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Development of a Scalable Synthesis of Dipeptidyl Peptidase-4 Inhibitor ABT-279

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Abstract:

A convergent, scalable synthesis of dipeptidyl peptidase-4 inhibitor, ABT-279, has been developed and demonstrated on multikilogram scale. The *cis*-2,5-disubstituted pyrrolidine is generated by cyclization of a Boc-amine onto an alkynyl ketone followed by stereospecific reduction of the resulting acyliminium intermediate. The amine coupling partner was prepared by a novel Hofmann rearrangement promoted by 1,3-dibromo-5,5-dimethylhydantoin. The final product was isolated as the L-malic acid salt. The scale-up campaign consisted of 15 steps and delivered 42 kg of ABT-279 in 14% overall yield. A second-generation synthesis that addresses some of the issues encountered during scale-up was developed and demonstrated on kilogram scale.

Introduction

Diabetes is a disease that affects 170 million people worldwide. The prevalence of diabetes is expected to more than double by 2030.[1] Inhibition of dipeptidyl peptidase-4 (DPP-4) has been shown to be effective at lowering levels in the blood of glucose and hemoglobin A_{1c} (HbA_{1c}) and has the potential to be disease altering by promoting regeneration of insulin-producing cells in the pancreas.[2] As part of an active program in the area of DPP-4 inhibition, multikilogram quantities of DPP-4 inhibitor ABT-279 (**1**), Figure 1, were necessary to support regulatory toxicology studies and clinical evaluation.[3]

The retrosynthetic analysis of **1** leads to aminopyridine **2** and chloroacetamide **3** (Scheme 1). Aminopyridine **2** is ultimately derived from commercially available ethyl isonipecotate **4** and *tert*-butyl chloroisonicotinate **5**, while chloroacetamide **3** comes from methyl *N*-Boc-pyroglutamate **6**.

Discussion

Synthesis of Amine Coupling Partner. Commercially available ethyl isonipecotate, **4**, was converted to salt **9·TsOH** by standard transformations (Scheme 2). Boc protection of **4** in toluene was followed by deprotonation with LDA in toluene/THF at −10 °C and then addition of methyl iodide to give ester **7**. After workup, the ester was converted to the corresponding amide **8** by treatment with sodium amide in toluene/THF at 50 °C. Finally, the Boc group was removed, and the *p*-toluenesulfonic acid salt, **9·TsOH**, was isolated as a crystalline solid. The overall yield for the four-step sequence was 69%.

The pyridine-coupling partner necessary to access aminopyridine **2** is *tert*-butyl-2-chloroisonicotinate, **5**. Commercially available 2-chloroisonicotinic acid, **10**, was protected as its *tert*-butyl ester by treatment with excess Boc_2O and catalytic DMAP in *N*-methyl-2-pyrrolidone (NMP) solvent (Scheme 3). Attempts

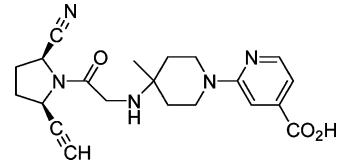
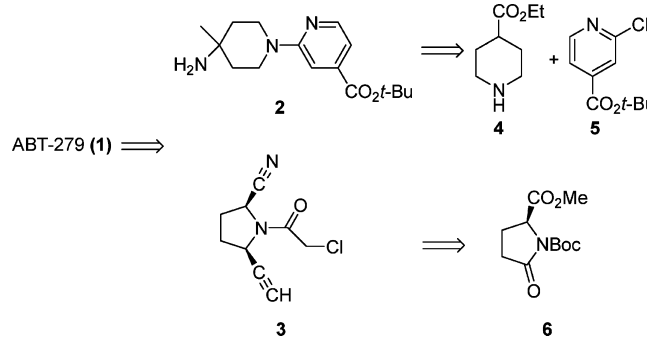
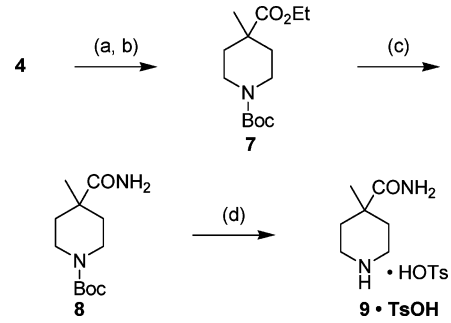


Figure 1. **DPP-4 Inhibitor ABT-279 (1).**

Scheme 1. **Retrosynthesis of ABT-279 (1)**



Scheme 2. **Synthesis of amide 9[a]**



[a] Reaction conditions: (a) Boc_2O, tol, RT. (b) LDA; MeI, THF/tol, −10 °C. (c) $NaNH_2$, THF/tol, 50 °C. (d) *p*-TsOH, IPA, 80 °C; 69% overall yield.

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§ Solid State Chemistry.

(1) Wild, S.; Roglic, G.; Green, A.; Sicree, R.; King, H. *Diabetes Care* **2004**, *27*, 1047.

(2) Zerilli, T.; Pyon, E. Y. *Clin. Ther.* **2007**, *29*, 2614.

(3) Madar, D. J.; Kopecka, H.; Pireh, D.; Yong, H.; Pei, Z.; Li, X.; Wiedeman, P. E.; Djuric, S. W.; Von Geldern, T. W.; Fickes, M. G.; Bhagavatula, L.; McDermott, T.; Wittenberger, S.; Richards, S. J.; Longenecker, K. L.; Stewart, K. D.; Lubben, T. H.; Ballaron, S. J.; Stashko, M. A.; Long, M. A.; Wells, H.; Zinker, B. A.; Mika, A. K.; Beno, D. W. A.; Kempf-Grote, A. J.; Polakowski, J.; Segreti, J.; Reinhart, G. A.; Fryer, R. M.; Sham, H. L.; Trevillyan, J. M. *J. Med. Chem.* **2006**, *49*, 6416.

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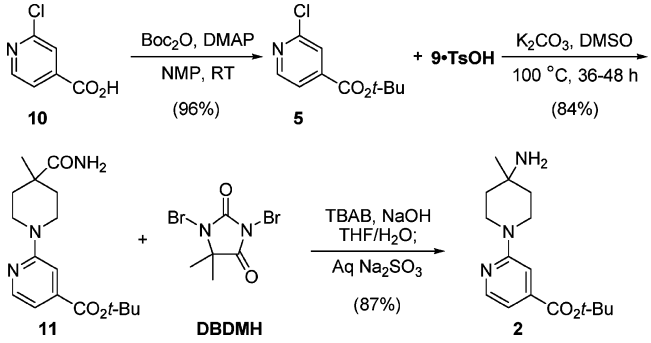
Scheme 3. **Synthesis of aminopyridine coupling partner 2**



to effect the *tert*-butyl ester formation under more standard conditions[4] resulted in low yields due to incomplete reactions. After extraction with methyl *tert*-butyl ether (MTBE) and concentration from toluene, compound **5** was obtained as an oil containing toluene and di-*tert*-butyl carbonate, which do not interfere with subsequent reactions.[5]

The strategy for coupling chloropyridine **5** and various substituted piperidines was initially focused on palladium-catalyzed *N*-arylation reactions.[6] Sensitivity of the *tert*-butyl ester of **5** to the highly basic conditions necessary for these coupling reactions led to low yields and complicated reaction mixtures. The major impurities were related to hydrolysis of the *tert*-butyl ester of starting material and product. An alternative thermal coupling strategy was developed. Treatment of chloropyridine **5** with mild base and 1.5 equiv of **9·TsOH** at 100 °C in dimethyl sulfoxide (DMSO) for 36 to 48 h led to amide **11** (Scheme 3). The major side reaction was cleavage of the *tert*-butyl ester of the starting chloropyridine. Upon completion, addition of water to the reaction mixture resulted in crystallization of amide **11**. Water washes of the solid completely removed the chloroisonicotinic acid byproduct resulting in pure material (>98 LC A%).

The final transformation to produce amine **2** was a Hofmann rearrangement of amide **11**. This transformation could be carried out under typical Hofmann rearrangement conditions; however, low yields or hard-to-control reactions resulted.[7] An alternative Hofmann reaction was developed, utilizing 2,5-dibromo-3,3-dimethylhydantoin (DBDMH) as the bromine source (Scheme 3).[8]

Initially, the Hofmann reaction was hampered by formation of acid **12**, by hydrolysis of the ester, and urea **13** due to buildup of product in the presence of the intermediate isocyanate (Figure 2). In order to increase the rate of isocyanate hydrolysis, the reaction was carried out in a biphasic system of THF/4 M NaOH in the presence of a phase transfer catalyst. The use of 1 equiv of tetrabutylammonium bromide (TBAB) limited the formation of urea while not greatly affecting the ester hydrolysis. The amount of TBAB could be reduced to about 0.4 equiv without an increase in urea formation, but the slower reaction time resulted in additional ester hydrolysis. During the preparation for scale up, it was noted that the Hofmann reaction is very sensitive to temperature. It was critical to keep the reaction temperature below 5 °C during the addition of DBDMH, which is very exothermic. On small scale, increasing the reaction temperature from 5 to 10 °C resulted in a 4-fold increase in the amount of urea **13** formed. During the pilot plant campaign, the reaction temperature was controlled by limiting the rate of addition of DBDMH and the reaction resulted in 87% yield of the desired amine (Scheme 3).

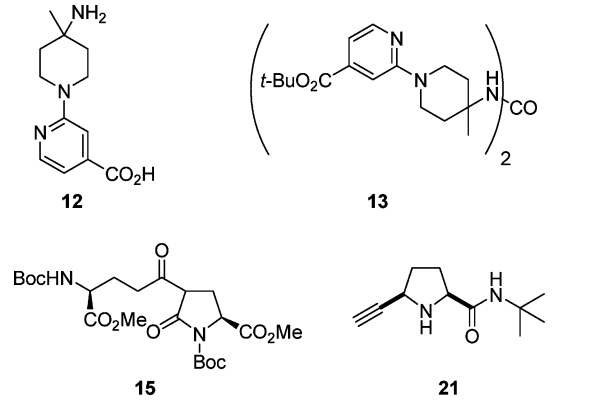


Figure 2. **Major impurities formed during the synthesis of ABT-279.**

Synthesis of Chloroacetamide Coupling Partner. The synthesis of the other coupling partner, chloroacetamide **3**, began with chemistry reported by Martin et al. in 2004.[9] They reported opening of carbamate-protected pyroglutamates followed by cyclization and reduction by treatment with $BF_3 \cdot OEt_2$ in the presence of triphenylsilane to give 2,5-*cis*-pyrrolidines. In the case of the isopropyl carbamate, the yield and selectivity were excellent. In the case of Boc-protected pyroglutamates, the protecting group was unstable to the Lewis acidic conditions, and alternative cyclization/reduction conditions were employed.

The Martin chemistry provided a good starting point for the synthesis of chloroacetamide **3**. For our purposes, the Boc protecting group was preferable to the isopropyl carbamate because of our previous experience with Boc-protected intermediates. The addition of the magnesium chloride salt of trimethylsilylacetylene to pyroglutamate **6** gave clean conversion to propargylic ketone **14** (Scheme 4). Although the ester was added to an excess of Grignard reagent, very little bis-addition product was detected, suggesting that the initially formed tetrahedral intermediate is stabilized by the presence of the adjacent Boc group. The major byproduct encountered was ketone **15**, the result of base-promoted self-condensation of **6** (Figure 2). This product could be avoided by slow addition of a solution of the ester to a cold THF solution of the Grignard

(4) (a) Baldwin, J. E.; Bamford, S. J.; Fryer, A. M.; Rudolph, M. P. W.; Wood, M. E. *Tetrahedron* **1997**, *53*, 5233. (b) Wright, S. W.; Hageman, D. L.; Wright, A. S.; McClure, L. D. *Tetrahedron Lett.* **1997**, *38*, 7345. (c) Dhaon, M. K.; Olsen, R. K.; Ramasamy, K. *J. Org. Chem.* **1982**, *47*, 1962.

(5) During the pilot-plant campaign, distillation of the MTBE/toluene product solution resulted in a higher than expected concentration, and compound **5** crystallized in the reactor. A crystallization procedure from MeOH/water was subsequently developed and demonstrated on 1-kg scale.

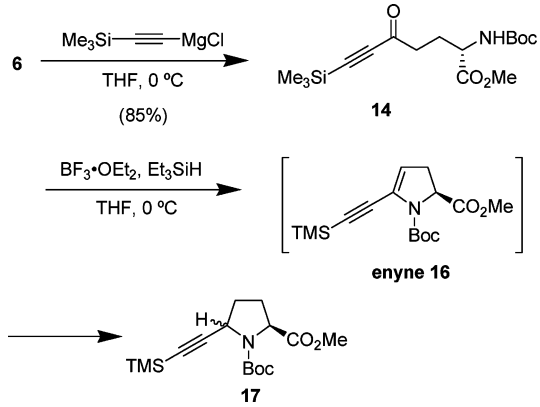
(6) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240.

(7) The use of NaOCl as oxidant led to incomplete reaction, whereas the use of 2,5-dichloro-3,3-dimethylhydantoin led to loss of the *tert*-butyl ester group due to long reaction times. The used of bromine as oxidant was possible, but addition rate and stoichiometry were difficult to control.

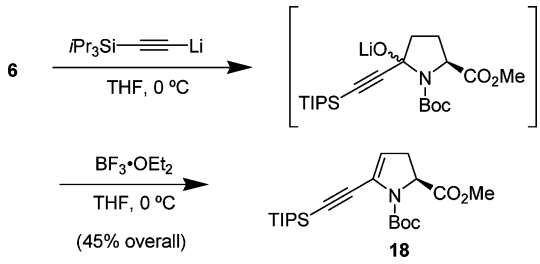
(8) Engstrom, K.; Henry, R.; Hollis, S.; Kotecki, B.; Marsden, I.; Pu, Y.-M.; Wagaw, S.; Wang, W. *J. Org. Chem.* **2006**, *71*, 5369–5372.

(9) Brenneman, J. B.; Machauer, R.; Martin, S. F. *Tetrahedron* **2004**, *60*, 7301.

Scheme 4. **Initial cyclization/reduction sequence**



Scheme 5. **Synthesis of enyne 18**



reagent. This reaction gave 85% yield during the pilot plant campaign and the product, which was about 95 LC A% pure (excluding IPAc), was used without purification after extractive workup.

Initial attempts to effect cyclization/reduction of **14** were unsuccessful. Using the conditions reported by Martin, the compound rapidly decomposed. Changing the solvent to THF led to cyclization to the corresponding enyne (**16**), which slowly reduced to pyrrolidine **17**. However, during the long reaction time degradation of enyne **16** and product was seen (Scheme 4).

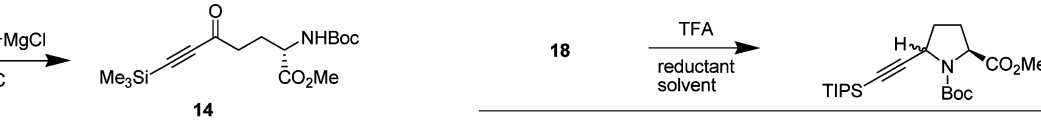
In order to work with a more stable system, the triisopropylsilyl (TIPS)-protected enyne (**18**) was produced by addition of tri-isopropylalkynyl lithium to **6** and treatment with $BF_3 \cdot OEt_2$ followed by silica gel chromatography (Scheme 5). Enyne **18** is a stable material isolated in 45% yield and allowed for the controlled investigation of the desired reduction.

The desired reduction could be achieved by treatment of **18** with trifluoroacetic acid (TFA) in the presence of reducing agents. Indeed, **18** could be selectively reduced to either the *trans*- or *cis*-pyrrolidine, depending on the conditions. Use of Et_3SiH as the reducing agent led preferentially to the *trans* product (Table 1, entries 1−3). Reduction with a bulkier reagent, sodium triacetoxyborohydride ($NaBH(OAc)_3$), led preferentially to the *cis*-pyrrolidine product (Table 1, entries 4−7). For both reducing agents, the use of polar solvents (IPA or THF) led to removal of the Boc group and decomposition. The highest *cis*-selectivity was observed when EtOAc was used as the solvent.[10]

Although the above reduction produced the desired *cis*-pyrrolidine product, it was preferable to use the TMS-protected acetylene, rather than the harder to remove TIPS protecting group. Unfortunately, isolation of enyne **16** was not possible

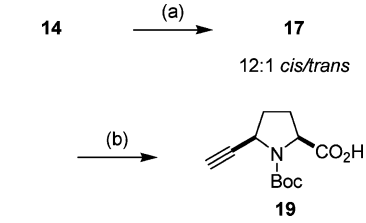
(10) An investigation of the scope and limitations of the cyclization/reduction reaction is underway and will be reported separately.

Table 1. **Cyclization/reduction of 18**



entry	solvent	reductant	*cis*/*trans*
1	toluene	Et_3SiH	1:8
2	DCM	Et_3SiH	1:7
3	acetonitrile	Et_3SiH	1:4
4	DCM	$NaBH(OAc)_3$	1.5:1
5	toluene	$NaBH(OAc)_3$	2:1
6	acetonitrile	$NaBH(OAc)_3$	5.1:1
7	EtOAc	$NaBH(OAc)_3$	11:1

Scheme 6. **Synthesis of Boc-acid 19**[a]



[a] Reaction conditions: (a) $NaBH(OAc)_3$; TFA, IPAc, −10 °C. (b) $LiOH \cdot H_2O$, THF/EtOH, 0 °C, crystallization from IPAc/heptane, (65%).

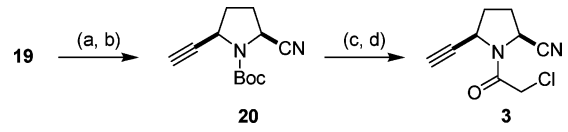
due to the lability of the TMS group. However, it was not necessary to isolate the enyne intermediate. Ketone **14**, when exposed to TFA in the presence of $NaBH(OAc)_3$, gave the desired pyrrolidine (**17**) in good yield and selectivity (Scheme 6).[11] In practice, a mixture of **14** and 1.5 equiv of $NaBH(OAc)_3$ in IPAc was treated with 3 equiv of TFA at −10 °C. Upon warming to room temperature the reaction was complete.[12] The crude product was solvent switched to EtOH and treated with LiOH to hydrolyze the methyl ester and the TMS group. On pilot-plant scale the cyclization, reduction, and hydrolysis sequence gave a 12:1 *cis*/*trans* ratio. Crystallization of acid **19** from IPAc/heptane resulted in material that contained less than 0.5% of the *trans* isomer, but substantial losses to the mother liquors occurred (about 19%). The overall yield of the process was 65% on 50-kg scale (Scheme 6), and the material produced was greater than 97% pure by HPLC analysis.

Carboxylic acid **19** was converted to the corresponding amide and then dehydrated to nitrile **20** under Vilsmeier conditions (Scheme 7). The Boc group was removed with *p*-TsOH. One of the side products of this reaction was the pyrrolidine *tert*-butyl amide **21** (Figure 2), resulting from attack of the nitrile on the *tert*-butyl cation produced during the Boc deprotection. The use of CH_3CN as solvent provided an excess of an alternative nitrile and resulted in formation of significantly lower amounts of **21** (2−4 LC A%) and the production of 1 equiv of *tert*-butylacetamide as a byproduct, which does not interfere with the next reaction. After removal of the Boc protecting group, the chloroacetamide (**3**) was formed directly

(11) For the use of TFA to convert a Boc-protected amino-ketone to a Boc-enamine see: Clark, R. D.; Muchowski, J. M.; Fisher, L. E.; Flippin, L. A.; Repke, D. B.; Souchet, M. *Synthesis* **1991**, 871.

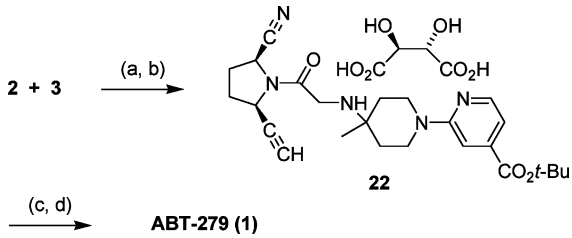
(12) Other protic acids (HCl, H_2SO_4, $MeSO_3H$, H_3PO_4) and TMSCl failed to effect the cyclization/reduction. The selectivity of the reaction is independent of temperature (12:1 at 0 or 25 °C), although slightly higher yields are obtained at 0 °C. IPAc and EtOAc are comparable solvents for the reduction reaction. IPAc was used to avoid issues with EtOAc hydrolysis in the subsequent step.

Scheme 7. **Synthesis of chloroacetamide 3**[a]



[a] Reaction conditions: (a) *i*-BuOCOCl; NH_4OH, IPAc, 0 °C. (b) $SOCl_2$/DMF, THF, rt, (87%). (c) TsOH, CH_3CN RT, (d) $ClCH_2COCl$, Hunig's base, CH_3CN, 0 °C; crystallization from IPA/water, (78%).

Scheme 8. **Endgame strategy**[a]



[a] Reaction conditions: (a) K_3PO_4/KI, NMP, 35 °C. (b) D-tartaric acid, IPA, (88%). (c) H_3PO_4/H_2O, 60 °C. (d) L-malic acid, $EtOH/H_2O$, 45 °C (93%).

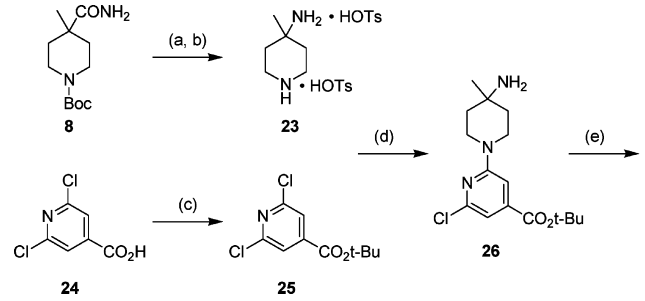
by treatment with chloroacetyl chloride in the presence of Hunig's base. Chloroacetamide **3** was crystallized from IPA/water to give 78% yield of material that was 99 LC A% pure and >200:1 *cis*/*trans*.

Endgame Strategy. With the coupling partners in place, all that remained was the final coupling and deprotection. The coupling of hindered amine **2** required slightly forcing conditions. An NMP solution of chloroacetamide **3** was added to a mixture of **2**, milled K_3PO_4, and KI in NMP solvent at 35 °C (Scheme 8). The key concern with this reaction was epimerization of the nitrile stereocenter. At temperatures above 40 °C, the amount of epimerization was beyond the level that could be removed during isolation. At 45 °C, the *cis*/*trans* ratio was 87:13, and salt formation and crystallization resulted in a final ratio of 89:11. A reaction temperature of 35 °C gave a good balance between reaction rate (completion in ~4 h) and epimerization (less than 1%). The product, **22**, was isolated by extraction with MTBE followed by crystallization as its D-tartaric acid salt. The isolation of the penultimate product allowed very clean material (>99 LC A%) to be taken into the final deprotection step.

Early attempts at the *tert*-butyl ester deprotection suffered from formation of Ritter reaction byproducts, as had been seen with the Boc deprotection of **20**. The strategy of using CH_3CN as a solvent, which had been successful previously, did not completely alleviate the problem. Carrying out the final deprotection with phosphoric acid in water avoided formation of the *tert*-butyl amide byproduct. After the deprotection step, ABT-279 (**1**) was isolated as its crystalline L-malic acid salt from $EtOH/H_2O$. The final deprotection/isolation sequence proceeded in 93% yield and gave 42 kg of product. The material was 99.8 LC A% pure and was 99.4% ee by HPLC analysis. The *cis*/*trans* diastereomeric ratio of the final solid was >99.9:0.1.

Alternative Synthetic Sequence. The synthesis carried out in the pilot plant produced material to support the project through phase I and into phase II development. However, there were several issues with the scale-up synthesis that needed to be addressed prior to further scale-up work. As described earlier,

Scheme 9. **Alternative Hofmann and amine coupling sequence**[a]



[a] Reaction conditions: (a) DBDMH, aq KOH/CH_3CN, 0 °C. (b) *p*-TsOH, MeOH, 60 °C, (92%). (c) Boc_2O, DMAP, NMP; Et_3N, RT (88%). (d) K_3PO_4, NMP 80 °C (97%). (e) H_2, Pd/Al_2O_3, K_3PO_4, NMP, 40 °C (96%).

the DBDMH Hofmann reaction is very sensitive to reaction temperature (see Scheme 3). The primary reason for this sensitivity is that amide **11** has low solubility in most solvents, making hydrolysis of the intermediate isocyanate slow. As an alternative, the Hofmann reaction was carried out on amide **8**, a compound with more favorable solubility characteristics (Scheme 9). Because of the improved solubility of **8**, a phase transfer catalyst was not necessary.[13] The resulting Boc amine was treated with *p*-TsOH in MeOH at 60 °C to effect cleavage of the Boc group. The product was isolated as its bis-*p*-TsOH salt directly from the reaction mixture. This sequence gave 92% isolated yield of salt **23** for two steps, which is a substantial improvement of the previous Hofmann protocol.

An additional improvement to the scale-up campaign was the use of the more activated *tert*-butyl 2,6-dichloroisonicotinate (**25**) as the pyridine coupling partner. Protection of the commercially available 2,6-dichloroisonicotinic acid (**24**) was carried out using conditions similar to those reported earlier for *t*-butyl ester formation.[14] In this case, the ester (**25**) was isolated as a crystalline solid in 88% yield. The *N*-arylation reaction using compound **25** is considerably more facile. Treatment of **25** with a slight excess of **23** in NMP in the presence of base gave a nearly quantitative yield of chloropyridine **26** in a few hours at 80 °C. Dechlorination of **26** was carried out by treatment with Pd/Al_2O_3 in the presence of H_2 and base in NMP to give 96% yield of coupling partner **2** (Scheme 9). After workup, the product was used in the final coupling reaction without further purification. During the first pilot-plant campaign the sequence from amide **8** to amine **2** proceeded in four steps and 66% overall yield. The alternative sequence proceeded in five steps and 76% overall yield and gave material that was indistinguishable from material produced during the pilot-plant campaign.

This sequence was carried out on 1-kg scale in order to demonstrate its scalability. In this case, each of the reactions was worked up as usual (see Experimental Section). However, the *tert*-butyl ester formation, the *N*-arylation, the dechlorination, and the final coupling (Scheme 9) are each carried out in the NMP/base system, allowing the possibility of telescoping these

(13) Mixtures of **8**, CH_3CN, and 2 M KOH became homogeneous upon addition of DBDMH. Running the reaction under dilute conditions, where layer separation occurred, resulted in formation of the corresponding urea byproduct.

(14) One equivalent of Et_3N was added to the reaction to increase the nucleophilicity of the acid. In the absence of base the reaction exhibits a long induction period and a hard-to-control exotherm.

reactions. In a small-scale run, these reactions were carried out without workup of any of the intermediates. Optimization of this sequence should allow telescoping of the final four steps of the process.

Conclusion

We have described a convergent and practical synthesis of ABT-279, a DPP-4 inhibitor. The synthesis was carried out in the pilot plant to produce 42 kg of ABT-279. The key transformations include cyclization of a Boc-protected aminoketone, stereospecific reduction of the resulting acyliminium ion with sodium triacetoxyborohydride, and a novel DBDMH-promoted Hofmann rearrangement to give the amine coupling partner. Substantial improvements were made to the initial synthesis and were demonstrated on 1-kg scale.

Experimental Section

All reactions were carried out under a nitrogen atmosphere in either glass vessels or glass-lined stainless steel vessels with overhead mechanical stirring unless otherwise noted. HPLC data were collected using an Agilent 1100 series HPLC. Gas chromatography data were collected using a Hewlett-Packard 6890 series gas chromatograph. Chromatographic conditions are reported as part of the experimental descriptions below. Retention times are uncorrected. Elemental analysis samples were run by Quantitative Technologies Inc., Whitehouse, NJ (U.S.A.). Reagents were purchased from commercial suppliers and used as received.

Preparation of 1-*tert*-Butyl 4-ethyl 4-methylpiperidine-1,4-dicarboxylate (7). *Boc protection.* A solution of Boc_2O (97 kg, 444 mol, 1.03 equiv) and toluene (140 kg, KF 0.16 wt % water) at 15 °C was treated with ethyl isonipecotate (**4**, 68 kg, 433 mol, 1 equiv) at <30 °C. The addition vessel and lines were rinsed with toluene (2 kg), which was added to the reaction vessel. The reaction was mixed for 15 min, at which time an in-process GC sample showed the starting ethyl isonipecotate (**4**) was consumed. GC conditions: Column: J&W Scientific, DB-5, 30 m × 0.53 mm, 5 μm, injector: 150 °C, split ratio 1:1, 5.0 mL/min constant pressure, 2.0 μL injection; Oven program: 110 °C then ramp 4 °C/min to 200 °C then ramp 40 °C/min to 250 °C and hold 2 min, run time: 25 min; Detector: 240 °C; Retention time (min): **4** (15.2). The excess Boc_2O was quenched by addition of *N*,*N*-dimethylethylenediamine (2 kg, 23 mol) and stirred until Boc_2O was consumed as determined by GC (typically about 30 min). GC conditions: Column: Alltech AT-1, 30 m × 0.53 mm, 1.2 μm, injector: 150 °C, split ratio 1:1, flow 5.0 mL/min constant pressure, 2.0 μL injection; Oven program: 110 °C then ramp 4 °C/min to 200 °C then ramp 30 °C/min to 270 °C and hold 5 min, run time: 30 min; Detector: 240 °C; Retention time (min): Boc_2O (6.7), **4** (7.4), *N*-Boc ethyl isonipecotate (19.8), **7** (20.0). The reaction was quenched with 1 M H_3PO_4 solution (prepared from 75 kg water and 10 kg of H_3PO_4). The layers were separated, and the organic phase was washed with a basic brine solution (prepared from 75 kg of water, 0.75 kg of NaOH pellets and 11 kg of NaCl). The organic layer was assayed (HPLC) for product at 110 kg (99% yield). HPLC conditions: Column: Phenomenex, Luna phenyl hexyl, 250 mm × 4.6 mm, 5 μm, 25 °C, 1 mL/min, 20 μL injection, λ 210 nm; Mobile phase A: 0.1% H_3PO_4; Mobile phase B: ACN; Gradient: 0 min 45% B, 30 min 50% B, 35 min 80% B, 38 min 80% B, 40 min 45% B, 50 min 45% B; Retention time (min): *N*-Boc ethyl isonipecotate (14.2), toluene (15.5), **7** (21.0), ethyl benzene (21.5). The product was carried forward as a toluene solution. An analytical sample was prepared by short-path distillation (1.5 mmHg, collected 128−134 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (td, J = 7.10, 0.75 Hz, 3 H) 1.45 (d, J = 0.69 Hz, 9 H) 1.53−1.69 (m, 3 H) 1.81−1.91 (m, 2 H) 2.37−2.47 (m, J = 11.01, 11.01, 3.95, 3.95 Hz, 1 H) 2.82 (t, J = 11.87 Hz, 2 H) 3.93−4.07 (m, 1 H) 4.13 (qd, J = 7.11, 0.75 Hz, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.54, 28.24, 28.69, 41.35, 43.0 (br), 60.57, 79.53, 154.26, 174.04. IR (KBr) 2977, 1730, 1690 cm^{-1}. Anal. Calcd for $C_{13}H_{23}NO_4$: C 60.68, H 9.01, N 5.44; found: C 60.58, H 9.13, N 5.46.

Methylation. LDA solution (27.3 wt % active, 189 kg, 482 mol, 1.2 equiv) and THF (190 kg) were chilled to −10 °C. The solution of starting material, **Boc-4**, (60.7 wt % active, 169 kg, 399 mol, 1 equiv) was added over 1 h with a maximum internal temperature of 5 °C (target −10 °C). The addition vessel was rinsed with THF (25 kg), which was added to the reaction vessel. The reaction was stirred for about 30 min at an internal temperature of approximately −10 °C. A mixture of methyl iodide (71 kg, 500 mol, 1.25 equiv) and THF (35 kg) was added to the reaction mixture over 6 h at not more than 5 °C. After 30 min, HPLC analysis showed no starting material remained (see HPLC conditions above). The reaction was quenched into −5 °C 1 M H_3PO_4 solution (prepared from 700 kg of water and 86 of kg H_3PO_4), while maintaining the temperature <20 °C. While mixing, the temperature was adjusted to RT. The layers were separated. HPLC analysis showed 105.4 kg (97.4% yield) in the organic layer. The organic layer was concentrated several times from toluene to remove water to <0.1 wt % as determined by Karl Fisher analysis. After filtration of precipitated salts, the filtrate was concentrated to ∼65−70 wt % product in toluene and used directly in the next step. An analytical sample was prepared by short-path distillation (0.5 mmHg, collected 124 °C) ^{1}H NMR (400 MHz, CD_3OD) δ 1.19 (s, 3 H) 1.25 (t, J = 7.14 Hz, 3 H) 1.31−1.40 (m, 2 H) 1.44 (s, 9 H) 1.99−2.09 (m, 2 H) 2.88−3.07 (m, 2 H) 3.75 (dt, J = 13.86, 4.12 Hz, 2 H) 4.16 (q, J = 7.14 Hz, 2 H) 4.82 (m, 4 H). ^{13}C NMR (101 MHz, CD_3OD) δ 14.69, 26.34, 28.79, 35.66, 43.0 (br), 42.79, 61.74, 80.84, 155.87, 177.07. IR (KBr) 2974, 1725, 1692 cm^{-1}. Anal. Calcd for $C_{14}H_{25}NO_4$: C 61.97, H 9.29, N 5.16; found: C 61.81, H 9.45, N 5.14.

Preparation of *tert*-Butyl 4-carbamoyl-4-methylpiperidine-1-carboxylate (8). A mixture of sodium amide (38 kg, 974 mol, 2.5 equiv) and THF (400 kg) was warmed to 40 °C. Ester **7** was charged as a solution in toluene (105 kg active, 387 mol, 1 equiv) over 4 h at a temperature of not more than 65 °C (target 50 °C). The addition vessel was rinsed with THF (25 kg), which was added to the reaction vessel. The reaction was adjusted to 50 °C and held 2 h. In a separate vessel was charged water (320 kg), concentrated HCl (60 kg), and toluene (200 kg), which was then chilled to <5 °C. The heterogeneous reaction mixture was quenched by addition to the 3 M HCl/toluene mixture, while maintaining the temperature at less than

25 °C. The reactor was rinsed with toluene (75 kg) and water (140 kg), which were added to the quench vessel. After warming to RT, the layers were separated. The organic solution was concentrated to about 300 L. Toluene (200 kg) was added, and the mixture was distilled to a total volume of ~300 L. The slurry was chilled to ~0 °C over 4 h, stirred for 3 h, and then filtered. The cake was rinsed with toluene (400 kg) and dried under vacuum at 50 °C for 48 h to provide 72.5 kg (77% yield) of amide **8**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 3 H) 1.37−1.51 (m, 2 H) 1.44 (s, 9H) 1.88−1.98 (m, 2 H) 3.19−3.32 (m, 2 H) 3.51−3.68 (m, 2 H) 5.56−5.76 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.82, 28.70, 34.98, 41.35, 79.53, 154.37, 178.22. IR (KBr) 3388, 3172, 1665 cm^{-1}. Anal. Calcd for $C_{12}H_{22}N_2O_3$: C 59.48, H 9.15, N 11.56; found: C 59.57, H 9.37, N 11.58.

Preparation of 4-Methylpiperidine-4-carboxamide 4-Methylbenzenesulfonate (9·TsOH). A mixture of amide **8** (72 kg, 299 mol, 1 equiv), *p*-toluenesulfonic acid monohydrate ($TsOH·H_2O$, 73 kg, 384 mol, 1.3 equiv), and isopropanol (IPA, 285 kg) was warmed to 80 °C. After 2 h at 80 °C HPLC analysis showed that no SM remained. HPLC Conditions: Column: Phenomenex, Synergi Hydro-RP, 250 mm × 4.6 mm, 4 μm, 25 °C, 1 mL/min, 20 μL injection, λ 210 nm; Mobile phase A: 10 mM phosphate buffer, pH 6.5; Mobile phase B: ACN; Gradient: 0 min 2% B, 30 min 60% B, 35 min 100% B, 38 min 100% B, 40 min 2% B, 50 min 2% B; Retention time (min): **9** (3.8), TsOH (11.5). The reaction solution was allowed to slowly cool; at ~78 °C the product began to precipitate from the reaction mixture.[15] When the mixture reached 70 °C, heptane (62 kg) was added to the mixture, which was then stirred for about 30 min. The mixture was cooled to 20 °C at a rate of 5 °C/h and was stirred for 3 h. The suspension was filtered, and the reactor and cake were rinsed with a mixture of IPA (142 kg) and heptane (125 kg). The combined mother liquor and rinse contained 3.1 kg of product salt (3.3% yield) by HPLC analysis. The cake was dried under vacuum at 55 °C to give 87.7 kg (93.4% yield) of **9·TsOH** that was 96.7 wt % pure by HPLC analysis. ^{1}H NMR (400 MHz, CD_3OD) δ 1.28 (s, 3H), 1.67 (ddd, J = 15.2, 11.5, 4.0, 2H), 2.33−2.16 (m, 2H), 2.39 (s, 3H), 3.07 (ddd, J = 13.1, 11.5, 3.1, 2H), 3.31−3.24 (m, 2H), 7.33−7.16 (m, 2H), 7.80−7.63 (m, 2H). ^{13}C NMR (101 MHz, MeOH-d_4) δ 21.61, 26.94, 32.97, 41.30, 43.04, 126.65, 129.55, 141.40, 143.08, 179.57. Anal. Calcd for $C_{14}H_{22}N_2O_4S$: C 53.48, H 7.05, N 8.91; found: C 53.36, H 6.96, N 8.70.

Preparation of *tert*-Butyl 2-Chloroisonicotinate (5). A mixture of 2-chloroisonicotinic acid (**10**, 40 kg, 253 mol, 1 equiv), Boc_2O (115 kg, 528 mol, 2.3 equiv), and NMP (80 kg) was cooled to 10 °C. A solution of DMAP (5.8 kg, 47.5 mol, 0.2 equiv) dissolved in NMP (30 kg) was added over 10 min, and the temperature was adjusted to 25 °C. After 12 h HPLC analysis showed no starting material remained. HPLC Conditions: Column: Phenomenex, Synergi Hydro-RP, 250 mm × 4.6 mm, 4 μm, 25 °C, 1 mL/min, 20 μL injection, λ 210 nm; Mobile phase A: 0.1% perchloric acid; Mobile phase B: ACN; Gradient: 0 min 20% B, 8 min 25% B, 25 min 80% B, 30 min 95% B, 35 min 95% B, 36 min 20% B, 45 min 20% B; Retention time (min): **10** (7.9), toluene (18.8), **5** (21.5). The reaction was quenched by the addition of a 0 °C solution of NaCl (15 kg) and KH_2PO_4 (15 kg) in water (160 kg). MTBE (140 kg) was added, and the mixture was stirred and allowed to settle. The layers were separated. The organic phase was washed three times with water (120 kg each), then filtered and diluted with toluene (120 kg) and distilled under vacuum. The product unexpectedly crystallized after the distillation. THF (10 kg) was added to dissolve the solid. The solution was assayed for 52.1 kg of **5** (96.3% yield). An analytical sample was prepared by crystallization from toluene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 9 H), 7.69 (dd, J = 5.08, 1.37 Hz, 1 H), 7.78 (dd, J = 1.37, 0.69 Hz, 1 H), 8.47 (dd, J = 5.08, 0.82 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.16, 83.03, 121.28, 123.61, 141.75, 149.76, 151.69, 162.14. IR (KBr) 1716 cm^{-1}. Anal. Calcd for $C_{10}H_{12}ClNO_2$: C 56.21, H 5.66, N 6.56; found: C 56.27, H 5.83, N 6.54.

Preparation of *tert*-Butyl 2-(4-carbamoyl-4-methylpiperidin-1-yl)isonicotinate (11). The crude solution of *tert*-butyl-2-chloroisonicotinate (**5**, 93 kg of a 56 wt % solution, 244 mol, 1 equiv) was concentrated to about 87 wt %, and DMSO (119 kg) was added. The resulting solution was added to a mixture of **9·TsOH** (88 kg, 280 mol, 1.5 equiv) and K_2CO_3 (325 mesh, 90 kg, 651 mol, 3.5 equiv). The mixture was stirred at 100 °C until HPLC analysis showed less than 1 LC A% of **5** remained (36 h total). HPLC Conditions: Column: Phenomenex, Synergi Hydro-RP, 250 mm × 4.6 mm, 4 μm, 25 °C; 1 mL/min, 20 μL injection, λ 210 nm; Mobile phase A: 0.1% perchloric acid; Mobile phase B: ACN; Gradient: 0 min 20% B, 8 min 25% B, 25 min 80% B, 30 min 95% B, 35 min 95% B, 36 min 20% B, 45 min 20% B; Retention time (min): **10** (7.8), **11** (9.1), **5** (21.5). The mixture was cooled to room temperature, and water (544 kg) was added, slowly at first. The addition of water caused the product to precipitate, and slow addition was necessary to control the rate of precipitation. After stirring for about 1 h, the mixture was filtered, and the solid was washed twice with water (272 kg each) and dried under vacuum to give 65.1 kg (83.6% yield) of white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 3 H) 1.53−1.63 (m, 2 H) 1.58 (s, 9 H) 2.03−2.11 (m, 2 H) 3.42−3.51 (m, 2 H) 3.78−3.86 (m, 2 H) 5.41−5.69 (m, 2 H) 7.03 (dd, J = 5.08, 1.24 Hz, 1 H) 7.18 (s, 1 H) 8.22 (dd, J = 5.15, 0.75 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.88, 28.33, 34.62, 41.53, 42.61, 81.87, 106.59, 111.48, 140.35, 148.12, 159.25, 164.53, 178.43. IR (KBr) 3425, 1723 cm^{-1}. Anal. Calcd for $C_{17}H_{25}N_3O_3$: C 63.93, H 7.89, N 13.16; found: C 63.56, H 7.80, N 12.90.

Preparation of *tert*-Butyl 2-(4-amino-4-methylpiperidin-1-yl)isonicotinate (2). A mixture of amide **11** (49 kg, 153 mol, 1 equiv) and tetrabutylammonium bromide (TBAB, 50 kg, 153 mol, 1 equiv) and THF (132 kg) were cooled to 0 °C. A portion of 4 M NaOH (393 kg, of a solution prepared by dissolving 96 kg of NaOH in 578 kg water) was added, and the temperature of the slurry was adjusted to −5 °C. 1,3-Dibromo-5,5-dimethylhydantoin (DBDMH, 24 kg, 84 mol, 0.55 equiv) was added in portions over 20 min, resulting in an exotherm to 1.6 °C. It is important to keep the reaction temperature below 5 °C in order to avoid formation of impurities. The reaction was stirred at 0 °C for 90 min, at which time HPLC analysis showed less

(15) If product does not precipitate, the reaction may be seeded with approximately 0.2 wt % seeds.

than 1 LC A% **11** remaining and less than 1 LC A% isocyanate intermediate. HPLC conditions: Column: Phenomenex, Synergi Hydro, 250 mm × 4.6 mm, 4 μm, 25 °C, 1 mL/min, 20 μL injection, λ 210 nm; Mobile phase A: 0.1% perchloric acid; Mobile phase B: ACN; Gradient: 0 min 10% B, 30 min 90% B, 35 min 90% B, 37 min 10% B, 45 min 10% B; Retention time (min): **2** (12.4), **11** (14.4), urea **13** (20.5), isocyanate (21.2). The reaction was transferred into the 10 °C quench solution of 6 M HCl (294 g), *tert*-butyl methyl ether (MTBE, 91 kg), and Na_2SO_3 (20 kg, 156 mol), which resulted in an exotherm to about 15 °C and the evolution of carbon dioxide gas. The rate of addition of the reaction mixture to the quench solution allowed the rate of CO_2 release to be controlled. The reaction vessel was rinsed with MTBE (91 kg), which was added to the quench vessel. The quenched reaction solution had a pH of approximately 3 as determined by pH paper. After stirring for 5 min, 4 M NaOH (196 kg) was charged to the quenched reaction solution such that the temperature remained below 20 °C. The quenched reaction solution had a pH of approximately 12 as determined by pH paper. The layers were separated, and the aqueous layer was back extracted with MTBE (91 kg). The combined organic layers were washed with a brine−sulfite solution (prepared from 12.3 kg Na_2SO_3, 24.5 kg NaCl, and 208 kg water). The combined organic layers were distilled to about half the original volume, NMP (60 kg) was added, and the distillation was continued until less than 1% MTBE remained as determined by NMR analysis. The NMP solution of product was assayed at 38.7 kg (86.8% yield) and 96.2 LC A% pure. Compound **2** was characterized as the succinate salt, formed by treatment of the amine in MeOH with 1 equiv of succinic acid and isolated by crystallization from 10% MeOH/IPAc. (1:1 salt ratio). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (s, 3 H), 1.53 (s, 9 H), 1.64 (t, J = 5.63 Hz, 4 H), 2.25 (s, 4 H), 3.30−3.39 (m, 2 H), 3.91 (ddd, J = 13.72, 4.87, 4.73 Hz, 2 H), 6.95 (dd, J = 5.1, 1.2, 1 H), 7.16 (s, 1 H), 8.22 (d, J = 5.1, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 23.72, 27.69, 32.07, 34.89, 40.75, 51.07, 81.45, 105.59, 110.64, 139.72, 148.11, 158.31, 163.67, 174.34. IR (KBr) 1753, 1709 cm^{-1}. Anal. Calcd for $C_{20}H_{31}N_3O_6$: C 58.66 H 7.63 N 10.26; found: C 58.60 H 7.70 N 10.21.

Preparation of (*S*)-1-*tert*-Butyl 2-methyl 5-((triisopropylsilyl)ethynyl)-2,3-dihydro-1*H*-pyrrole-1,2-dicarboxylate (18). To a THF solution of triisopropylsilylacetylene (12.0 mL, 53.5 mmol, 1.3 equiv) cooled in an ice bath was added dropwise butyllithium (2.5 M in hexane, 20 mL, 50 mmol, 1.2 equiv), keeping the temperature less than 5 °C. The resulting mixture was stirred for 1 h at 0 °C. The solution of alkynyl lithium was cooled to −20 °C, and a solution of **6** (10.0 g, 41.1 mmol) in THF (50 mL) was added dropwise over 2 h. After an additional 1.5 h, BF_3·OEt_2 (50 mL, 395 mmol, 9.6 equiv) was added, and the resulting mixture was stirred for 3 h at −20 °C. The reaction mixture was quenched into saturated aq $NaHCO_3$ (50 mL) and stirred for 15 min, and the layers were separated. The organic layer was washed with saturated aq $NaHCO_3$ (50 mL), and the combined aqueous layers were extracted with EtOAc (100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography eluting with 5% EtOAc in hexane afforded 7.6 g (45%) of clear colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (t, J = 3.1, 1 H), 4.70 (dd, J = 11.9, 5.4, 1 H), 3.75 (s, 3 H), 2.98 (ddd, J = 18.1, 11.9, 2.9, 1 H), 2.59 (ddd, J = 18.1, 5.4, 3.3, 1 H), 1.47 (s, 9 H), 1.18−0.99 (m, 21 H).

Preparation of (*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-5-oxo-7-(trimethylsilyl)hept-6-ynoate (14). A solution of octylmagnesium chloride (2.1 M, 190 kg, 429 mol, 1.1 equiv) and THF (75 kg) was cooled to 0 °C. Trimethylsilylacetylene (44 kg, 448 mol, 1.15 equiv) was added by subsurface addition over about 25 min such that the temperature remained below 15 °C. The solution was stirred at 0 °C for 1 h and was then cooled to −10 °C. A solution of ester **6** (95 kg, 391 mol, 1 equiv) in THF (180 kg) was added by subsurface addition over a 2-h period. Slow, subsurface addition was necessary to minimize local concentration of **6**. The vessel and lines were rinsed with about 5 kg of THF, which was added to the reaction vessel. HPLC analysis after 2.5 h showed less than 2 LC A% **6** remained. HPLC conditions: Column: Phemomenex, Luna C8(2), 4.6 mm × 250 mm, 5 μm, 25 °C, 1.0 mL/min, 20 μL injection, λ 210 nm; Mobile phase A: 0.1% H_3PO_4; Mobile phase B: 0.1% H_3PO_4 in ACN; Gradient: 0 min, 30% B; 12 min, 40% B; 16 min, 72% B; 26 min, 74% B; 30 min, 95% B; 35 min, 95% B; 36 min, 30% B; 45 min, 30% B; Retention time (min): **6** (10.9), **14** (23.0). The reaction solution was added to a 0 °C mixture of IPAc (290 kg) and 20% NH_4Cl solution (378 kg, prepared by dissolving 126 kg of NH_4Cl in 630 kg water) over about 30 min such that the temperature remained below 10 °C. The mixture was allowed to warm to above 10 °C, and the layers were separated. The aqueous layer was extracted with IPAc (250 kg), and the organic layers were combined. HPLC analysis of the aqueous layer showed no product. The organic layer was washed with the remainder of the 20% NH_4Cl solution (378 kg) and with 20% NaCl solution (377 kg, prepared by dissolving 62 kg of NaCl in 315 kg water). HPLC analysis of the organic layer showed 111.9 kg (84.8% yield) of ketone **14**. An analytical sample was prepared by silica gel chromatography using 10% EtOAc/hexanes as an eluent followed by crystallization from heptane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.18 (s, 9 H), 1.39 (s, 9 H), 1.82−1.97 (m, 1 H), 2.14 (tdd, J = 5.3, 6.7, 11.9, 1 H), 2.62−2.73 (m, 2 H), 3.70 (s, 3 H), 4.25 (bs, 1 H), 5.08 (bs, 1 H). ^{13}C NMR (101 MHz,) δ −0.2, 26.9, 28.7, 41.5, 52.7, 53.0, 80.2, 98.5, 101.6, 155.1, 172.2, 185.4. MS (DCI − NH_3) (M + 18) 359.1 *m/e* IR (KBr) 3378, 2972, 2157, 1737, 1719, 1673 cm^{-1}. $[\alpha]_D$ = +14.89° (c = 0.991, $CHCl_3$). Anal. Calcd for $C_{16}H_{27}NO_5Si$: C 56.28, H 7.97, N 4.10; found: C 56.18, H 7.92, N 4.06.

Preparation of (2*S*,5*R*)-1-(*tert*-Butoxycarbonyl)-5-ethynylpyrrolidine-2-carboxylic Acid (19). *Cyclization/Reduction.* A mixture of sodium triacetoxyborohydride (94 kg, 444 mol, 1.3 equiv), IPAc (110 kg), and a 26.6 wt % IPAc solution of TMS ketone **14** (421 kg, 328 mol, 1 equiv) was cooled to −10 °C. Trifluoroacetic acid (160 kg, 1400 mol, 4.3 equiv) was added over a 2-h period at an internal temperature of less than 10 °C. The temperature was adjusted to 10 °C, and the mixture was stirred until HPLC analysis indicated complete consumption of starting material (about 8 h). HPLC conditions: Column: Phenomenex, Hydro-RP, 4.6 mm × 250 mm, 4 μm, 25 °C, 1 mL/min, 20 μL injection, λ 210 nm; Mobile phase A: 0.1%

H_3PO_4; Mobile phase B: 0.1% H_3PO_4 in ACN; Gradient: 0 min, 45% B; 10 min, 70% B; 25 min, 80% B; 30 min, 95% B; 35 min, 95% B; 36 min, 45% B; 45 min, 45% B; Retention time (min): **14** (7.5), **17** (19.2). The reaction was added to 750 kg of 25% K_2HPO_4 (prepared by dissolving 250 kg of K_2HPO_4 in 750 kg of water). The pH of the mixture was adjusted to 6.6 using 20% KOH (prepared by dissolving 100 kg of KOH in 400 kg water). The layers were separated. The organic layer was washed with the remaining 25% K_2HPO_4 solution (250 kg) and with water (250 kg). The organic layer was distilled to remove IPAc, which was chased with EtOH to a final volume of about 250 L. An analytical sample was prepared by silica gel chromatography using EtOAc/hexane as an eluent. ^{1}H NMR (400 MHz, DMSO-d_6, 333 K) δ −0.01 (s, 9 H), 1.25 (s, 9 H), 1.66−1.90 (m, 2 H), 1.92−2.16 (m, 2 H), 3.51 (s, 3 H), 4.00−4.07 (m, 1 H), 4.27−4.38 (m, 1 H), 12.15 (br s, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 0.03, 28.2, 32.4, 49.5, 51.8, 59.5, 79.8, 107.0, 172.7. MS (DCI − NH_3) (M + 1) 326.1 *m/e*. IR (KBr) 2959, 2176, 1760, 1703 cm^{-1}. $[\alpha]_D = +61.67°$ (c = 1.028, $CHCl_3$). Anal. Calcd for $C_{16}H_{27}NO_4Si$: C 59.04, H 8.36, N 4.30; found: C 58.76, H 8.29, N 4.27.

Hydrolysis. The EtOH solution of **17** was cooled to 0 °C, and a 3.5 M LiOH solution (287 kg, prepared by dissolving 37 kg of LiOH·H_2O in 250 kg of water) was added such that the temperature remained below 30 °C. The reaction progress was followed by HPLC until no ester remained (2 h). HPLC conditions: Column: Zorbax, Eclipse, XDB-C8, 250 mm × 4.6 mm, 5 μm, 25 °C, 1 mL/min, 20 μL injection, λ 210 nm; Mobile phase A: 0.1% H_3PO_4; Mobile phase B: 0.1% H_3PO_4 in ACN; Gradient: 0 min, 25% B; 25 min, 72% B; 30 min, 95% B; 35 min, 25% B; 45 min, 25% B; Retention time (min): **19-cis** (10.2), **19-trans** (11.0), **17** (28.5). The ethanol was replaced with MTBE (185 kg) by distillation under vacuum, and the layers were separated. The MTBE layer was extracted with water (100 kg) and discarded. The aqueous layer was cooled to 0 °C and neutralized to pH 7 with concentrated HCl. IPAc (220 kg) was added, and the pH was adjusted to 3 with concentrated HCl. The layers were separated, and the aqueous layer was extracted with IPAc (220 kg). The combined organic layers were washed with water (100 kg). The organic solution was distilled under vacuum to a total volume of about 180 L. IPAc (200 kg) was added, and the organic solution was distilled under vacuum to a total volume of about 180 L and then cooled to 0 °C. Crystals formed over a 30-min period. Heptanes (50 kg) was added over a 2-h period, and the resulting mixture was stirred for 2 h at 0 °C. The mixture was filtered, and the solid was washed with cold 1:1 IPAc/heptanes (50 L) and dried under vacuum at 40 °C. The procedure gave 52 kg of acid **19** (65% yield). The final *cis*/*trans* ratio was >99.5 *cis*/<0.5% *trans*. ^{1}H NMR (600 MHz, DMSO-d_6, 343 K) δ 1.39 (s, 9 H), 1.91 (dt, J = 7.7, 15.6, 1 H), 1.98 (dt, J = 7.2, 15.8, 1 H), 2.08−2.16 (m, 2 H), 2.22 (td, J = 7.1, 12.1, 1 H), 4.05−4.12 (m, 1 H), 4.40−4.49 (m, 1 H). ^{13}C NMR (151 MHz, DMSO-d_6, 343 K) δ 27.7, 28.4, 31.8, 48.2, 59.0, 71.7, 78.9, 83.8, 152.4, 172.6. MS (DCI − NH_3) (M + 18) 257.1 *m/e* IR (KBr) 1745, 1648 cm^{-1}. $[\alpha]_D = +23.45°$ (c = 0.99, $CHCl_3$). Anal. Calcd for $C_{12}H_{17}NO_4$: C 60.24, H 7.16, N 5.85; found: C 60.26, H 7.30, N 5.83.

Preparation of (2*S*,5*R*)-1-(2-Chloroacetyl)-5-ethynylpyrrolidine-2-carbonitrile (3). *Amide Formation.* A mixture of acid **19** (50 kg, 209 mol, 1 equiv), IPAc (214 kg) and *N*-methylmorpholine (NMM, 27 kg, 267 mol, 1.25 equiv) was cooled to 0 °C. Isobutyl chloroformate (34 kg, 249 mol, 1.2 equiv) was added over about 30 min at a temperature of less than 30 °C, and the charge vessel and lines were rinsed with IPAc (5 kg), which was added to the reaction vessel. The resulting solution was stirred at 0 °C for 1 h. A portion of the reaction was quenched into benzyl amine and analyzed by HPLC to evaluate the progress of the mixed anhydride formation, which is typically complete at 1 h reaction time. HPLC conditions: Column: Phenomenex, Synergi 4 μm Fusion-RP 80, 250 mm × 4.6 mm column, 1.0 mL/min, 35 °C, λ 205 nm, 10 μL injection; Mobile phase A: 0.1% H_3PO_4; Mobile phase B: 0.1% H_3PO_4 in ACN; Gradient starts at 85% A and decrease to 65% A at 12 min and decrease to 5% A at 25 min, hold at 5% A to 35 min; Retention time (min): amide intermediate (13.9), **3** (14.6) **19** (17.4), **20** (21.0), benzyl amide intermediate (25.0). The reaction mixture was added to cold (0 °C) 28% NH_4OH solution (135 kg) such that the internal temperature of the quench remained below 30 °C. The reaction vessel was rinsed with IPAc (20 kg), which was added to the quench vessel. The mixture was diluted with 26% NaCl solution (150 kg, prepared by dissolving 39 kg of NaCl in 111 kg of water), and the layers were separated. The aqueous layer was extracted with IPAc (100 kg). The combined organic layers were washed with 20% KH_2PO_4 (2 × 250 kg, prepared by dissolving 100 kg of KH_2PO_4 in 400 kg water). The organic solution was concentrated under vacuum to a total volume of about 85 L. IPAc (219 kg) was added, and the solution was concentrated under vacuum to a total volume of about 85 L. IPAc (219 kg) was added, and the solution was concentrated under vacuum to a total volume of about 85 L. The solution contained 0.4% water by Karl Fischer titration.

Nitrile Formation. A solution of THF (233 kg) and DMF (37 kg, 506 mol, 2.4 equiv) was cooled to 0 °C. Thionyl chloride ($SOCl_2$, 57 kg, 479 mol, 2.3 equiv) was added slowly such that the internal temperature remained below 30 °C. The Vilsmeier solution was stirred at 0 °C for 1.5 h. The IPAc solution of the amide from above was added such that the internal temperature remained below 30 °C. IPAc (10 kg) was used to rinse the vessel containing the solution of amide and was added to the reaction vessel. The resulting mixture was stirred for 1 h at 0 °C and was analyzed for reaction completion by HPLC (see HPLC conditions above). The reaction solution was added to cold (0 °C) 5 M NaOH solution (300 kg, prepared by dissolving 50 kg of NaOH in 250 kg of water) such that the internal temperature remained below 25 °C. The layers were separated, and the organic layer was washed with 20% KH_2PO_4 solution (250 kg, prepared by dissolving 50 kg of KH_2PO_4 in 200 kg of water) and 5% NaCl solution (250 kg, prepared by dissolving 12 kg of NaCl in 238 kg of water). The organic layer was distilled to a total volume of about 80 L and was diluted with CH_3CN (197 kg) a total of three times. The organic solution was analyzed by GC to verify that the level of IPAc was below 10% and by HPLC for yield. The organic layer contained 40.1 kg of nitrile **20** (87% yield) and was used directly in the next

step. The HPLC of the crude solution typically contains DMF (9 LC A%), IPAc (9 LC A%), and *N*-formyl-isobutylcarbamate (18 LC A%). These materials do not interfere in subsequent reactions.

Boc Deprotection. The CH_3CN solution of nitrile **20** (40 kg active, 183 mol, 1 equiv) was further diluted with CH_3CN (39 kg) to bring the total to 10 L of CH_3CN/kg **20**. *p*-Toluenesulfonic acid monohydrate ($TsOH \cdot H_2O$, 71 kg, 365 mol, 2 equiv) was added in portions, keeping the internal temperature below 30 °C. CO_2 gas evolution was vigorous; thus, venting for CO_2 was essential. The reaction was stirred for 8 h at 25 °C during which time the reaction became heterogeneous. Disappearance of the starting material was followed by HPLC (see HPLC conditions above). The product solution was used directly in the next reaction. An analytically pure sample was prepared by crystallization from cold (0 °C) IPAc (10 g/g product). ^{1}H NMR (400 MHz, CD_3OD) δ 2.17−2.29 (m, 1 H), 2.36 (s, 3 H), 2.39−2.51 (m, 2 H), 2.53−2.65 (m, 1 H), 3.41 (d, J = 2.33 Hz, 1 H), 4.59 (td, J = 7.03, 2.40 Hz, 1 H), 4.81 (dd, J = 8.71, 6.79 Hz, 1 H), 4.86−5.03 (m, 2 H), 7.23 (d, J = 7.82 Hz, 2 H), 7.70 (d, J = 8.23 Hz, 2 H). ^{13}C NMR (101 MHz, CD_3OD) δ 21.5, 30.5, 32.5, 47.3, 51.7, 77.0, 79.7, 115.9, 126.5, 129.4, 141.4, 142.7. IR (KBr) 3269, 2956, 2560, 2257, 2135 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O_3S$: C 57.52 H 5.52 N 9.58; found: C 57.21, H 5.48, N 9.49.

Chloroacetamide Formation. Upon complete deprotection, the reaction was cooled to 0 °C and *N*,*N*-diisopropylethylamine (52 kg, 401 mol, 2.2 equiv) was added such that the internal temperature remained below 10 °C. The transfer line was rinsed with CH_3CN (2 kg), which was added to the reaction vessel. After the addition the reaction mixture was cooled to 0 °C, and chloroacetyl chloride (25 kg, 219 mol, 1.2 equiv) was added such that the internal temperature remained below 10 °C. The reaction was mixed at 0 °C, followed by HPLC for the reaction completion (see HPLC conditions above). The reaction was slowly added to a cold (0 °C) solution of IPAc (360 kg) and 1 N K_2HPO_4 (490 kg, prepared by dissolving 109 kg of K_2HPO_4 in 625 kg of water). The transfer line was rinsed with CH_3CN (20 kg), which was added to the reaction vessel. The mixture was concentrated to about 500 L and chased with IPAc (720 kg) and water (335 kg) to a total volume of about 450 L. Upon removal of the CH_3CN (less than 1% as determined by NMR) the layers were separated. The aqueous layer was extracted with IPAc (2 × 180 kg). The combined organic layers were washed with the remaining 1 N K_2HPO_4 solution (244 kg).

Crystallization. The organic solution was azeotropically dried by distillation from IPAc (400 kg) and filtered to remove inorganic salts. Karl Fischer analysis of the solution showed 0.5 wt % water. The IPAc solution was solvent exchanged with IPA by a constant volume distillation with the addition of 380 kg of IPA. The IPA solution was concentrated to about 80 L and stirred at room temperature overnight. Solids typically started to crash out during the solvent exchange to IPA. Water (450 kg) was added over 2 h, and the mixture was stirred for 1 h at room temperature. The mixture was cooled to 0 °C to bring the liquor concentration to about 4.5 mg/mL, as determined by HPLC. Product was filtered, and the solid was washed with cold (2 °C) 1:7 IPA/water (72 kg). The product was dried at 40 °C in a vacuum oven for 48 h to obtain 25.4 kg (78.6% yield, 99.2 LC A%) of tan solid. The minor diastereomer was not detectable; HPLC Conditions: Column: Daicel Chiralcel OD-H, 250 mm × 4.6 mm, 0.8 mL/min, 35 °C, λ 205 nm, 5 μL injection; Mobile phase: 80:20 heptane/ethanol; Retention time (min): *trans*-**3** (11.2), *cis*-**3** (14.0). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33−2.49 (m, 4 H), 2.63 (d, J = 2.06 Hz, 1 H), 4.26 (d, J = 13.50 Hz, 1 H), 4.46 (d, J = 13.50 Hz, 1 H), 4.69−4.76 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.65, 33.29, 41.74, 46.82, 48.43, 74.33, 80.18, 117.35, 164.50. IR (KBr) 3252, 1669 cm^{-1}. Anal. Calcd for $C_9H_9ClN_2O$: C 54.97, H 4.61, N 14.25; found: C 54.89, H 4.39, N 14.31.

Preparation of *tert*-Butyl 2-(4-(2-((2*S*,5*R*)-2-cyano-5-ethynylpyrrolidin-1-yl)-2-oxoethylamino)-4-methylpiperidin-1-yl)-isonicotinate (2*S*,3*S*)-2,3-Dihydroxysuccinate (22). A mixture of amine **2** in NMP (123 kg of a 31.4 wt % solution, 131 mol, 1 equiv), milled K_3PO_4 (42 kg, 212 mol, 1.5 equiv), and KI (2.2 kg, 13.3 mol, 0.1 equiv) was degassed by nitrogen sparging for 15 min, then the solution was warmed to 35 °C. Chloroacetamide **3** (27.5 kg, 140 mol, 1.05 equiv) was dissolved in NMP (45 kg) and added over 30 min, maintaining the temperature between 35 and 40 °C. The transfer lines were rinsed with NMP (5 kg), which was added to the reaction vessel. After 3 h, HPLC analysis of the reaction mixture indicated >95% conversion. HPLC conditions: Column: Phenomenex, Synergi Hydro, 250 mm × 4.6 mm, 4 μm, 25 °C, 1 mL/min, 20 μL injection, λ 210 nm; Mobile phase A: 0.1% perchloric acid; Mobile phase B: ACN; Gradient: 0 min 10% B, 30 min 90% B, 35 min 90% B, 37 min 10% B, 45 min 10% B; Retention time (min): **2** (12.4), **3** (13.3), **22** (16.0). After cooling to 25 °C, MTBE (425 kg) and water (450 kg) were charged, and the phases were separated. The MTBE layer was sequentially washed with 5% KH_2PO_4 (453 kg, prepared by dissolving 23 kg of KH_2PO_4 in 430 kg of water) and then water (450 kg). The MTBE layer was filtered through a Cuno R53SP carbon filter, rinsing with MTBE (20 kg). The carbon filtration is necessary to remove color that can be carried into the final product. The source of the color was never identified. The MTBE solution was distilled to approximately 340 L. As the distillation continued, IPA (680 kg) was added to maintain the solvent level around 340 L. The resulting IPA solution was warmed to 60 °C, and D-tartaric acid (20 kg, 132 mol, 1.0 equiv) was charged, and the solution was stirred for 30 min at 60 °C. After nucleation occurred, the slurry was cooled to ambient temperature over 30 min, filtered, and washed with IPA (2 × 150 kg). The cake was dried under vacuum at 50 °C with a nitrogen bleed to give 71 kg of a yellow solid. The color of the product was the result of ineffective washing of the wetcake due to an equipment malfunction. A reslurry procedure was carried out to further purify the material. The isolated solid (71 kg) was suspended in IPA (330 kg). The mixture was stirred at 25 °C for 1 h and filtered. The wetcake was rinsed with two portions of IPA (80 kg each) and dried under vacuum to give 68.7 kg of white solid (88% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.20 (s, 3 H) 1.53 (s, 9 H) 1.55−1.74 (m, 4 H) 2.07−2.16 (m, 1 H) 2.17−2.43 (m, 3 H) 3.33−3.45 (m, 2 H) 3.61 (d, J = 2.20 Hz, 1 H) 3.73−3.87 (m, 3 H) 4.12 (s, 2 H) 4.77 (t, J = 7.00 Hz, 1 H) 4.91−4.98 (m, 1 H) 6.94 (dd, J =

5.08, 1.10 Hz, 1 H) 7.14 (s, 1 H) 8.21 (d, J = 5.08 Hz, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 22.06, 27.69, 28.44, 32.58, 34.33, 34.39, 40.88, 42.59, 45.97, 47.53, 53.17, 71.65, 75.67, 81.36, 81.65, 105.51, 110.42, 118.51, 139.59, 148.05, 158.49, 163.70, 167.44, 172.87. IR (MIC) 3417, 3007, 1719, 1666 cm^{-1}. Anal. Calcd for $C_{29}H_{39}N_5O_9$: C 57.89 H 6.53 N 11.64; found: C 57.81, H 6.56, N 11.42.

Preparation of (*S*)-2-Hydroxysuccinic Acid Compound with 2-(4-(2-((2*S*,5*R*)-2-Cyano-5-ethynylpyrrolidin-1-yl)-2-oxoethylamino)-4-methylpiperidin-1-yl)isonicotinic Acid (ABT-279, 1). *Ester Deprotection.* A mixture of **22** (69 kg, 115 mol, 1 equiv), water (648 kg), and 85% H_3PO_4 (37 kg, 382 mol, 3 equiv) was heated to 60 °C and held at this temperature for 16 h to drive the reaction to completion as determined by HPLC analysis. HPLC conditions: Column: Thermo Aquasil C18, 4.6 mm × 150 mm, 3 μm, 25 °C, 1 mL/min, 20 μL injection, λ 210 nm; Mobile phase A: 0.1% perchloric acid; Mobile phase B: ACN; Gradient: 0 min 5% B, 2 min 5% B, 30 min 90% B, 31 min, 5% B, 40 min 5% B; Retention time (min): **ABT-279** (10.4), **22** (18.0). Upon completion the solution was cooled to room temperature and filtered to remove solids. The filter was rinsed with water (60 kg). The product was crystallized at room temperature as a zwitterion by neutralizing the filtrate. A solution of 8.5% NaOH (prepared by dissolving 30 kg of NaOH in 325 kg water) was added over 30 min to adjust the pH to 6.5. After stirring at 20 °C for 3 h, the slurry was cooled to 10 °C, stirred for 2 h, filtered, and washed with two 162-kg portions of water. The wetcake was 99 LC A% pure, and the zwitterion was carried on to the next step as a wetcake. ^{1}H NMR (400 MHz, CD_3CO_2D) δ 1.65 (s, 2 H) 2.09−2.22 (m, 2 H) 2.22−2.37 (m, 3 H) 2.37−2.54 (m, 3 H) 3.01 (d, J = 2.06 Hz, 1 H) 3.46 (t, J = 11.60 Hz, 2 H) 4.13−4.36 (m, 3 H) 4.38−4.53 (m, 1 H) 4.78−4.86 (m, 1 H) 4.86−4.94 (m, 1 H) 7.30 (dd, J = 6.17, 0.96 Hz, 1 H) 7.64 (s, 1 H) 8.11 (d, J = 6.18 Hz, 1 H). ^{13}C NMR (101 MHz, CD_3CO_2D) δ 19.36, 29.41, 33.47, 33.49, 33.78, 43.00, 43.13, 47.66, 49.30, 59.60, 75.79, 80.84, 112.06, 112.71, 117.94, 140.95, 146.40, 154.69, 165.28, 168.18, 177.08. IR (MIC) 3190, 2113, 1674 cm^{-1}.

Salt Formation/Crystallization. A mixture of the zwitterion wetcake (57 kg, 76 wt %, 109 mol, 1 equiv), water (264 kg), ethanol (215 kg), and L-malic acid (15.6 kg, 116 mol, 1.06 equiv) was heated to 70 °C to achieve dissolution. The clear solution was filtered and 1:1 ethanol/water (59 kg) was used to rinse the vessel and filter. The clear solution was cooled to 20 °C over 2 h and allowed to crystallize. The thin slurry was distilled under reduced pressure to approximately 250 L and further chased with ethanol (568 kg) to a final volume of 250 L. The desired solvent makeup of 15 wt % water in ethanol was achieved by addition of ethanol (305 kg). In order to minimize losses from product buildup on the reactor wall during the distillation, the slurry was heated to 40 °C, held for 1 h, cooled to 0 °C over 4 h, and stirred for 2 h. The product slurry was filtered and washed with cold ethanol (2 × 83 kg). Product was dried at 50 °C under reduced pressure to yield 41.6 kg of **ABT-279·L-malate salt** (99.5 wt %, 99.6 LC A%, 99.4% ee, 93.2% yield). Chiral HPLC conditions: Column: Astec Chirobiotic T, 4.6 mm × 250 mm, 5 μm, 40 °C, 1 mL/min, 20 μL injection, λ 245 nm; Mobile phase A: 0.2% acetic acid in MeOH; Mobile phase B: 0.2% Et_3N in MeOH; Mobile phase composition: 60% A/40% B; Retention time (min): **ent-ABT-279** (6.9), **ABT-279** (8.9). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.26 (s, 3 H) 1.56−1.79 (m, 4 H) 1.96−2.17 (m, 1 H) 2.17−2.46 (m, 4 H) 2.56 (dd, J = 15.64, 7.14 Hz, 1 H) 3.23−3.38 (m, 2 H) 3.51−3.75 (m, 2 H) 3.82−3.99 (m, 3 H) 4.08 (dd, J = 7.14, 6.17 Hz, 1 H) 4.62−4.83 (m, 1 H) 4.91−5.26 (m, 1 H) 6.99 (dd, J = 5.01, 1.03 Hz, 1 H) 7.20 (s, 1 H) 8.20 (d, J = 5.08 Hz, 1 H) 8.62−10.82 (br m, 4 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 20.82, 28.48, 32.56, 33.72, 40.36, 40.94, 42.17, 46.03, 47.64, 54.59, 66.48, 73.82, 75.88, 81.51, 106.03, 111.17, 118.44, 140.70, 147.78, 158.43, 166.45, 171.33, 174.78. IR (MIC) 3295, 3092, 1731, 1672 cm^{-1}. Anal. Calcd for $C_{25}H_{31}N_5O_8$: C 56.70, H 5.90, N 13.23: found: C 56.68, H 5.85, N 13.15.

Alternative Hofmann/Amine Coupling Strategy. *Preparation of 4-Methylpiperidin-4-amine bis(4-methylbenzenesulfonate) (23). Hofmann Reaction.* A mixture of amide **8** (110 g, 0.454 mol, 1 equiv), CH_3CN (260 g), and water (990 g) was cooled to 10 °C, and KOH (131 g, 2.04 mol, 4.5 equiv) was added, resulting in an exotherm from 10 to 24 °C. The slurry was cooled to 1 °C, and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH, 71.4 g, 0.250 mol, 0.55 equiv) was added in one portion, resulting in an exotherm from 1 to 3 °C. After 30 min the reaction was warmed to 23 °C. After stirring for 1 h, no starting material remained as determined by HPLC analysis. HPLC conditions: Column: Phenomonex, Synergi Hydro RP, 4.6 mm × 250 mm, 4 μm, 35 °C, 1 mL/min, 10 μL injection, λ 205 nm; Mobile phase A: 0.1% H_3PO_4; Mobile phase B: ACN; Gradient: 0 min 10% B, 2 min 10% B, 17 min 90% B, 25 min, 90% B; Retention time (min): Boc amine (8.9), **8** (12.2). Sodium sulfite (Na_2SO_3, 5.5 g, 0.044 mol, 0.1 equiv) was added, and the reaction was stirred for 15 min. EtOAc (496 g) was added and the reaction cooled to 11 °C. K_3PO_4 (110 g, 0.482 mol, 1.06 equiv) was added, resulting in an exotherm from 11 to 13 °C. The reaction was warmed to 23 °C, and the layers were separated. The organic layer was washed once with a 25% aqueous NaCl solution (138 g). The product lost to the combined aqueous layers was 1.9% as determined by HPLC analysis. The organic layer was distilled to an oil, which was dissolved in MeOH (500 mL) and distilled to an oil. The oil was dissolved in MeOH (740 mL) and held for use in the next reaction.

Boc Deprotection. A mixture of *p*-toluenesulfonic acid monohydrate ($TsOH\cdot H_2O$, 197 g, 1.04 mol, 2.3 equiv) and IPA (290 g) was heated to 60 °C. The MeOH solution from the previous reaction was added over 30 min, during which time the product crystallized. The resulting slurry was stirred for 19 h, cooled to 0 °C, stirred for 1 h, and filtered. The wet cake was washed twice with IPA (145 g) and dried under vacuum at 50 °C to give 192 g of **23** (92% yield for the two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.33 (s, 3 H) 1.77−1.91 (m, 4 H) 2.29 (s, 6 H) 3.03−3.14 (m, 2 H) 3.18−3.27 (m, 2 H) 3.33 (br s, 2 H) 7.08−7.15 (m, 4 H) 7.44−7.52 (m, 4 H) 8.04−8.43 (br s, 3 H). ^{13}C NMR (DMSO-d_6) δ 20.93, 22.35, 31.55, 39.17, 50.17, 125.01, 127.81, 137.71, 144.22. IR (KBr) 3336, 1724

cm^{-1}. Anal. Calcd for $C_{20}H_{30}N_2O_6S_2$: C 52.38, H 6.59, N 6.11; found: C 52.43, H 6.49, N 6.08.

Preparation of *tert*-Butyl 2,6-dichloroisonicotinate (25). A mixture of 2,6-dichloroisonicotinic acid **24** (875 g, 4.56 mol, 1.0 equiv), DMAP (110 g, 0.90 mol, 0.2 equiv), and NMP (2.4 kg) was stirred for 15 min to dissolve the solids. Boc_2O (2.0 kg, 9.3 mol, 2.1 equiv) was charged as a melt. Triethylamine (0.45 kg, 4.5 mol, 1.0 equiv) was charged over 15 min while maintaining the temperature at 25 ± 10 °C. After 19 h, HPLC analysis indicated 95% conversion. HPLC conditions: Column: Zorbax, Eclipse XDB-C8, 4.6 mm × 250 mm, 5 μm, 35 °C, 1 mL/min, 10 μL injection, λ 210 nm; Mobile phase A: 0.1% H_3PO_4; Mobile phase B: ACN; Gradient: 0 min 5% B, 14 min 55% B, 20 min 90% B, 30 min 90% B; Retention time (min): **2** (10.4), **24** (13.8), **26** (17.2), **25** (21.2). The reaction mixture was diluted with MTBE (6 L) and water (8 L) containing KH_2PO_4 (0.84 kg, 6.2 mol, 1.4 equiv). After cooling to 30 °C the aqueous phase was separated, and the MTBE layer was filtered through a Hyflo bed to remove insoluble material. The MTBE layer was then extracted with water (2 × 6 L). To the MTBE layer was charged Darco-G60 (85 g) and the mixture was stirred for 1 h and filtered through a Hyflo pad. The Darco-G60 treatment was necessary to remove color and extraneous material present in some of the vendor lots of **24**. The MTBE was distilled under vacuum to a volume of approximately 5 L. The distillation was continued, maintaining the volume by the addition of MeOH (8 L). The slurry in MeOH was warmed to 50 °C to dissolve the solids and then cooled to RT to crystallize. Water (1.5 L) was added over 30 min. The slurry was filtered and washed with a mixture of MeOH (5.0 L) and water (2.0 L) in 2 portions. The cake was dried with heat and vacuum, resulting in 0.97 kg of light-brown powder (88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 9 H) 7.71 (s, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.16, 83.76, 122.28, 143.98, 150.76, 161.03. IR (MIC) 2977, 1730, 1546 cm^{-1}. Anal. Calcd for $C_{10}H_{11}Cl_2NO_2$: C 48.41, H 4.47, N 5.65; found: C 48.46, H 4.42, N 5.58.

Preparation of *tert*-Butyl 2-(4-amino-4-methylpiperidin-1-yl)-6-chloroisonicotinate (26). To a mixture of dichloropyridine **25** (1.0 kg, 4.0 mol, 1.0 equiv) and salt **23** (2.03 kg, 4.4 mol, 1.1 equiv) was added NMP (4.1 kg). To the well-stirred reaction mixture was added K_3PO_4 (1.8 kg, 8.5 mol, 2.1 equiv) and the mixture was warmed to 80 °C for 12 h. HPLC analysis indicated 97% conversion (see HPLC conditions above). After cooling the reaction mixture to 25 °C, MTBE (4.8 L) and a solution of K_3PO_4 (1.28 kg) in water (12 L) was added. The addition resulted in three layers. The bottom two layers were separated and extracted with MTBE (4.8 L). The combined MTBE layers were extracted with a solution of K_3PO_4 (0.43 kg) dissolved in water (6.5 L). Analysis of the MTBE layer showed 1.27 kg of chloroamine **26** (97% yield). The solution was concentrated to an oil, which was dissolved in NMP (5 kg) prior to the final coupling reaction. Compound **26** was characterized as the hemi-L-tartrate salt (2:1 base to salt ratio), which was formed in and crystallized from MeOH (5 mL/g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.24 (s, 3 H), 1.53 (s, 9 H), 1.59 (t, J = 5.00 Hz, 4 H), 3.41−3.52 (m, 2 H), 3.74−3.83 (m, 3 H), 6.88 (d, J = 1.00 Hz, 1 H), 7.11 (d, J = 1.00 Hz, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 25.47, 27.49, 35.82, 40.87, 49.85, 71.15, 82.45, 105.04, 109.50, 143.44, 149.25, 158.88, 163.44, 174.80. IR (KBr) 1724 cm^{-1}. Anal. Calcd for $C_{36}H_{54}Cl_2N_6O_{10}$: C 53.93, H 6.79, N 10.48; found: C 53.84, H 6.85, N 10.45.

Preparation of *tert*-Butyl 2-(4-amino-4-methylpiperidin-1-yl)isonicotinate (2). To a Parr hydrogenation vessel under nitrogen was charged 5% Pd/Al_2O_3 (132 g, 10 wt % load) and K_3PO_4 (908 g, 4.3 mol, 1.05 equiv) followed by an NMP solution of **26** (4.17 kg solution, 31.8 wt %, 1.33 kg active, 4.1 mol, 1.0 equiv). NMP (650 mL) was used to rinse the product flask and was added to the reaction vessel. The vessel was sealed, sparged with hydrogen, and warmed to 40 °C with shaking. An HPLC sample after 3 h indicated <0.1% of **26** remained (see HPLC conditions above). The vessel was sparged with N_2, cooled to ambient, and filtered. The solution assayed for 1.14 kg of **2** (96% yield).

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Supporting Information Available

^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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