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Development of a Scalable Synthesis of a Pyridinyl-3-azabicyclononene, a Novel Nicotinic Partial Agonist

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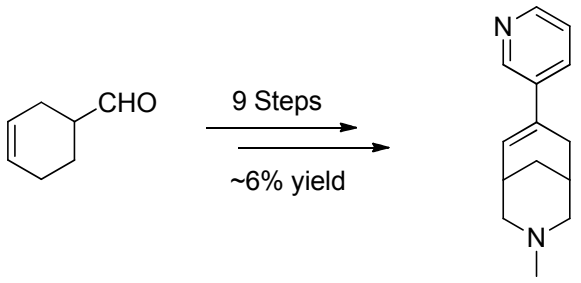
KEYWORDS: Nicotinic, smoking cessation, 3-azabicyclo[3.3.1]nonene, asymmetric, Corey catalyst

ABSTRACT: The process research and development of two syntheses of a novel nicotinic partial agonist TC-8817 ((+)-**5**), are described. The original Medicinal Chemistry route had multiple flaws, making it unsuitable for further development. A second approach was explored which was more amenable to optimization. The key steps were an intramolecular Lewis Acid promoted cyclization, a dibromination/elimination sequence to provide a vinyl bromide and subsequent Suzuki coupling with 3-pyridineboronic acid. The overall yield of ~3-16% over nine steps was offset by the low cost of goods and ease of synthesis. A major drawback was the need for SMB chiral separation on the penultimate intermediate to afford the subsequently desired single enantiomer version. A third- generation, asymmetric variation afforded a key intermediate

in good yield and enantiomeric purity, providing proof of concept for a more efficient production of the desired (+)-enantiomer.

TOC GRAPHIC



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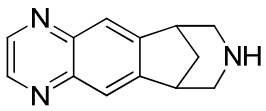
INTRODUCTION

Smoking is the single largest preventable cause of disease and premature death. Smoking related-diseases are considered responsible for the deaths of one in 10 adults globally; this figure continues to rise steadily.[1] In 2006, Pfizer's Chantix® (varenicline, Figure 1, **1**), a novel treatment for the nicotine addiction believed responsible for smoking behavior, was approved by the FDA. Varenicline is characterized as an α4β2 nicotinic acetylcholine receptor partial agonist, the first of this therapeutic class to have reached the market and validate this mechanism.[2] Further characterization has since suggested the mechanism of action may be more complicated, involving activity at additional subtypes of nicotinic receptors containing α7 and α6 subunits.[3,4] Consequently, we chose to pursue novel triple pharmacology ligands (α4β2,α7, α6) with a range of potency and efficacy across these three subtypes to provide additional therapeutic possibilities for treatment of nicotine addiction. Our initial Discovery efforts identified the 3-methyl-7-

(pyridin-3-yl)-3-azabicyclo[3.3.1]non-6-ene (**5,** Scheme 1) as a promising compound for further development.[5]

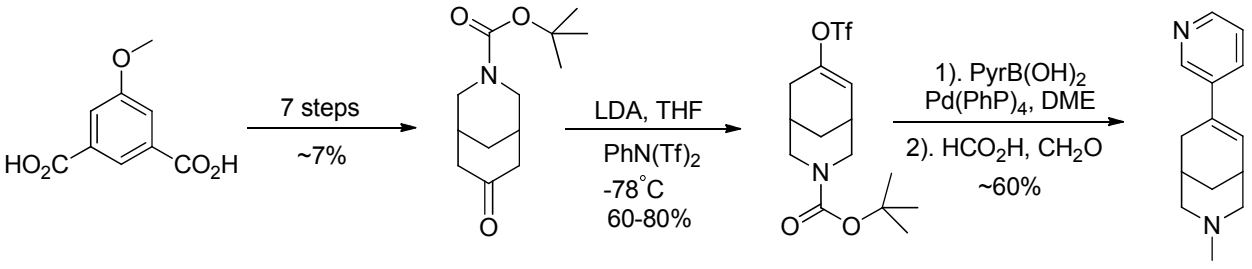
Figure 1. **Varenicline (1).**



Varenicline (1)

The original Medicinal Chemistry route is shown in Scheme 1. This route served to support synthesis of >250 analogs as well as the initial multi-gram batches for behavioral assays.[6] The route was tedious, low yielding, extremely costly and deemed impractical for further scale-up development.

Scheme 1. **Original Medicinal Chemistry Route to Racemic 5.**

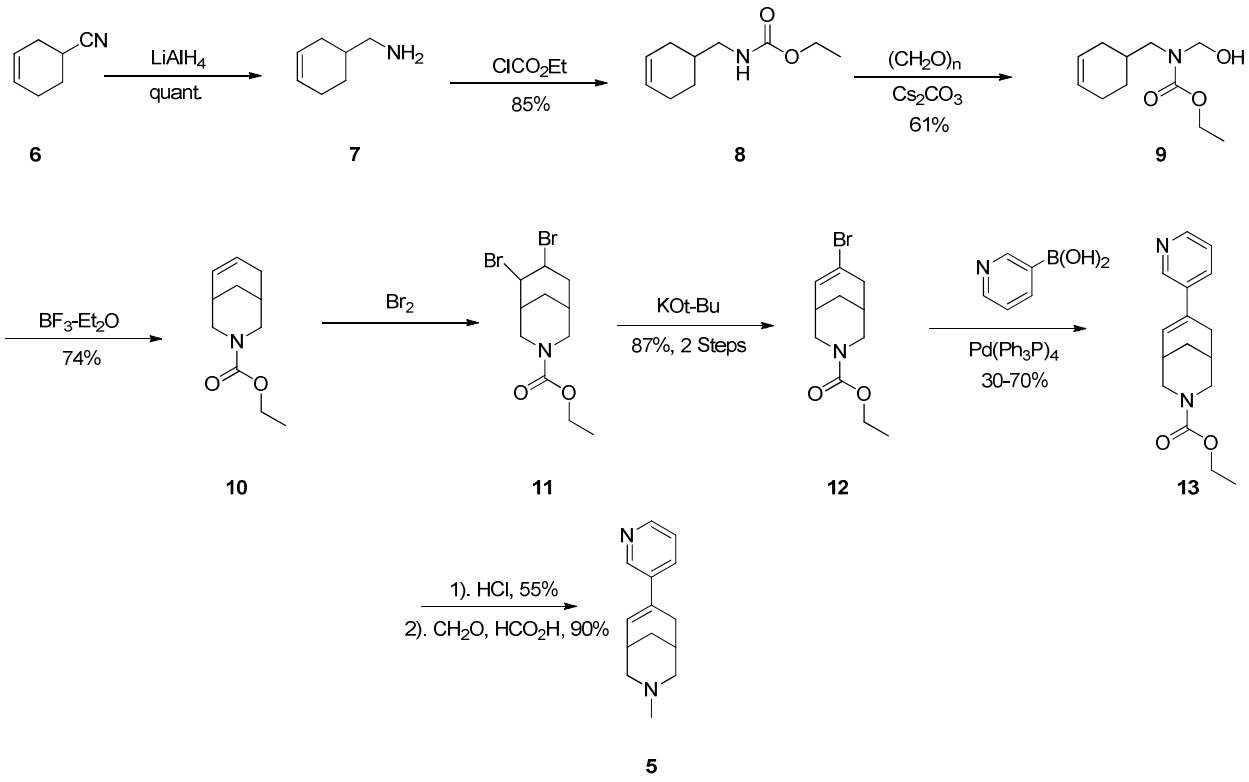


2 **3** **4** **5**

A new route was designed within the Medicinal Chemistry group which addressed many of the issues inherent in the original route shown in Scheme 1. This route (Scheme 2) relied on three key steps: an intramolecular Lewis Acid promoted cyclization of **9** to give **10**[7], the elimination of dibromide **11** to afford vinyl bromide **12**, and the subsequent Suzuki[8] coupling with 3-

pyridineboronic acid to give **13**. While still lengthy, the sequence worked fairly well and appeared amenable to further optimization and scale-up to support a development campaign.

Scheme 2. **Improved Medicinal Chemistry Route to Racemic 5.**

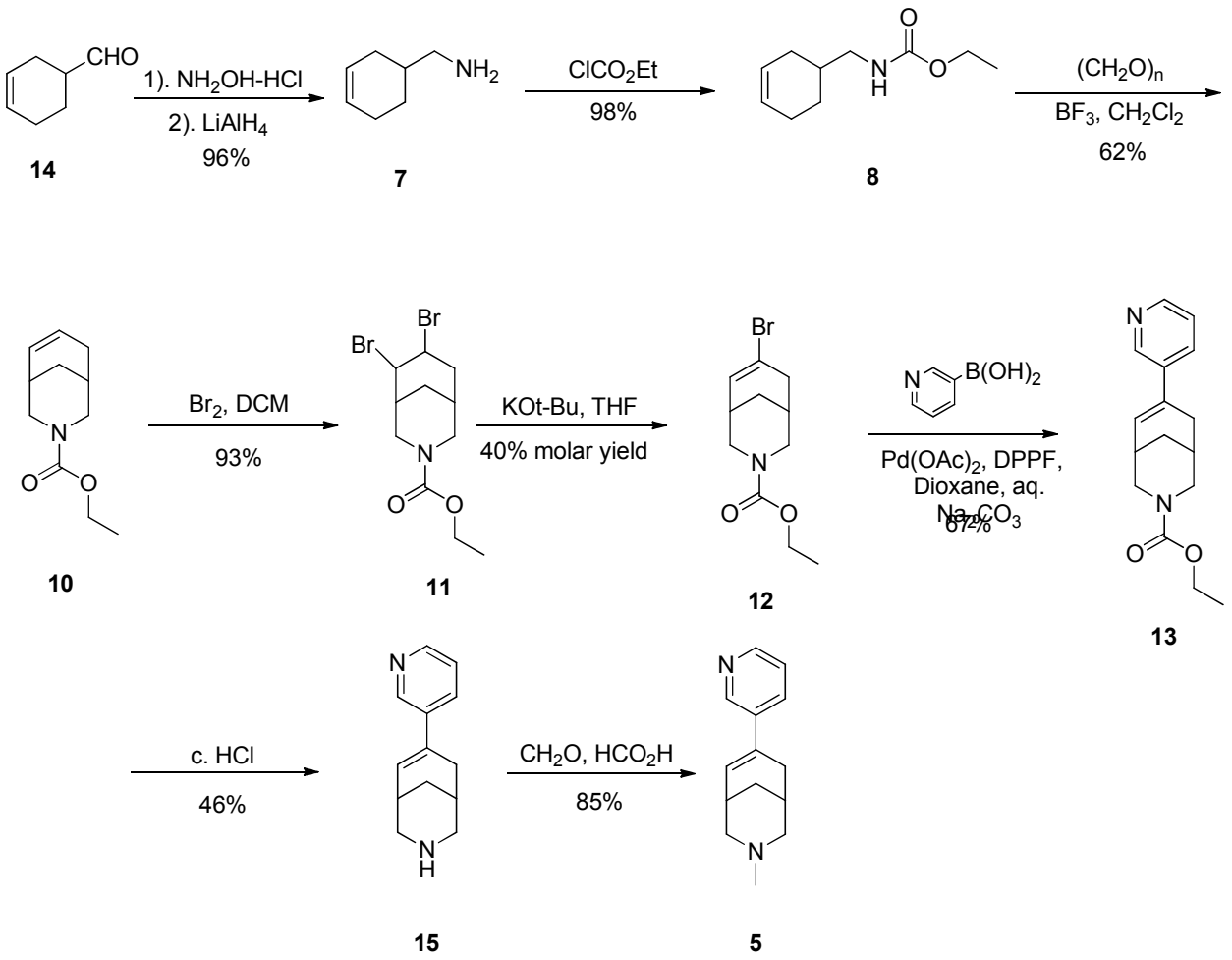


RESULTS AND DISCUSSION

While the improved route shown in Scheme 2 was adequate to meet the initial needs of the program with respect to preclinical profiling, any further advancement of this compound would need a more robust, efficient and cost-effective synthetic access. Scheme 3 illustrates the route refinements developed within the Process group. Due to the high cost and limited availability of the nitrile **6**, an alternative method to obtain amine **7** was sought. Conversion of the inexpensive, readily available carboxaldehyde **14** to an oxime was performed. Initially, this was conducted by

addition of hydroxylamine to sodium hydroxide solution and aldehyde. On larger scale, this resulted in multiple impurities. A simple order of addition switch, adding sodium hydroxide solution to a binary solution of aldehyde and hydroxylamine hydrochloride, resulted in a much cleaner product. Extraction of product from the aqueous mixture with 2-methyltetrahydrofuran (2-MeTHF) gave a solution suitable for direct use in the subsequent lithium aluminum hydride step. This reduction proceeded well on scale to give amine **7** without need for further modification. The formation of carbamate **8** required a thorough investigation, as multiple side products were formed, particularly the undesired urea byproduct. Under the initial conditions employing triethylamine as base, urea formation could actually predominate and yields and purity of carbamate were highly variable. Other carbamates (benzyl, *tert*-butyl) were prepared and carried through the subsequent steps, but these groups proved labile during the Lewis acid cyclization step. A switch to bicarbonate or carbonate base in combination with the ethyl chloroformate alleviated the issue of urea formation. A drawback on scale was the potential for foaming due to carbon dioxide. Aqueous sodium hydroxide solution was shown to be an effective base, provided the base was added slowly to a solution of amine **7** and ethyl chloroformate to avoid exothermic decomposition of ethyl chloroformate in the presence of excess base. A yield of 98% of carbamate **8** was achieved when this step was conducted on 64 kg scale.

Scheme 3. **Process Route to Racemic 5.**



Formation of azabicyclononene **10** originally called for a two-step sequence of hydroxymethylation to **9**, followed by cyclization (as illustrated in Scheme 2). Many conditions were screened to optimize the hydroxymethylation step, including varying equivalents of paraformaldehyde, base (cesium carbonate, potassium carbonate, potassium phosphate), temperature and solvent. The reaction was prone to stalling and sublimation of paraformaldehyde often clogged the reactor; thus, this method proved untenable on larger scales. It was subsequently discovered that use of ~1 eq. of BF_3-etherate gave the desired product **10** in a single step (62% yield), reducing reactor time and providing a more controllable reaction. The

only drawback was the need to employ halogenated solvents such as dichloromethane; use of THF, 2-MeTHF or MTBE did not allow the reaction to go to completion.

Bromination to give dibromide **11** was conducted per the Medicinal Chemistry procedure but with a critical change in workup. It was found that the thiosulfate quench originally employed resulted in a suspension that was difficult to filter, and the product contained sulfur impurities which had to be removed by column chromatography to avoid poisoning the palladium catalyst in the later Suzuki reaction step. A switch to an ascorbic acid quench obviated the need for purification. Dichloromethane was the solvent of choice, as the reaction had a tendency to stall with other solvents. On 7 kg scale, a yield of 93% and purity of 88% were obtained.

Elimination of HBr to provide the vinyl bromide **12** was conducted in THF in the presence of 2.5 eq. of potassium *tert*-butoxide. While near quantitative on smaller scales at room temperature, the yields were reduced on scale-up. On the large scale runs, heating was required in order to achieve rapid completion (room temperature reactions took several days and tended to stall). The increased temperature is a likely cause of reduced yields, though this reaction was not thoroughly studied due to time constraints. A silica gel plug filtration was added on a kilogram scale run to remove some minor impurities, but it was not strictly necessary. Material was obtained with 97% mass recovery and 37% purity on an 11.8 kg scale (reported as a corrected molar yield of 40%) and used directly in the subsequent step. Additional studies of the reaction indicated that an isomeric impurity (likely the allylic bromide based on preliminary spectral data) present in the vinyl bromide, but not readily removed by silica gel plug filtration, substantially reduced the yield, reaction rate and product purity in the subsequent Suzuki coupling. Since the yields and purities were much higher in smaller scale runs, and as this represents a major limitation to the overall route, further study and optimization of this step are clearly needed.

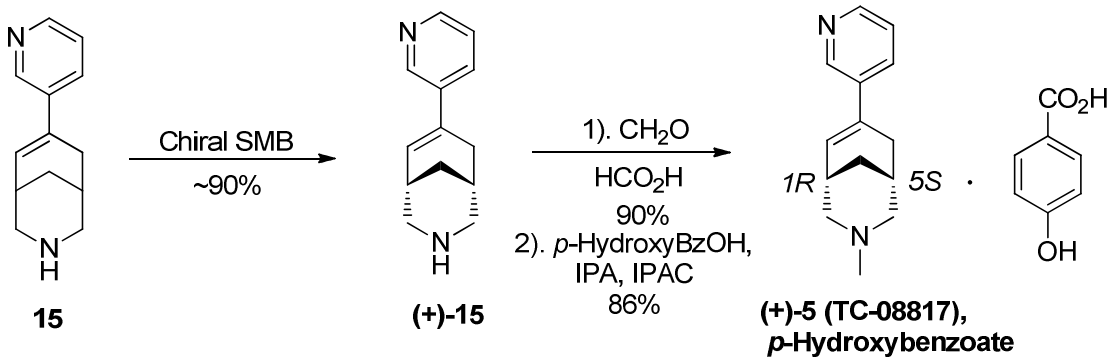
The Suzuki coupling reaction of **12** was thoroughly explored, resulting in a switch from $Pd(Ph_3P)_4$ to palladium(II) acetate/dppf and replacement of dimethoxyethane with dioxane. Other variables were evaluated, such as temperature, stirring speed, choice of base, stoichiometry and water-solvent ratio. No enhancements in yield or variability were achieved, though a DOE approach was not undertaken to further improve this step. On a 2.95 kg scale, **13** was obtained in a yield of 67% (corrected for the purity of the vinyl bromide **12**) and a purity of 80.5%, but this was dependent on scale and the quality of the vinyl bromide employed. The major impurity was found to be ~14% of 3,3-bipyridyl resulting from homocoupling of the 3-pyridineboronic acid. It should be possible to reduce this side reaction by charging the boronic acid gradually, avoiding the presence of a large excess.

Removal of the ethyl carbamate protecting group from **13** required the very harsh conditions of heating under reflux with conc. HCl. Unfortunately, attempts to alter pH and temperature did not improve yields (46% on 3.9 kg scale; 57% corrected for purity of starting material) or variability, though column chromatography was avoided by use of a neutral rinse followed by basification and heptane slurry. When necessary, reduction of palladium levels was achieved through a thiolized silica treatment of **15**.

Finally, methylation under Eschweiler-Clark[9] conditions afforded the desired *N*-methyl product **5** cleanly, rapidly and in high yield (85%). At this point, complete *in vitro* and *in vivo* evaluation indicated a preference for the (+)-enantiomer of **5**, the eventual clinical candidate TC-8817 (Scheme 4). An extensive classical resolution study was performed utilizing 46 chiral acids to separate the desired enantiomer from the racemate. The only acid providing a significant degree of enrichment was di-*p*-anisoyl-D-tartaric. Attempts to find appropriate chromatographic conditions for large scale chiral separation were also unsuccessful. It was discovered that the

intermediate secondary amine **15** was more readily separable by chiral Supercritical Fluid Chromatography (SFC) or Simulated Moving Bed (SMB) chromatographic techniques. Ultimately, SMB chromatography was employed for the separation of material comprising the batch for toxicology studies. It was necessary to make a salt selection at this point as well, as the free base was an oil and the dihydrochloride salt utilized in early preclinical studies proved hygroscopic. A salt screen provided the *p*-hydroxybenzoate as the best candidate, yielding product as a white, crystalline solid (86% yield).

Scheme 4. **Chiral Separation Method for (+)-5 (TC-8817).**

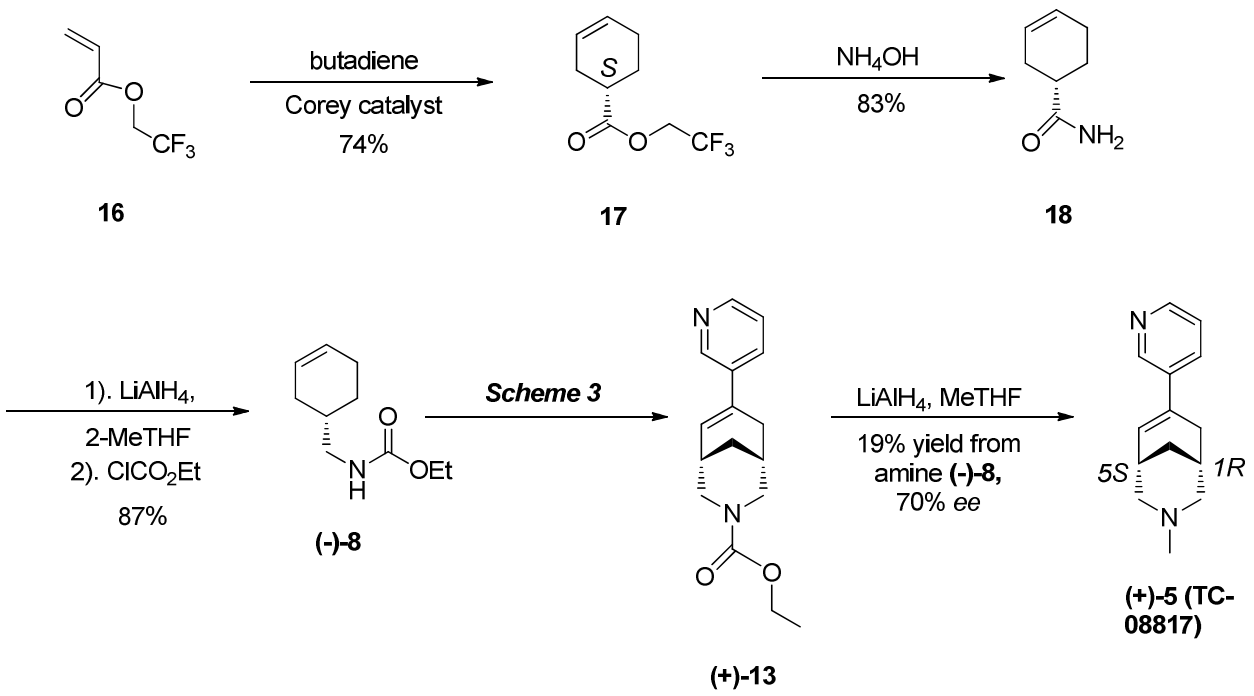


Chiral route process development

While chiral separation of the large batch was ongoing, investigations were conducted into the feasibility of an asymmetric route. Literature precedent existed for the preparation of chiral ester **17**, which would serve as a suitable starting point for elaboration to the single enantiomer version of amine **7**. Several methods, catalysts and conditions were explored, resulting in a facile and robust method (Scheme 5). Cyclization of butadiene with trifluoroethyl acrylate **16** in the

presence of Corey's catalyst, (*R*)-(+)-*o*-tolyl-CBS-oxazaborolidine trifluromethanesulfonimide[10] afforded the desired ester **17** in good yield (74%). A three-step conversion to **(-)-8** via aminolysis to **18**, reduction and ethyl carbamate formation proceeded in good yield (72% overall). Chiral analytical methods were not yet developed for analysis of these intermediates, so material was pushed through using the methods in Scheme 3 and the final product **(+)-5** was evaluated for chiral purity. One change to note was the use of a reductive removal of the carbamate in **(+)-13** to directly give the desired **(+)-5**. This approach had the benefit of avoiding the difficult acid hydrolysis. The overall yield from carbamate **(-)-8** for this third-generation, asymmetric synthesis of product **(+)-5** was 19%, providing ~20 g with an *e.e.* of 70%. It was not clear if the erosion of chirality was occurring in a single step or over multiple steps. In any event, classical resolution through the di-*p*-anisoyl-D-tartrate was sufficient to obtain the desired chiral purity (>98% single enantiomer). Unfortunately, the project was discontinued before the asymmetric route could be further optimized and implemented.

Scheme 5. **Asymmetric Route to (+)-5 (TC-8817).**



CONCLUSIONS

A scalable, nine step synthesis of (±)-**5** was developed. The key steps were an intramolecular Lewis Acid promoted cyclization, a dibromination/elimination sequence to provide a vinyl bromide and subsequent Suzuki coupling with 3-pyridineboronic acid. Though somewhat lengthy and low yielding (~3-16% over nine steps), the route provided the necessary GMP material on kilogram scale in racemic form, which would have been unobtainable by the previous route. The major drawback was the need for chiral SMB separation on the penultimate intermediate to afford the desired single enantiomer version, (+)-5, effectively further reducing the yield by half. A third generation, asymmetric version was identified and explored on laboratory scale. The (*S*)-cyclohexenecarboxylic acid ester **17** was prepared in high yield and enantiomeric purity according to known methods. This was subsequently converted to the (-)-

enantiomer version of the key intermediate, amine **7**. This material was processed according to the optimized route, providing proof of concept for a more efficient production of the desired **(+)-5**, the clinical candidate TC-8817.

EXPERIMENTAL SECTION

General

Purities were determined by HPLC and reported as area % according to the appropriate method. Analytical method for the determination of purity: Column: Xterra RPl 8, 3.5 μm, 100 x 4.6 mm; Gradient elution of 0-100% B over 45 min; Mobile Phase A: 0.01M NH_4HCO_3 : MeCN 95/5(v/v); Mobile Phase B: 0.01M NH_4HCO_3 : MeCN 50/50 (v/v); Flow Rate of 1 mL/min; Wavelength of detection: 220 nM; Run time: 58 min. Analytical method for the determination of chiral purity: Column: Chiralpak IC, 250 x 4.6 mm, 5 μm, Chiral Technologies; Eluant: 95:5:0.1 Heptane:Ethanol:Diethylamine. Analytical method for the determination of chiral purity of **(+)-14** as prepared by SMB: Pump: LPG-3400A or equivalent quaternary pump; Detector: VWD-3400 or equivalent UV detector; Autosampler: WPS-3000 or equivalent autosampler; Column: Daicel Chiralpak AD-H, 250 x 4.6 mm; Column temperature: 40°C; Eluent: Isopropanol / Ethanol / Diethylamine 800:200:1 (v/v/v); Flow: 0.7 ml/min; Run time: 30 min; Detection: UV at 245 nm; Maximum pressure: 100 bar; Injection volume: 5 μL (Autosampler). Proton NMR spectra were recorded on a Varian VNMR at 300 or 400 MHz in the solvent indicated.

Optimized Second-Generation Route

Cyclohex-3-enylmethanamine (7).

A reaction vessel was charged hydroxylamine hydrochloride (44.8 kg, 644.7 mol) and water (305 L) under a nitrogen atmosphere. Stirring was initiated and 2-MeTHF (301.1 L) was charged. Aldehyde **13** (71.3 kg, 647.3 mol) was charged followed by a rinse with 2-MeTHF (11.0 L). A solution of 50% NaOH (34 L, 425 mol) was charged over 2 h to keep the pH at 9 and the reaction temperature between 22-29°C. The reaction mixture was held for 1.5 h at 23°C. Upon completion of reaction (>97% by GC), stirring was stopped and the phases were allowed to separate over 20 min. The lower aqueous phase was removed. A 26% (w/w) solution of NaCl (46.5 kg) was charged to the reactor. Stirring was initiated and the phases were mixed for 20 min. Stirring was stopped and the phases were allowed to separate over 15 min. The lower aqueous phase was removed. A second charge of a 26% (w/w) solution of NaCl (46.5 kg) was added to the reactor. Stirring was initiated and the phases were mixed for 20 min. Stirring was

stopped and the phases were allowed to separate over 20 min and the lower aqueous phase was removed. 2-MeTHF (220.0 L) was added to the reactor containing the product-rich 2-MeTHF fraction and stirring was initiated. The solvent was removed under reduced pressure (250→120 mbar) at 27°C over 10 h to collect 223 L of distillate. The yield of the cyclohex-3-enecarboxaldehyde oxime intermediate was 79.5 kg (98.1%) as a 28.9% (w/w) solution in 2-MeTHF (275.1 kg).

A reaction vessel was purged with nitrogen and charged with a 2.3 M solution of lithium aluminium hydride (295 kg, 763.2 mol) in THF. Stirring was initiated and the above solution of cyclohex-3-enecarboxaldehyde oxime (274.5 kg) was charged at 19-23°C over 5.5 h. The reactor contents were then heated to 56-57°C over 2 h, and the mixture was held for 12 h. The reaction mixture was cooled to 24°C over 2 h. Water (29.3 L) was charged over 2 h keeping the pot temperature between 20-48°C. A 15.5 % (w/w) solution of NaOH (33.2 kg) was charged at 35-38°C over 1 h. Water (28.9 L) was charged at 35-37°C over 40 min. The reaction mixture was then cooled to 25°C over 1 h. The suspension was centrifuged (3 loads) to collect the filtrate. The wet cake (180 kg) was discharged and returned to the reactor. THF (196 L) was charged to the reactor and stirring was initiated. The mixture was stirred for 8 h at 21-22°C. The suspension was centrifuged (3 loads) to collect the filtrate. The wet cake (151 kg) was discharged and returned to the reactor. THF (175 L) was charged to the reactor and stirring was initiated. The mixture was stirred for 2 h at 21-22 °C. The suspension was centrifuged to collect the filtrate. The wet cake (151 kg) was discarded. The three filtrates (731 kg) were concentrated under reduced pressure (700→32 mbar) at 28-40°C over 10 h, collecting 345 L of distillate. The resulting 16% (w/w) solution (422.3 kg) of **7** (67.6 kg, 95.9% yield) was used directly for the preparation of **8.** An analytical sample was obtained by treatment of an aliquot with excess methanolic HCl and evaporation of solvent. ^{1}H NMR (400 MHz, CD_3OD) 5.76-5.65 (m, 2H), 2.87 (d, J=7.1 Hz, 2H), 2.18 (d, J=6.9 Hz, 1H), 2.11 (s, 2H), 1.98-1.75 (m, 3H), 1.39-1.29 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) 129.2, 126.7, 36.9, 34.8, 31.0, 28.1, 26.5. MP: 218-220°C. HRMS (ES) m/z Calcd. for $C_7H_{13}N$+H: 112.1126. Found: 112.1130.

Ethyl cyclohex-3-enylmethylcarbamate (8).

To an inerted reactor was charged a 32% NaOH solution (74.5 kg, 596.0 mol). The reactor contents were cooled to 5°C with stirring. A 16% (w/w) solution of **7** (401.5 kg of solution, 64.2 kg, 577 mol) in 2-MeTHF/THF (401.5 kg) was charged at 2-5°C over 1 h. Ethyl chloroformate (64.5 kg, 594.3 mol) was charged at 0-5°C over 4 h. The reaction mixture was stirred for 1 h at 2-4°C. Upon completion of reaction (< 1.0% of **6** by GC), water (66.8 L) was charged at 2-4°C over 10 min. A 26.2 % (w/w) solution of NaH_2PO_4 (12 kg) was charged to the reactor at 3-5°C over 15 min. The reaction mixture was stirred for 7.5 h at 5-10°C. The reactor contents were warmed to 22°C and stirring was stopped. The phases were allowed to separate over 30 min. The lower aqueous layer (140 L) was removed. Water (67 L) was charged and the reactor contents were mixed for 20 min. Stirring was stopped and the phases allowed to separate over 45 min at 24°C. The lower aqueous layer was removed (60 L). A 26% (w/w) brine solution (81 kg) was charged to the reactor, and the contents mixed for 20 min at 20-23°C. Stirring was stopped and phases were allowed to separate over 30 min. The lower aqueous layer (90 L) was removed. The organic phase was concentrated to dryness under reduced pressure (300→3 mbar) at 36-40°C over 15 h, removing 290 L of solvent. The yield of **8** was 104 kg (98.3%) as a

yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) 5.68 (m, 2H), 4.70 (br s, 1H), 4.12 (q, J=6.6 Hz, 2H), 3.10 (br s, 2H), 2.12-2.06 (m, 3H), 1.77-1.62 (m, 4H), 1.24 (t, 6.7 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) 159.1, 129.7, 128.3, 63.2, 49.0, 36.9, 31.8, 28.8, 27.3, 17.3. HRMS (ES) m/z Calcd. for $C_{10}H_{17}NO_2$+H: 184.1338. Found: 184.1337.

Ethyl 3-azabicyclo[3.3.1]non-7-ene-3 carboxylate (10).

To an inerted reaction vessel was charged paraformaldehyde (18.9 kg, 630 mol) and dichloromethane (399.0 L). Stirring was initiated and **8** (104 kg, 567.5 mol) was charged to the reactor at 25°C. Boron trifluoride etherate (32.8 kg, 231.0 mol) was charged over 6 h at 25-26°C and held for 30 min at 25°C. Upon completion of reaction (< 1% of **8** by GC), the suspension was filtered over a pressure filter. The reactor was rinsed with dichloromethane (43.0 L). The wet cake (1.5 kg) was discarded. A 7.9 % (w/w) solution of $NaHCO_3$ (308.6 kg) was charged at 20-23°C over 2 h. The reactor contents were stirred at 23°C for 5 h. More $NaHCO_3$ solution (4 kg) was charged to bring the pH up to 7. Stirring was stopped and the phases were allowed to separate over 15 min. The top aqueous layer was removed (285.0 L). Water (285.0 L) was charged and the mixture was stirred at 20-22°C for 20 min. Stirring was stopped and the phases were allowed to separate over 15 min. The lower organic layer (477.2 L) was separated from the aqueous layer and charged to a different reactor. The organic layer was dried over $MgSO_4$ (17.9 kg) with stirring for 1 hour at 20°C. The $MgSO_4$ was removed via filtration, and the filter cake was washed with dichloromethane (27 L). The organic solutions were combined and charged to a different 630 L reactor. The solvent was removed under reduced pressure (832→18 mbar) at 35-40°C over 12 h, removing 470 L of solvent. The solution was further concentrated under vacuum (18→9 mbar) at 40°C over 30 min, removing a total of 5.0 L of solvent. Crude **10** (108.5 kg) was discharged and transferred to a thin-film evaporator. Olefin **10** was purified by vacuum distillation at 108-120°C (jacket temperature), at 0.1 mbar, at a feed rate of 2.5-3.5 L/h. The yield was 69.0 kg (62.3%) of **10** as a clear, colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) 5.60-5.45 (m, 2H), 4.17-3.75 (m, 4H), 2.97-2.63 (m, 2H), 2.24-2.07 (br s, 2H), 2.05-1.82 (m, 2H), 1.63 (dd, J=12.2, 36 Hz, 2H), 1.10 (t, J=6.5 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) (complicated by presence of rotamers; individual rotamers not assigned) 159.7, 158.8, 131.9, 131.2, 130.4, 129.95, 63.4, 53.8, 53.6, 49.7, 33.6, 32.6, 32.5, 17.2. HRMS (ES) m/z Calcd. for $C_{11}H_{17}NO_2$+H: 196.1338. Found: 196.1345.

Ethyl 6,7-dibromo-3-azabicyclo[3.3.1]nonane-3 carboxylate (11).

To an inerted reactor vessel was charged **10** (7.0 kg, 35.8 mol) and dichloromethane (49 L). Stirring was initiated and the solution was cooled to 10-15°C. A 42% (w/w) solution of bromine (6.07 kg, 38.0 mol) in dichloromethane (11.9 kg) was charged over 30 min maintaining the temperature around 15°C. The reaction mixture was warmed to 20°C and was held for 2 h at 20°C. To the reaction mixture was charged a 9% (w/w) solution of ascorbic acid (31.0 kg) over 5 min keeping the temperature below 25°C. The reaction mixture was held for 10 min before stirring was stopped and the layers were allowed to phase separate over 10 min. The lower organic layer was transferred to different reactor, and the upper aqueous layer was discarded. Water (28.0 L) was charged to the reactor containing the organic layer. Stirring was initiated and the phases were mixed for 10 min. Stirring was stopped and the layers allowed to phase separate over 10 min. The upper aqueous phase was discarded. The lower organic layer was drummed

and then transferred portion-wise to a rotary evaporator for concentration to dryness under reduced pressure (630→400 mbar) at 30-35°C over 13 h. THF (139.9 L) was charged to the reactor, and the reactor contents were stirred for 10 min. The contents were drummed and then transferred to a rotary evaporator where the solution was concentrated under reduced pressure (116 mbar) at 30-35°C over 5 h until the distillate flow ceased. The yield of **11** was 11.84 kg (92.7%) as an amber oil. The purity by HPLC was 88.2% for the combined areas of both rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) 4.81-4.70 (m, 1H), 4.70-4.68 (br s, 1H), 4.20-4.12 (q, J=17.0 Hz, 2H), 4.12-3.95 (br s, 2H), 3.18-3.15 (d, J=11 Hz,1H), 3.09-3.06 (d, J=11 Hz, 1H), 2.54-2.51 (m, 2H), 2.44-2.37 (dt, J=3 Hz, 17 Hz, 1H), 2.16-2.12 (d, J=13 Hz, 1H), 2.02 (s, 1H), 1.57-1.55 (m, 1H), 1.30-1.26 (t, J=7 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) 155.4, 62.8, 62.0, 49.5, 48.5, 47.2, 39.2, 39.0, 31.0, 26.5, 15.3.

Ethyl 7-bromo-3-azabicyclo[3.3.1]non-7-ene-3-carboxylate (12).

In a reaction vessel equipped with temperature probe and reflux condenser, a solution of potassium *tert*-butoxide (9.32 kg, 83.05 mol) in anhydrous THF (70.8 L) was cooled to 3°C. In another reaction vessel, a solution of **11** (11.84 kg, 33.34 mol, 88.2% purity) in anhydrous THF (23.6 L) was prepared and added to the potassium *tert*-butoxide solution over a minimum of 60 min, while maintaining the temperature at 5°C. Following addition, the suspension was heated at 40°C for a total of 4 h. An IPC by HPLC indicated complete consumption of **11**. The reaction mixture was cooled to 20°C and was quenched into 10% NH_4Cl solution (35.4 L). Following phase separation, the organic layer was concentrated under vacuum at 28-29°C to approximately half volume, removing 45 L of THF. The aqueous layer was extracted with MTBE (47 L), the layers separated and the organic layer was combined with the residue from the concentrated THF layer. The MTBE-THF solution was dried over $MgSO_4$ (5.9 kg) with stirring for 45 min. The mixture was filtered under vacuum via pressure filter fitted with a polypropylene filter disk, and the filter cake was washed with MTBE (5.7 L). The filtrate was concentrated to dryness under vacuum on a rotary evaporator at 29°C, collecting 77 L of distillate. The residue was then dissolved in 1,4-dioxane (16.6 L) and filtered via pressure filter, fitted with Whatman Grade 1 filter paper to remove residual inorganic material. The filter bed was washed with 1,4-dioxane (4.6 L), and the combined organic filtrate was concentrated to dryness under vacuum (174 mbar) on a rotary evaporator at 35°C. The raw yield of **12** was 8.88 kg with an HPLC purity of 36.6%. Based on the purity of the starting material and product, the corrected molar yield was 40.3%. ^{1}H NMR (400 MHz, $CDCl_3$) 6.02 (dd, J=5.8 Hz, 15.6 Hz, 1H), 4.32-3.87 (m, 4H), 3.01-2.67 (m, 3H), 2.42 (d, J=18 Hz, 2H), 2.03 (br d, J=12.6 Hz, 1H), 1.75 (dd, J=12.6 Hz, 36 Hz, 2H), 1.26 (m, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) (complicated by presence of rotamers; individual rotamers not assigned) 159.4, 159.1, 132.2, 131.9, 126.5, 125.7, 63.9, 53.5, 53.3, 49.6, 49.4, 43.3, 42.9, 35.3, 35.2, 32.6, 32.5, 31.9, 17.5. HRMS (ES) m/z Calcd. for $C_{11}H_{16}NO_2Br$+H: 274.0443. Found: 274.0444.

Ethyl 7-(pyridin-3-yl)-3-azabicyclo[3.3.1]non-7-ene-3-carboxylate (13).

Water (11.92 L) and sodium carbonate (3.19 kg, 30.1 mol) were charged to a reaction vessel equipped with a temperature probe and reflux condenser. The mixture was stirred and 3-pyridinylboronic acid (1.319 kg, 10.73 mol) and 1,4-dioxane (17.67 L) were then added. A solution of crude **12** (7.97 kg, containing 2.95 kg actual **12**, 10.75 mol) in 1,4-dioxane (2.95 L) was prepared and was added to the reactor, rinsing the transfer lines with additional 1,4-dioxane (2.99 L). Bis(diphenylphosphino)ferrocene (dppf) (0.291 kg, 0.525 mol) was then added. By using a nitrogen dip tube, the reactor contents were sparged with nitrogen for 30 min while stirring. Palladium(II) acetate (0.116 kg, 0.52 mol) was then added, and under a nitrogen atmosphere, the reaction mixture was heated under reflux (80°C) for 3 h and then cool to ≤ 50°C. An IPC by ^{1}H NMR showed complete consumption of **12**. The reaction mixture was then cooled to ≤ 25°C and was filtered through an in-line filter bag, washing with 1,4-dioxane (5.93 L). Because of equipment limitations, the work-up was done in two additional 50 L vessels; the reaction mixture was divided into two equal portions for the work-up. Each half was processed as follows: Most of the organic solvents were removed by vacuum distillation at 35 °C, collecting ~15 L of distillate and leaving the product residue in water. Water (7.39 L) and 2-MeTHF (16.27 L) were added, and the mixture was stirred for 10 min. Following phase separation, the lower aqueous layer was separated. Water (6.40 L) and concentrated HCl solution (1.37 kg) were then added to the remaining organic layer, and the mixture was stirred for a minimum of 10 min. Following phase separation, the lower aqueous layer was separated and 2-MeTHF (7.26 L) and water (1.47 L), were added as a line rinse. The mixture was basified by the addition of a solution of NaOH (0.784 kg) in water (1.5 L), keeping the temperature ≤ 30°C. After stirring for a minimum of 5 min, and allowing for phase separation, the upper organic phase was separated from the lower aqueous phase (pH 13.27). The organic phase was dried over $MgSO_4$ (1.18 kg) for 30 min and filtered under vacuum via bag filtration. The filter cake was washed with 2-MeTHF (3.05 L) and added to the filtrate. Once the work-up was completed, the product rich organic layers from each half were combined and concentrated to dryness under vacuum on a rotary evaporator at a temperature of ≤ 35°C. The yield of **13** was 1.965 kg (67.1%) as a brown, viscous oil. The purity by HPLC was 80.5%. ^{1}H NMR (400 MHz, $CDCl_3$) 8.60 (s, 1H), 8.45 (s, 1H), 7.63 (s, 1H), 7.22 (m, 1H), 6.11 (d, J=19.6 Hz, 1H), 4.36 (d, J=13.3 Hz, 0.5 H), 4.18 (d, J=12.9 Hz, 0.5 H), 4.08 (d, J=12.9 Hz, 0.5 H), 3.97 (m, 2.5 H), 3.09-2.89 (m, 2H), 2.78-2.40 (m, 3H), 2.19 (br s, 1H), 1.86-1.82 (m, 2H), 1.07 (m, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) (complicated by presence of rotamers; individual rotamers not assigned) 159.8, 159.1, 150.7, 149.5, 149.3, 139.7, 139.0, 138, 135.2, 135.1, 129.7, 129.2, 125.7, 125.6, 63.7, 53.9, 53.8, 50.3, 50.1, 35.5, 35.3, 33.4, 33.3, 32.4, 30.6, 30.5, 17.3. HRMS (ES) m/z Calcd. for $C_{16}H_{20}N_2O_2$+H: 273.1603. Found: 273.1611.

7-(pyridin-3-yl)-3-azabicyclo[3.3.1]non-6-ene (15).

Water (3.9 L), concentrated HCl (21.45 L), and **13** (3.90 kg, 14.32 mol) were charged to a vessel equipped with a temperature probe and reflux condenser. The mixture was heated at ~100°C for a total of 30 h until the IPC by HPLC showed < 1% of **13** remaining. The mixture was cooled to 25°C. In a separate vessel, a 33% solution of NaOH was prepared by dissolving NaOH (10.04 kg) in water (19.97 L), keeping the internal temperature ≤ 45°C. Because of equipment limitations, the work-up was done in two vessels; the reaction mixture was divided into two equal portions for the work-up. Each half was processed as follows: The reaction mixture was brought to pH 7.0 with 33% NaOH solution (12.08 kg), keeping the internal temperature < 30°C.

After stirring for 10 min, the aqueous solution was washed with toluene (2 x 7.8 L), stirring each extraction for 15 min. Following the 2nd toluene wash, the lower product-rich aqueous layer was separated. Toluene (7.8 L) was added to this aqueous layer, and the mixture was basified with 33% NaOH solution (1.40 kg) to pH 13.1, keeping the internal temperature < 30°C. After stirring for 15 min and allowing for phase separation, the lower aqueous layer was separated and extracted with toluene (7.8 L). The product-rich toluene extracts were combined. Once the work-up was completed, the product rich organic layers from each half were combined and azeotropically dried by vacuum distillation (76 mbar) at 27→24°C, removing 8 L of distillate. At 24°C, $MgSO_4$ (1.99 kg) and thiolized silica gel (Silicycle Cat. No. R51030B) (0.4 kg) were added. This was done to remove traces of palladium (725 ppm by ICP-MS), residual water, and black, insoluble, tarry material. The mixture was stirred for 30 min before filtering using a 1 μm filter bag, washing the filter cake with toluene (4 L). The filtrate was concentrated under reduced pressure (43 mbar) at 52→27°C until a volume of 7.4 L remained. Heptane (19.91 L) was added. The resulting slurry was concentrated under reduced pressure (51 mbar) at 30°C until a volume of about 13.2 L remained. Heptane (11.7 L) was added, and the reactor contents were cooled to 24°C. The product was collected by vacuum filtration using a bag filter. The solids were washed with heptane (7.81 L) and dried under vacuum on a rotary evaporator at 35°C for 19 h. The yield of **13** was 1.328 kg (46.3%) as a brown solid. The HPLC purity was 99.8%. Based on the purity of the starting material and product, the corrected molar yield was 57.4%. The palladium content was 46 ppm as determined by ICP-MS. ^{1}H NMR (400 MHz, $CDCl_3$) 8.71 (d, J=2 Hz, 1H), 8.54 (m, 2H), 7.90 (dd, J=5.8 Hz, 8.2 Hz, 1H), 6.49 (d, J=6.3 Hz, 1H), 3.27 (d, J=13 Hz, 1H), 3.19-3.11 (m, 3H), 2.9-2.81 (m, 2H), 2.48-2.43 (m, 2H), 1.79 (dd, J=13.3 Hz, 26 Hz, 2H). HRMS (ES) m/z Calcd. for $C_{13}H_{16}N_2$+H: 201.1392. Found: 201.1394.

3-Methyl-7-(pyridin-3-yl)-3-azabicyclo[3.3.1]non-6-ene (5).

Thiolized silica gel (75 g) was added to a 29% (w/w) solution of **15** in isopropanol (1.725 kg of solution, 0.5 kg, 2.5 mol). This treatment was done to reduce the level of palladium. The suspension was heated to 40°C for 2 h, cooled to 20°C and then stirred for 16 h. The solids were filtered through a pressure filter fitted with Whatman Grade 1 filter paper, washing the filter cake with isopropanol (1 L). The filtrate was diluted with heptane (1.8 L) and the resulting solution was concentrated under reduced pressure (180 mbar) at 45°C until about 2.5 L of the solvent was removed. The isopropanol was then solvent swapped with three separate charges of heptane (1.8 L, 2.5 L, 2.9 L), with vacuum distillation (161-169 mbar) to remove 50% of the solvent following each of three heptane charges. Precipitation was observed, and the flask contents were then vacuum distilled to dryness at 45°C (~50 mbar), leaving 0.465 kg (2.32 mol) of material in the flask. The material was treated with formaldehyde (1.27 kg of 37% aqueous solution, 0.47 kg, 15.7 mol) and formic acid (1.42 kg, 30.7 mol), keeping the temperature < 40°C. The solution was stirred and heated under reflux for 2 h and then cooled to 45°C. An IPC by HPLC indicated the absence of **15**. The reaction mixture was cooled to 20°C. Isopropyl acetate (2.3 L) was added followed by 10 M NaOH solution (4.36 kg) to bring the pH to 13-14, keeping the internal temperature < 40°C. The phases were separated and the lower aqueous phase was extracted with isopropyl acetate (0.9 L). The combined isopropyl acetate extracts were washed with 2 M NaOH solution (1 kg), followed by a water (0.9 L) wash. The isopropyl acetate phase was separated and dried over $MgSO_4$ (0.47 kg). The resulting suspension was filtered through a pressure filter fitted with Whatman Grade 1 filter paper, washing the filter cake with isopropyl acetate (0.6 L).

The concentration of **5** in this isopropyl acetate solution was determined to be 13.48% (w/w). The yield of **5** was 0.456 kg (85.3%). ^{1}H NMR (400 MHz, $CDCl_3$) 8.72-8.71 (d, J=3.0 Hz, 1H), 8.43-8.41 (dd, J=3 Hz, J=15 Hz, 1H), 7.73-7.70 (dt, J=8 Hz, J=3 Hz, 1H), 7.21-7.18 (dd, J =7 Hz, J=4 Hz, 1H), 6.41-6.40 (dd, J=7 Hz, J=1Hz, 1H), 2.86-2.83 (d, J=11 Hz, 1H), 2.79-2.76 (dt, J=10 Hz, J=1Hz, 1H), 2.70-2.64 rotamers (d, J=8 Hz, 1H), 2.50-2.46 (m, 2H) 2.24-2.20 (m, 1H), 2.18 (s, 3H), 2.17-2.13 (dt, J=13Hz, J=3 Hz, 1H), 2.04-2.02 (dd, J=11 Hz, J=3 Hz, 1H), 1.74-1.69 rotamers (m, 1H), 2.04-2.02 (dd, J=13 Hz, J=3 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) 147.2, 146.4, 136.8, 135.6, 132.2, 129.1, 123.2, 63.7, 59.0, 47.0, 33.5, 31.1, 29.8, .28.5.

(1*R*,5*S*)-7-(pyridin-3-yl)-3-azabicyclo[3.3.1]non-6-ene ((+)-15).

Eight positions of a Simulated Moving Bed (SMB) chromatograph were equipped with Supelco Chiralpak AD 20 μm columns. A solution of isopropanol/diethylamine (2.92 kg, 1000:1 (v/v)) was added to **15** (1.30 kg) and the solids were dissolved. The resulting solution was transferred to a flask, followed by an isopropanol/diethylamine (0.14 kg, 1000:1) rinse. The solution was stirred for 3 h 14 min and was applied to the SMB system, eluting with isopropanol/diethylamine (1000:1). During the separation, an IPC by chiral HPLC was done on the extracts. Eight fractions of raffinate with a total volume of 267 L were collected. The raffinate fractions were combined and were concentrated to dryness under vacuum (338→20 mbar) at 45-49°C. The concentrate was further dried under vacuum (14-19 mbar) at 49°C for 2 h, followed by further drying at 49→17°C (heating switched off) for 14 h. Isopropanol (2.27 L) was added to the concentrate *via* cartridge filter, and the solids were dissolved at 29 °C. The product solution was filtered over a POR3 Nutsche filter, followed by a rinse with isopropanol (0.14 L). The resulting clear, dark brown solution (2.61 kg) was stirred until homogeneous. A titration analysis indicated a 23.1% (w/w) solution containing 0.61 kg (46.9%) of **(+)-15**. The achiral purity was 99.3%, and the chiral purity was 99.9%. The palladium content was < 10 ppm as determined by ICP-OES. Analytical data were obtained on a sample of the di-HCl salt. ^{1}H NMR (400 MHz, CD_3OD) (br s, 1H), 8.78 (s, 1H), 8.76 (s, 1H), 8.10 (br s, 1H), 6.65 (d, J=4.2 Hz, 1H), 3.43 (d, J=12.9 Hz, 1H), 3.35-3.25 (m, 3H), 3.01 (dd, J=6.3 Hz, 18 Hz, 1H), 2.93 (s, 1H), 2.69 (d, J=18 Hz, 1H), 2.58 (s, 1H), 2.05 (d, J=13 Hz, 1H), 1.94 (d, J=13.3 Hz, 1H). ^{13}C NMR (400 MHz, D_2O) 142.8, 139.5, 139.3, 137.8, 135.2, 129.9, 126.9, 49.9, 45.7, 31.0, 27.3, 26.1, 24.8. HRMS (ES) m/z Calcd. for $C_{13}H_{16}N_2$+H: 201.1392. Found: 201.1389. $[\alpha]_D^{20}$ = +36.70° (c= 1.0, MeOH).

(1*R*,5*S*)-3-methyl-7-(pyridin-3-yl)-3-azabicyclo[3.3.1]non-6-ene ((+)-5) (TC-8817).

Thiolized silica gel (62.8 g) was added to a 23.1% (w/w) solution of **(+)-15** in isopropanol (2.60 kg of solution, 0.60 kg, 2.99 mol). This treatment was done as a precautionary measure to further reduce the level of palladium. The suspension was heated to 42°C for 2 h, cooled and then stirred at 22°C for 14 h. The solids were filtered through a pressure filter fitted with Whatman Grade 1 filter paper, washing the filter cake with isopropanol (0.35 L). The filtrate was concentrated under reduced pressure (180 mbar) at 45 °C until about 50% of the solvent was removed. The isopropanol was then solvent swapped with three separate charges of heptane (3 x 3 L), with vacuum distillation at 161-169 mbar to remove 50% of the solvent following each heptane charge. The flask contents were then vacuum distilled to dryness at 52 mbar, leaving 0.588 kg of material in the flask. Formaldehyde (1.636 kg of 37% aqueous solution, 0.61 kg,

20.2 mol) and formic acid (1.835 kg, 39.9 mol) were added, and the solution was stirred and heated at reflux (85-87 °C) for 2 h and then cooled to 41 °C. An IPC by HPLC indicated < 0.5% of **(+)-15** remaining. The reaction mixture was cooled to room temperature. Isopropyl acetate (3 L) was added followed by 10 M NaOH solution (4.46 kg), keeping the internal temperature < 40 °C. Additional 10 M NaOH solution (1.0 kg) was added to bring the pH to 13. The phases were separated and the lower aqueous phase was extracted with isopropyl acetate (0.87 L). The combined isopropyl acetate extracts were washed with 2 M NaOH solution (1.60 kg), followed by a water (1.5 L) wash. The isopropyl acetate phase was separated and dried over $MgSO_4$ (0.63 kg). After stirring for 30 min, the solids were filtered through a pressure filter fitted with Whatman Grade 1 filter paper, washing the filter cake with isopropyl acetate (0.6 L). The concentration of **(+)-5** in this isopropyl acetate solution (4.109 kg) was determined to be 14.04% (w/w). The yield of **(+)-5** was 0.577 kg (89.9%), and the purity by HPLC was 99.0%. The palladium content was < 10 ppm in the solid as determined by ICP-OES. Analytical data were obtained on a sample of the mono-fumarate salt. ^{1}H NMR (400 MHz, CD_3OD) (br s, 1H), 8.46 (br s, 1H) 7.95 (d, J=7.8 Hz, 1H), 7.43 (br s, 1H), 6.60 (s, 2H), 6.43 (d, J=6.3 Hz, 1H), 3.55 (d, J=12.5 Hz, 1H), 3.46 (d, J=12 Hz, 1H), 3.22 (dd, J=3Hz, 12.5 Hz, 1H), 3.17 (dd, J=3.6 Hz, 12.1 Hz, 1H), 2.94 (dd, J=12.5 Hz, 19.5 Hz, 1H), 2.89 (br s, 1H), 2.81 (s, 3H), 2.67 (d, J=19.4 Hz, 1H), 2.57 (br s, 1H), 1.97-1.89 (m, 2H). HRMS (ES) m/z Calcd. for $C_{14}H_{18}N_2$+H: 215.1548. Found: 215.1544. $[\alpha]_D^{20}$ = +22.27° (c= 1.0, MeOH, HCl salt).

(1*R*,5*S*)-3-Methyl-7-(pyridin-3-yl)-3-azabicyclo[3.3.1]non-6-ene *p*-Hydroxybenzoate ((+)-5 *p*-Hydroxybenzoate) (TC-8817 *p*-Hydroxybenzoate).

A 14.04% w/w solution of **(+)-5** in isopropyl acetate (4.095 kg of solution, 0.575 kg, 2.68 mol) was filtered through GF/F paper into reactor. The in-line filter was washed with isopropyl acetate (0.27 L) and this wash was added to the filtrate. This solution was then heated under reflux (~88°C). A solution of *p*-hydroxybenzoic acid (0.37 kg, 2.68 mol) in isopropanol (1.58 L) was prepared at 40°C ±5°C. The *p*-hydroxybenzoic acid solution was then cooled to 20°C ±5°C and filtered through GF/F paper, rinsing the inline filter with isopropanol (0.16 L). With vigorous stirring, the filtered *p*-hydroxybenzoic acid solution was then added to the hot solution of (+)-**5** in isopropyl acetate over a minimum of 5 min. The solution was maintained under reflux for 5-10 min before cooling to 0°C ± 5°C over a period of 3.5 h. Stirring was continued at 0°C ±5°C for 2.2 h. The solids were filtered under vacuum through Whatman Grade 1 filter paper and washed with a solution of isopropyl acetate-isopropanol (2.5:1 (v/v), 0.84 L). The solids were dried under vacuum for 30 min and then further dried under rotary evaporatoration to constant weight at 40°C ±5°C. The yield was 0.813 kg (86.0%) of a white, crystalline solid. The achiral HPLC purity was 100.5%. The chiral HPLC purity was determined to be 99.83% ((+)-**5** retention time: 16.4 minutes, (-)-**5** retention time: 17.7 minutes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44-8.43 (d, J=1.5 Hz, 1H), 8.27-8.25 (dd, J=4 Hz, J=1 Hz, 1H), 7.76-7.73 (dt, J=9 Hz, J = 2Hz, 1H), 7.63-7.60 (d, J =9 Hz, 2H), 7.28-7.25 (m, 1H), 6.75-6.71 (d, J=8 Hz, 2H), 6.23-6.11 (d, J= 6 Hz, 1H), 3.38-3.35 (dd, J=13 Hz, J=1Hz, 1H), 3.29-3.26 (d, J=12 Hz, 1H) 3.09-3.05 (dd, J=16 Hz, J=1Hz, 1H), 3.03-3.00 (dd, J=16 Hz, J=3Hz, 1H) 2.76-2.70 (m, 2H), 2.67 (s, 3H), 2.41-2.37 (br s, 2H), 1.73-1.71 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 175.0, 158.3, 147.2, 145.0, 137.5, 135.6, 134.0, 131.1, 128.1, 125.4, 124.0, 114.7, 60.8, 56.7, 44.0, 31.2, 28.4, 26.4, 26.0. Calcd.

for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.43, 71.45; H, 6.74, 6.77; N, 7.88, 7.88.

Third-Generation Asymmetric Route

(*S*)-2,2,2-Trifluoroethyl cyclohex-3-enecarboxylate (16).

Corey's catalyst ((*R*)-(+)-*o*-Tolyl-CBS-oxazaborolidine trifluromethanesulfonimide [(*R*)-(+)-3,3-diphenyl-1-*o*-tolyl-tetrahydropyrrolo(1,2-*c*)(1,3,2)oxazaborole-1,1,1-trifluoro-N-((trifluoromethyl)sulfonyl)methanesulfonamide], (26.0 g, 0.0438 mol), prepared according to known procedures,[10,11] and CH_2Cl_2 (70 mL) were charged to a pressure vessel. The mixture was cooled to -78°C and 1,3-butadiene gas was passed in through a long needle until the required quantity was condensed (58 g, 1.07 mol). 2,2,2-Trifluoroethyl acrylate (67.4 g, 0.438 mol) was added, and the pressure vessel was sealed with a screw cap. The resulting mixture was stirred at room temperature for 2 days. TLC and GC-MS indicated that the reaction was complete. The reaction was quenched by addition of triethylamine (6 mL) and the solvent was evaporated. The crude product was purified by silica gel chromatography, eluting with 5% ether in hexanes. Concentration of selected fractions afforded 66.5 g (74.0%) of **16** as a colorless oil. The enantiomeric purity was determined using chiral GC (gamma-TA column, 60°C). The chiral purity was 98.5% for the (*S*)-enantiomer (RT 29.385 min); the (*R*)-enantiomer (RT 30.900 min) was present at a level of 1.5%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75-5.65 (m, 2H), 4.56-4.42 (m, 2H), 2.72-2.65 (m, 1H), 2.37-2.28 (m, 2H), 2.16-2.06 (m, 2H), 2.05-2.01 (m, 1H), 1.79-1.69 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 176.7, 129.3, 127.3, 125.5 (q, J=277 Hz), 62.8 (q, J=36 Hz), 41.5, 29.8, 27.4, 26.8.

(*S*)-Cyclohex-3-enecarboxamide (17).

To a heavy-walled pressure reactor equipped with a stir bar, stirrer-hotplate, and heating mantle was charged **16** (20.0 g, 0.096 mmol), THF (120 mL) and concentrated ammonium hydroxide (60 mL, 462 mmol). Stirring was initiated and the reactor was sealed. The turbid bi-phasic mixture was warmed to give a clear solution, which was held for 4 h before sampling for COR (TLC; hexanes : EtOAc (1:1) and ^{1}H NMR). TLC indicated the absence of the high Rf starting material spot. Examination of the reaction mixture by ^{1}H NMR also indicated the absence of starting material. The reaction mixture was cooled to room temperature and $CHCl_3$ (100 mL) was added. After mixing for 10 min, the layers were separated. The lower organic phase was collected and the aqueous layer was extracted with $CHCl_3$ (75 mL). After mixing for 10 min, the lower organic phase was collected. The combined $CHCl_3$ layers were dried over Na_2SO_4 (10 g) and filtered. The filtrate was concentrated under reduced pressure at 45-50°C to give 10.0 g (83.1%) of **17** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (br s, 1H), 5.70 (br s, 2H), 2.47-2.39 (m, 1H), 2.25 (m, 2H), 2.17-2.05 (m, 2H), 1.98-1.95 (m, 1H), 1.75-1.65 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 181.4, 129.5, 127.9, 43.3, 30.7, 28.3, 27.2. Mp: 153.5-154.1 °C. $[\alpha]_D^{20}$ = -69° (c= 1.0, $CHCl_3$). HRMS (ES) m/z Calcd. for $C_7H_{11}NO$+H: 126.0919. Found: 126.0922.

Ethyl cyclohex-3-enylmethylcarbamate ((-)-8).

To an inerted reactor equipped with a stir bar, stirrer-hotplate, thermocouple, rubber septum, and nitrogen inlet adapter was charged **17** (26.1 g, 0.209 mol) and 2-MeTHF (312 mL). Stirring was initiated and a 2.0 M solution of lithium aluminum hydride (156 mL, 0.312 mol) was added drop-wise over 45 min while keeping the temperature below 45°C. The reaction mixture was held for 90 min at 45°C. Upon completion of reaction (<1% of **17** by GC-MS), the reaction mixture was cooled to 5°C. Water (9.0 mL) was charged drop-wise over 10 min, followed by addition of a 10% NaOH solution (9.0 mL) over 10 min, then water (20 mL) over 10 min. During the quench, the temperature was held below 40°C. The suspension was stirred for 30 min at 25°C before filtering the mixture. The wet cake was washed with 2-MeTHF (2 x 80 mL) and combined with the filtrate. The resulting solution of (1*S*)-cyclohex-3-enylmethanamine (-)-**7** (510 mL) was used directly in the next step without further purification.

To an inerted reactor equipped with a stir bar, stirrer-hotplate, thermocouple, rubber septum, and nitrogen inlet adapter, was charged a 13.1% (w/w) $NaHCO_3$ solution (240 g of solution, 31.6 g, 0.37 mol) and 2-MeTHF (100 mL). Stirring was initiated and ethyl chloroformate (39 mL, 0.408 mmol) was charged. A solution of the above amine in 2-MeTHF (510 mL) was slowly added over 2 h keeping the temperature at 20-25°C. The reaction mixture was held at 25°C for 45 min. Upon completion of reaction (< 1% amine remaining by GC-MS), stirring was stopped and the layers were allowed to separate over 10 min. The lower aqueous layer was discarded, and the upper organic layer was added back to the reactor along with a 10% (w/w) NaOH solution (200 mL). The mixture was stirred for 30 min. Stirring was stopped and the layers were allowed to separate over 10 min. The lower aqueous layer was discarded, and the upper organic layer was added back to the reactor along with a saturated NH_4Cl solution (250 mL). The mixture was stirred for 30 min. Stirring was stopped and the phases were allowed to separate over 10 min. The lower aqueous layer was discarded, and the upper organic layer was dried over sodium sulfate (10 g) for 2 h. The drying agent was filtered, and the filtrate was concentrated under reduced pressure at 42-46°C to afford 33.25 g (87.0%) of **(-)-8** as a pale yellow oil. $[\alpha]_D^{20}$ = -54° (c= 1.0, $CHCl_3$). Spectral characteristics were identical to racemic **8**.

(1*R*,5*S*)-3-methyl-7-(pyridin-3-yl)-3-azabicyclo[3.3.1]non-6-ene ((+)-5).

To a flask equipped with a stir bar, stirrer/hotplate, septum, thermocouple, and nitrogen inlet line was charged (*1R,5S*)-ethyl 7-(pyridin-3-yl)-3-azabicyclo[3.3.1]non-6-ene-3-carboxylate **13** (*prepared from **(-)-8** according to the same procedures reported above for the racemic material*) (0.6 g, 2.20 mmoles) and Tetrahydrofuran (10 mL). Stirring was initiated and the mixture cooled to 0°C. Drop-wise addition of Lithium Aluminum Hydride (1.8 mL of 2M in THF; 3.60 mmoles;) was performed *via* a syringe and needle. Immediate off-gassing was observed and the solution lightened (deep red-black to a lighter red). After complete addition, the mixture was warmed to 20-25°C and held overnight. An aliquot was analyzed for completion of reaction: 1 drop of the reaction mixture added to 1 drop of 10% NaOH and diluted with methanol to 1 mL and filtered through a 0.45µm filter. LC-MS indicated a ratio of product to starting material of >95:5. (Rt =1.85 min, 215 AMU for product; 2.91 min, 274 AMU for SM). The reaction mixture was cooled to 0°C and 10% NaOH (0.5 mL) was charged drop-wise, followed by water (1 mL). The resulting suspension was stirred for 15 minutes then filtered, washing solids with

THF (2 x 5 mL). The filtrates were concentrated to a red, viscous oil (0.67 g), which was purified by chromatography on 12 g of silica gel, eluting with Dichloromethane:Methanol:Ammonium hydroxide (8:2:0.2). Desired fractions were collected and concentrated to a viscous oil (0.42 g) whose spectral data were identical to that of a **(+)-5** reference standard. Analysis for chiral purity by HPLC indicated an 85:15 mixture in favour of (+)-**5**.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ABBREVIATIONS

IPC, in process control; COR, completion of reaction; TLC, Thin Layer Chromatography; SFC, Supercritical Fluid Chromatography; SMB, Simulated Moving Bed chromatography.

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