L) was added. The homogeneous reaction mixture was cooled to 20 °C prior to allowing the phases to separate and to collecting the aqueous. The organic phase was washed with aqueous 0.1 M hydrochloric acid (15 L), separated from the aqueous phase, and charged with Ecosorb C-941 (0.75 kg). The batch was aged for 16 h at 20 °C, before the activated carbon was collected on a filter pot filled with solka floc. The filter pot was washed with 5 L of toluene before the combined organic streams were concentrated to 600 mg/mL at 40 °C under reduced pressure. At atmospheric pressure and 48 °C, heptane (8 L) was added slowly to the reaction mixture to start crystallization. The batch was aged for one hour and allowed to cool to 20 °C before 72 L of heptane was added to reduce mother liquor losses and was finally aged for 16 h. After cooling the slurry to 0 °C, the solids were collected by filtration on a filter pot. The cake was washed with 2 L of a toluene/heptane mixture (1:9) and dried under nitrogen for 18 h to afford 1.69 kg as a white solid (4.31 mol; 97.5 LCWP,[17] HPLC retention time: 10.3 min; ee >99% by HPLC (retention time: 6.8 min)). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.17 (s, 1 H); 7.25−7.36 (m, 3H), 6.92 (d, J = 7.38 Hz, 1 H), 5.42−5.51 (m, 1 H), 2.57 (s, 3 H), 2.02 (s, 3 H), 1.47 (d, J = 6.68 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.1, 169.2, 163.0, 161.0 (d, J = 255 Hz), 155.4 (d, J = 263 Hz), 149.1 (d, J = 15 Hz), 144.1 (d, J = 3.8 Hz), 140.1, 137.8 (d, J = 7.5 Hz), 134.3, 126.5 (d, J = 7.5 Hz), 123.7 (d, J = 15 Hz), 117.0 (d, J = 30 Hz), 113.9 (d, J = 15 Hz), 44.2, 23.4, 21.5, 12.4.

(2*R*)-3-{[(1*R*)-1-{5-[5-Chloro-3-fluoro-2-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-3-fluoropyridin-2-yl}ethyl]amino}-1,1,1-trifluoro-2-methylbut-3-en-2-ol (1) via (1*R*)-1-{5-[5-Chloro-3-fluoro-2-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-3-fluoropyridin-2-yl}ethanamine (14). *N*-[(1*R*)-1-{5-[5-Chloro-3-fluoro-2-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-3-fluoropyridin-2-yl}ethyl]acetamide (**13**) (3.11 kg, 7.92 mol) and 40 L of an aqueous 2 M hydrochloric acid solution were combined, and the reaction mixture was warmed to 75 °C, when all solids were dissolved. After 9 h a sample analyzed by HPLC indicated the consumption of the starting material. The reaction was cooled to 20 °C and aged for 16 h. The aqueous stream was extracted three times with 20 L of a 1:1 mixture of methyl *tert*-butylether/heptane. The aqueous stream was diluted with 15 L of toluene before the mixture was cooled to 8 °C. The pH was adjusted to 11.3 by the addition of 7 L of an aqueous 10 M sodium hydroxide solution and 2.9 L of an aqueous 5 M sodium hydroxide solution. The batch temperature was maintained below 23 °C by the rate of addition of the sodium hydroxide solutions. After 0.5 h the phases were allowed to separate and were collected. The aqueous layer was extracted with an additional 9 L of toluene. The combined organic layers were filtered before they were washed with 10 L of an aqueous 15 wt % ammonium chloride solution. The layers were separated, and the organic layer was concentrated to 85 mg/mL. The organic stream was charged with 1.28 kg of NuChar. The batch was aged for 16 h at 20 °C before the activated carbon was collected on a filter pot filled with Celite 545. The wet cake was washed two times with 17.5 L of toluene. The combined organic phases were concentrated again to 85 mg/mL. The filtration step was repeated one more time, before the batch was concentrated to 250 mg/mL. HPLC retention time: 4.3 min. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.19 (s, 1 H), 7.21−7.29 (m, 3 H), 4.42 (q, J = 7.0 Hz; 1 H), 2.57 (s, 3 H), 1.87 (s, 2 H), 1.41 (d, J = 7.0 Hz; 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.0, 163.1, 161.1 (d, J = 255 Hz), 155.7 (d, J = 255 Hz), 153.3 (d, J = 15 Hz), 144.4 (d, J = 7.5 Hz), 140.5, 137.7, 133.6, 126.5 (d, J = 3.8 Hz), 123.2 (d, J = 7.5 Hz), 116.8 (d, J = 11.3 Hz), 113.9 (d, J = 15.0 Hz), 46.4, 23.6, 12.4.

Under nitrogen *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (1.95 kg, 10.2 mol) was charged with 2.38 kg of (1*R*)-1-{5-[5-chloro-3-fluoro-2-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-3-fluoropyridin-2-yl}ethanamine (**14**) as a toluene stream. The suspension was stirred vigorously at 20 °C. A solution of 1-hydroxybenzotriazole (0.26 kg; 1.69 mol) and (2*R*)-3,3,3-trifluoro-2-hydroxy-2-methylpropanoic acid (**C**) (1.18 kg; 7.45 mol) in tetrahydrofuran (8 kg) was added at a rate that allowed the batch temperature to remain below 32 °C. The reaction mixture was agitated for 30 min before the reaction progress was monitored by HPLC. After 2 h the reaction mixture was charged with 7.05 L of an aqueous 1 M sodium hydroxide solution and aged for 0.5 h at 20 °C. The aqueous layer was collected, and the organic layer was charged with another 4.0 kg of an aqueous 1 M sodium hydroxide solution and agitated for 5 min. The aqueous layer was collected, and the organic layer was charged with 7.05 L of an aqueous 1 M hydrochloric acid solution. The reaction mixture was agitated for 5 min, and the aqueous layer was collected and discarded. The organic phase was dried using 7.05 L of 15 wt % brine. The reaction mixture was agitated for 10 min before the aqueous phase was collected and discarded. The organic layer was concentrated prior to the addition of 10 L of toluene and was further concentrated to 150 mg/mL. The organic stream was passed through an in-line filter, and the solvent was removed under reduced pressure at 45 °C to a final concentration of 250 mg/mL. After the initial addition of 3.6 L of heptane, the product started to crystallize. The crystallization was completed by the addition of 8.4 L of heptane. The solid was collected by filtration on a filter pot and washed with 5 L of a 1:2 mixture of toluene/heptane. Finally the cake was washed with 2 L of heptane before the cake was dried under nitrogen for 24 h to afford 2.9 kg as a white solid (5.9 mol, 87% overall yield). Mp: 121.8 °C, HPLC retention time: 16.2 min. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.22 (s, 1 H), 7.76 (d, J = 7.14 Hz, 1 H), 7.34−7.37 (m, 2 H), 7.27−7.29 (m, 1 H), 5.44−5.53 (m, 1 H), 4.58 (broad s, 1 H), 2.60 (s, 3 H), 1.61 (s, 3H), 1.49 (d, J = 6.68 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.7, 167.4, 161.2 (d, J = 263 Hz), 155.5 (d, J = 255 Hz), 147.8 (d, J = 15 Hz), 144.3, 139.9, 137.9 (d, J = 15 Hz), 134.8, 130.0, 126.5 (d, J = 7.5 Hz), 124.1 (d, J = 22.5 Hz), 122.4, 117.2 (d, J = 22.5 Hz), 113.9 (d, J = 15 Hz), 74.2 (q, J = 22.5 Hz), 45.2, 21.0, 20.3, 12.3.

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