Organic Process Research & Development

Article

pubs.acs.org/OPRD

Practical Asymmetric Synthesis of an Edivoxetine·HCl Intermediate via an Efficient Diazotization Process

Michael E. Kopach,* Perry C. Heath, Roger B. Scherer, Mark A. Pietz, Bret A. Astleford, Mary Kay McCauley, Utpal K Singh, Sze Wing Wong, David M. Coppert, Mark S. Kerr, and Peter G. Houghton

Small Molecule Design and Development, Eli Lilly and Company, Indianapolis, Indiana 46285, United States

Gary A. Rhodes

Technical Services & Manufacturing Science, Elanco External Manufacturing & Commercialization, Greenfield, Indiana 46140, United States

Gregg A. Tharp

Manufacturing Technical Services, Eli Lilly and Company, Indianapolis, Indiana 46285, United States

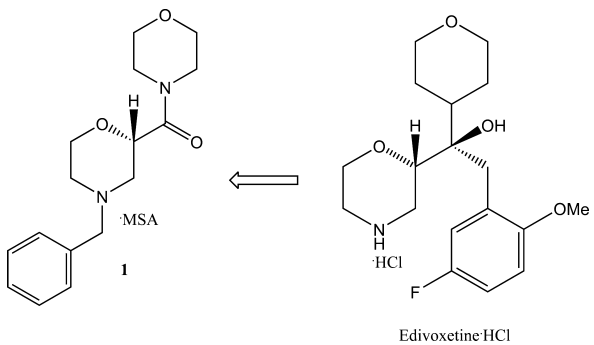
Supporting Information

ABSTRACT: A convergent synthesis of (*S*)-(4-benzylmorpholin-2-yl)(morpholino)methanone methanesulfonate (**1**), a key regulatory starting material for edivoxetine·HCl, was developed at Eli Lilly & Company. This novel synthesis utilizes D-serine as the source of chirality, which is preserved throughout the synthesis. Key features include the development of a scalable diazotization process to produce (*S*)-epoxy acid **7**, which was optimized to improve the process safety profile. The final (*S*)-morpholino acid intermediate **11** was converted to the title compound using T3P with >99.9% purity in 75% yield. Life cycle analysis of the new route revealed a 69% reduction in global warming potential (GWP) for solvent usage relative to the prior route of manufacture.

INTRODUCTION

One of the key regulatory active pharmaceutical ingredient starting materials (API SMs) for the preparation of edivoxetine HCl is (*S*)-(4-benzylmorpholin-2-yl)(morpholino)methanone methanesulfonate (**1**) (Scheme 1). The original route to produce **1** utilized 2-chloroacrylonitrile (2-CAN, **2**) as the key raw material (Scheme 2).[1] One of the major drawbacks of this synthesis was the inherent toxicity of 2-CAN, which is highly toxic in all routes of administration, including oral, dermal, and inhalation.[2] In addition, 2-CAN is corrosive to both the skin and mucous membranes.[2] Another drawback of this synthesis is an inefficient resolution, which is a primary contributor to the high process mass intensity (PMI) of 219 realized for this route.[1a] In addition, prior production campaigns utilized high quantities of dichloromethane, which is a suspect carcinogen, in the amide bond formation step. Finally a salt break and reformation were required to produce the target API SM **1**. With these considerations in mind, we undertook the development of an asymmetric synthesis of **1** (Scheme 3) that addresses these shortcomings of the original route.

Scheme 1. Edivoxetine·HCl retrosynthesis



Edivoxetine·HCl

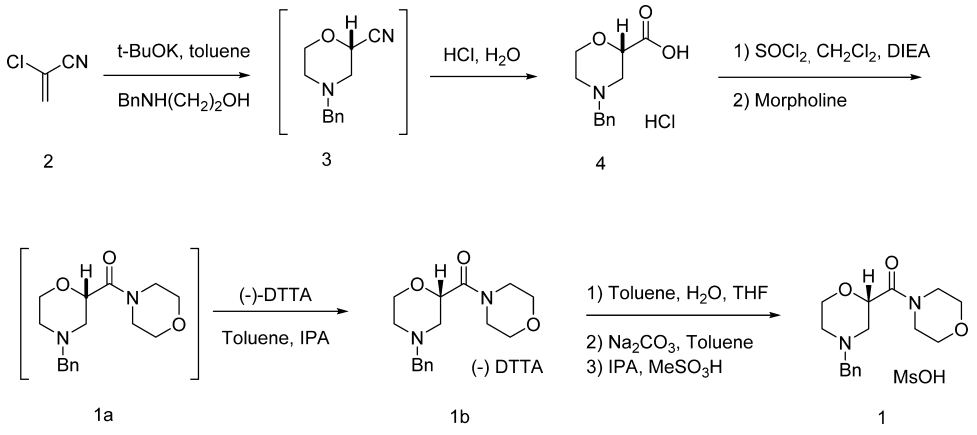
RESULTS AND DISCUSSION

The key raw material for this synthesis is the chiral feedstock D-serine, which is commercially available. It was anticipated that D-serine could be readily converted to epoxide **7** via diazotization, which is a well-known approach to produce chiral epoxides and halohydrin intermediates.[3] The stereochemical course of these reactions proceeds with overall retention of configuration. For the serine system, this is most likely achieved by double inversion through a lactone intermediate (Scheme 4). The proof that is generally cited for the double inversion is the stereochemical outcome. An S_N1 process to produce a carbocation is expected to be energetically unfavorable (carbocation adjacent to the carbonyl). If a pure

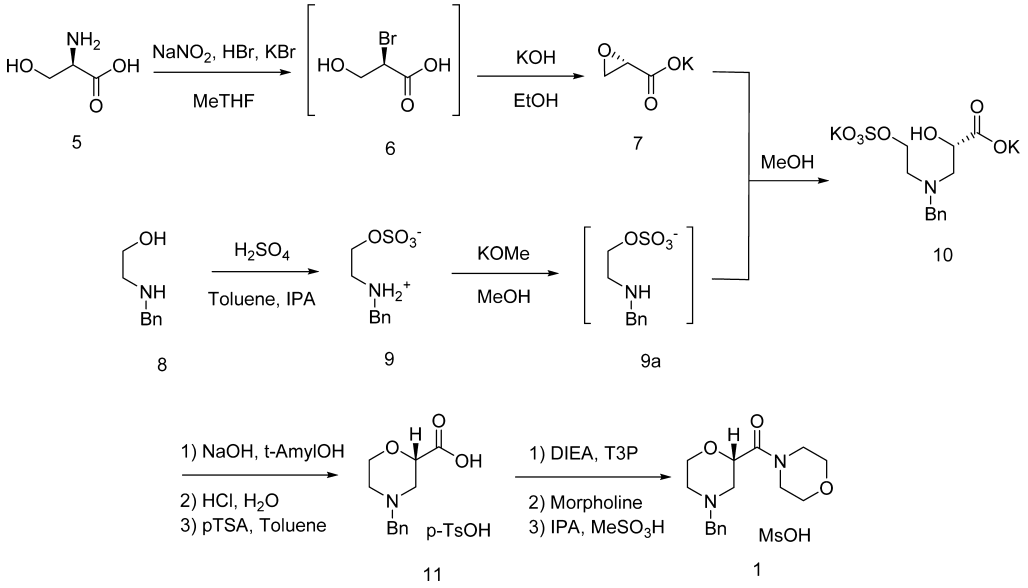
Received: January 9, 2015

DOI: 10.1021/acs.oprd.5b00014
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

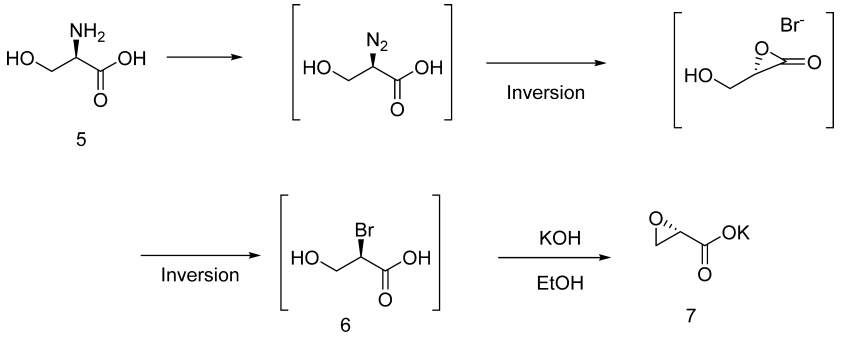
Scheme 2. 2-Chloroacrylonitrile (2) route to produce compound 1



Scheme 3. D-Serine-based route for the preparation of compound 1



Scheme 4. Diazotization mechanistic pathway



S_N1 process were in operation, some racemization due to the carbocation instability would likely be expected.[4] Invoking Occam's razor, we conclude that double inversion through the lactone intermediate is the most likely explanation for the preservation of the stereochemical integrity with overall retention of configuration. However, on the basis of the current data set we cannot definitively rule out a pure retention or other related mechanisms.

While the literature conditions were satisfactory for small-scale work, significant modifications were required to improve the process safety for scale-up. In this system, the addition of aqueous sodium nitrite solution was of concern because of the potential for heat generation and pressure buildup from byproduct gases. Colorimetric measurements revealed a 290 kJ/mol exotherm for the sodium nitrite addition, which translated to a potential adiabatic heat rise of 70 °C for this step. The diazotization step was operated safely on scale by

DOI: 10.1021/acs.oprd.5b00014
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

using a carefully controlled addition rate of the sodium nitrite solution and temperature control (<5 °C reaction temperature) in combination with adequate venting. In addition, feeding the sodium nitrite solution over at least 2 h minimized inadvantageous foaming. Since the diazotization step is run in water, there was no risk of a thermal runaway, as the maximum exotherm associated with an accidental all-at-once feed of the sodium nitrite solution would result in temperatures below the boiling temperature of the reaction solvent (i.e., water). In addition, the worst-case adiabatic temperature rise (70 °C) was also below the decomposition temperature of the reaction mixture (121 °C onset, 360 J/g exotherm).

The next unit operation was extraction of the bromohydrin **6** from the aqueous mixture, which was initially accomplished with several methyl *tert*-butyl ether (MTBE) extractions. These were mass-inefficient, requiring ∼30 volumes (L/kg of **5**) of MTBE, which is a solvent of environmental concern.[5] Several potential replacement solvents were screened, and 2-methyltetrahydrofuran (2-MeTHF) was found to be a superior extraction solvent, allowing 90% partitioning of bromohydrin **6** into the organic layer with two extractions. From an environmental standpoint, 2-MeTHF affords many benefits, as it is a sustainable solvent derived from furfural with a global warming potential (GWP) of 0.2, which is the lowest of all commercial solvents.[6] After the extractions are completed, the volume is reduced to give a 25−40 wt % composition in order to remove residual HBr, which is an important requirement prior to the epoxidation step. On scale we found it beneficial to add back 2-MeTHF and perform a second distillation to the desired final concentration, which assured removal of residual HBr. Bromohydrin **6** was found to lose potency after 1 week of storage, so this intermediate was not campaigned but generated in situ and processed directly to give chiral epoxide **7**. Differential scanning calorimetry (DSC) data were collected for the concentrated 2-MeTHF solution of bromohydrin **6** (40 wt %) and revealed two significant exothermic events. The first transition occurred at a 150 °C onset with an enthalpy of 561 J/g. The second transition occurred at 242 °C with an enthalpy of 496 J/g. For these reasons, the maximum jacket temperatures during the distillations were maintained at not more than 50 °C.

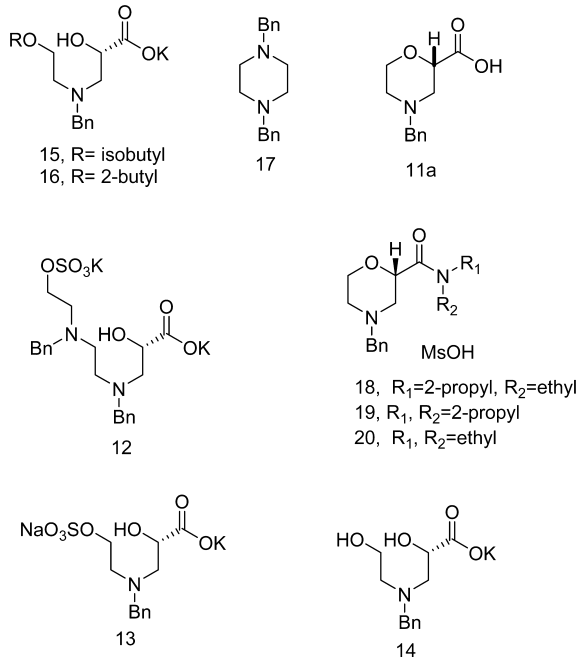
The 2-MeTHF solution of bromohydrin **6** was converted to epoxide **7** by addition of ethanolic KOH at 0 °C. On pilot-plant scale, epoxide **7** was isolated as a crystalline solid in 82% yield. DSC data revealed the onset of an exothermic (262 J/g) decomposition at 130 °C. For this reason, the maximum drying temperature for epoxide **7** was restricted to not more than 50 °C. As noted in the literature, the epoxide was isolated as a 1:1 mixture with potassium bromide.[3] A known purification method is an ethanolic recrystallization of epoxide **7**, but this procedure has low throughput due to the poor solubility of both the epoxide and KBr in ethanol. Ultimately, we decided to take advantage of the 6.5-fold-enhanced solubility of epoxide **7** versus KBr in methanol for the purification.[7] It should be noted that other literature references mentioned the use of methanol for the preparation of **7**, but the yield and purity from these procedures were unclear.[8] Since the optimal solvent in the next processing step is methanol, we decided to telescope the purification of **7** with the subsequent nucleophilic addition reaction. We found that slurrying **7** in 10 volumes of methanol at room temperature followed by removal of the majority of KBr salts by filtration resulted in 90% recovery of **7** in the filtrate. The filtered solution of epoxide **7** containing reduced KBr content was then used directly in the next step of the synthesis.

The other starting material for the convergent synthesis, **9**, was prepared by reacting *N*-benzylethanolamine (**8**) with sulfuric acid in refluxing toluene. Water was removed by azeotropic distillation during the reaction to drive the conversion of **8** to sulfate intermediate **9**. The reaction mixture was then cooled, and IPA was added, after which the solids were filtered and dried to produce **9** in 93% yield on a 20 kg scale. This approach represents a significant improvement relative to other approaches to produce the desired target.[9]

A methanolic suspension of **9** (2 volumes) was treated with KOMe to deprotonate the zwitterion to produce **9a**. The methanolic solution of epoxide **7** was added to **9a**, and the mixture was vacuum-distilled to ∼10 volumes. The mixture was then heated to 40−50 °C, where reactive crystallization of intermediate **10** occurred. An important parameter is to maintain at least a 10 volume composition in order to achieve a stirrable mixture in the reaction vessel. After approximately 8 h the reaction mixture was cooled, and the product was filtered, rinsed with 2 volumes of methanol, and dried to afford intermediate **10** in 80% yield with 90% purity and >99.5% ee on a pilot-plant scale.

A number of low-level impurities were formed in the reaction, but the major impurity **12**, resulting from displacement of the sulfate group in the product **10** with **9a**, was produced in approximately 10% yield in the reaction mixture, of which about 3% remained in the isolated product (Scheme 5).

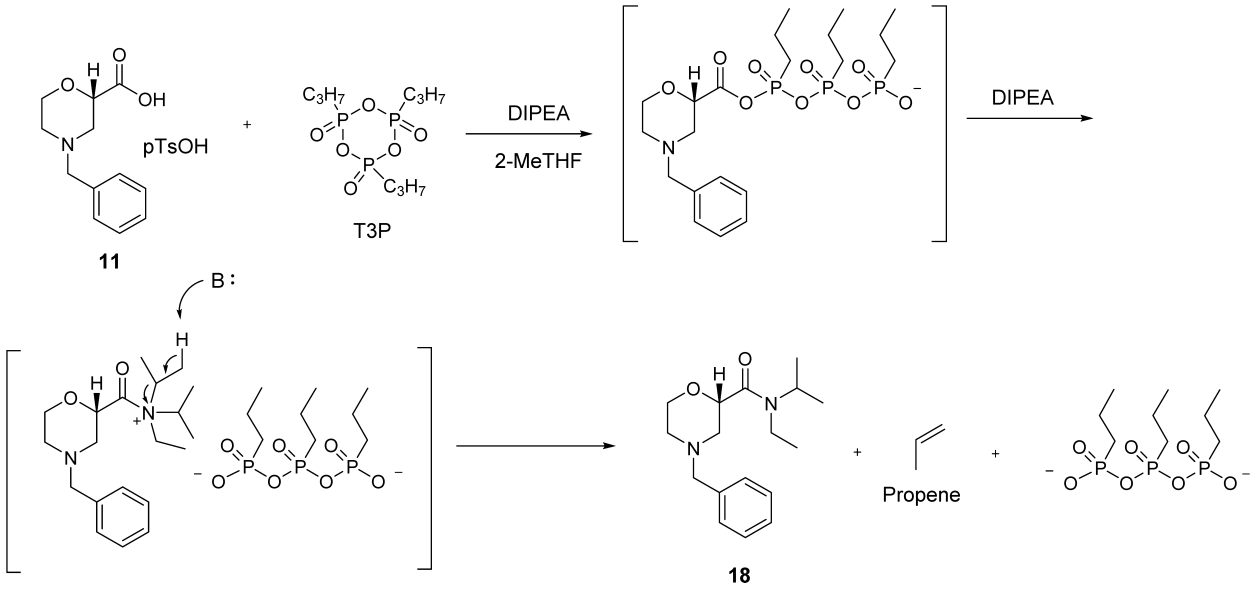
Scheme 5. Impurities formed in the D-serine route



On a small scale, potassium *tert*-butoxide was effective at promoting the reaction, but on a large scale a homogeneous base was preferable for handling and operational ease. KOMe, which is available as a 25 wt % methanolic solution, was evaluated and found to be the best option. Sodium *tert*-butoxide worked well in the reaction and produced the analogous mixed salt **13**. Unfortunately, the necessary methanol desolvation of intermediate **13** proved to be problematic at temperatures even as high as 60 °C. The residual methanol

DOI: 10.1021/acs.oprd.5b00014
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 6. Hofmann elimination pathway to produce impurity 18



level could not be reduced to <2 wt % for **13**, whereas this target could be achieved under the same drying conditions for dipotassium salt **10**. Since methanol is detrimental to the next processing step, dipotassium salt **10** was selected as the preferred salt form.

The ring closure of **10** under basic conditions to produce unsalted morpholine acid was examined, and several bases were screened. Potassium bases such as potassium *tert*-butoxide, potassium *tert*-amylate, and potassium hydroxide in alcoholic solvents resulted in complete conversion but also caused partial racemization. Although up to an 8% yield of the undesired *R* enantiomer could be rejected in the downstream crystallization of **1**, it was nevertheless preferential to avoid any racemization, which increased during late stages of the cyclization and after extended stirs. Sodium bases such as sodium *tert*-butoxide, sodium *tert*-amylate, and sodium hydroxide in alcoholic solvents all gave good conversion without racemization. While alcoholic solvents were the most effective for cyclization, the primary and secondary alcohols isobutanol and 2-butanol produced substantial amounts of ether impurities **15** and **16**, respectively, from displacement of the sulfate group by the corresponding alcohol (Scheme 5). Because this side reaction is prevented with a tertiary alcohol, *tert*-amyl alcohol became the preferred solvent for the cyclization reaction.

An additive crucial to the success of the ring-closure reaction was water. On a small scale, 2 equiv of 50% NaOH(aq) was effective in promoting the cyclization. However, on a larger scale the cyclization reaction would stall under these conditions. A key parameter governing the conversion and purity was found to be the overall water content. The addition of more water beyond the nominal amount brought in by the 50% aqueous base improved the conversion but produced higher levels of diol impurity **14**, which suppressed the yield. We found that the addition of at least 8 equiv of water after 1−2 h of reaction time solved this problem. We surmised that on larger scales mass transfer issues were prevalent and that large particles of starting material were not efficiently broken up by the mechanical agitation. The addition of water during the course of the reaction assisted with solubilizing these large particles, and adding the water late suppressed diol impurity **14** since the starting material was approximately 50% consumed. The preferred concentration for the reaction was 15−20 volumes (L/kg of **10**) in order to maintain good mixing, since sulfate salts formed and precipitated from the solution as the ring closure progressed. The optimum temperature for the ring closure was 80 °C, with higher temperatures leading to increased impurity formation and lower temperatures resulting in excessive reaction times. On a pilot-plant scale, the ring closure was performed in 16 volumes of *tert*-amyl alcohol with 2 equiv of 50% NaOH(aq) and the addition of 17 equiv of water after 1−2 h of reaction time. Under these conditions, the reaction was complete after 4.5 h at 80 °C.

A purification point in the reaction sequence prior to the final isolation of **1** was essential in order to ensure that **1** having a purity ≥99.5% could be routinely attained. We examined salts of the morpholine acid as a possible crystalline intermediate that would provide an appropriate purity upgrade. The *p*-TsOH salt **11** was the only acid salt identified that was both crystalline and possessed low solubility in water.[10] The formation of the *p*-TsOH salt and its isolation were incorporated into the ring-closure step in the following manner. At the completion of the ring closure, the suspension was cooled to 23 °C, and the pH was adjusted to 5 with 5 N HCl. The aqueous layer was extracted with *n*-heptane (1 volume) to remove a key impurity, *N*,*N*′-dibenzylpiperazine (**17**) (Scheme 5). Since impurity **17** was not effectively rejected by the downstream purification, removal at the tosylate salt stage became a critical parameter. After the *n*-heptane extraction, a solution of *p*-TsOH monohydrate (2 equiv) in deionized water (1 volume) was added to the combined aqueous layers. The mixture was seeded and cooled to 0 °C, and the product was filtered and dried to produce tosylate **11**. On a 50 gallon scale, the isolated yield of **11** was 56−57% over three batches, with achiral and chiral purities of >99.9%.[11]

The primary focus in the development of the conversion of **11** to morpholine amide **1** was to develop an efficient process that would prepare material having a purity of >99.5% with no single impurity >0.1%. The peptide coupling reagent T3P was of interest because of its known successes of minimizing epimerization with sensitive substrates and overall mild

DOI: 10.1021/acs.oprd.5b00014
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

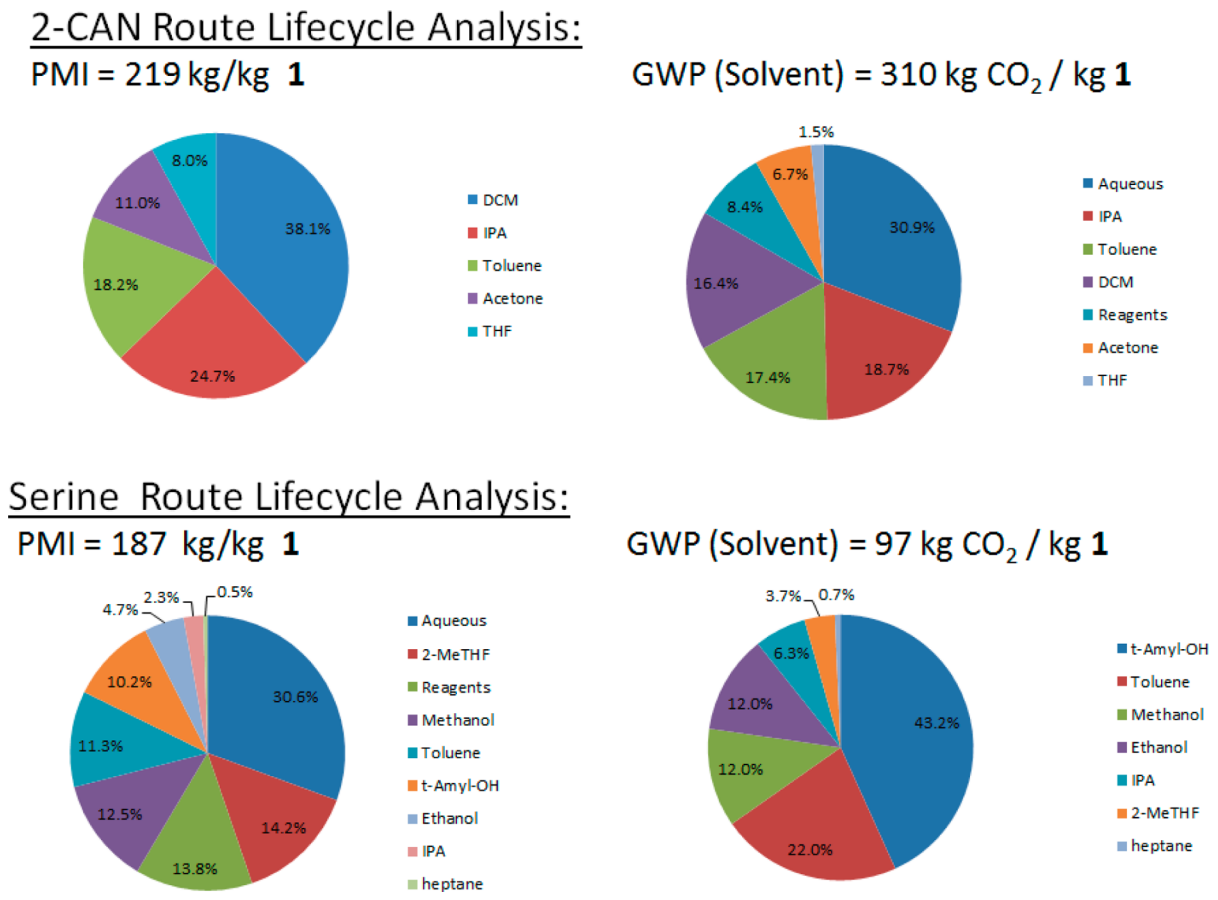


Figure 1. Life cycle analysis comparing the serine and 2-CAN processes.

processing conditions.[12] Initial evaluation of T3P as a coupling reagent produced levels of amide impurity **18** (>0.1%), likely via a Hofmann elimination-type mechanism (Scheme 6).[13] We found that the formation of this impurity could be suppressed (<0.05%) by maintaining the reaction mixture at less than 5 °C. A second minor impurity was also observed, namely, dipropylamide **19** (also formed by Hofmann degradation), but the levels of this impurity were quite low (<0.02%) compared with **18** (Scheme 5). Alternative conditions where the carboxyl group was activated with pivaloyl chloride worked well when trimethylamine was used in place of diisopropylethylamine (DIEA), but this activation method produced >0.1% diethylamide impurity **20**, which was more difficult to control (Scheme 5).[14]

Ultimately toluene/DIEA was the best solvent/base combination for the amide formation. The reaction components were combined, and the solution was cooled to 0 °C, after which 1.2 equiv of T3P was slowly added, keeping the reaction temperature below 5 °C.[15] At the completion of the acylation reaction, the organic layer was washed twice with 0.5 M aqueous sodium carbonate to remove residual *p*-TsOH. The organic solvent layer was vacuum-distilled to give a final concentration of 7 volumes. Isopropyl alcohol (1 volume) and methanesulfonic acid (1 equiv) were slowly added. The resulting suspension was stirred for 1 h at 0 °C, and the product was filtered, rinsed with isopropyl alcohol, and dried to produce the title compound **1** in 85% yield in the laboratory. On a pilot-plant scale 13 kg of intermediate **11** was converted into 9.3 kg of **1** in two batches in 73% average yield with >99.9% achiral purity and >99.9% ee.

Life Cycle Analysis. When routes are compared, useful metrics to consider are PMI and GWP (kg of CO_2/kg of product).[16] PMI is readily calculated as the sum of the total material inputs divided by total kilograms of product produced, and this metric has emerged in recent years as a preferred life cycle analysis (LCA) metric in the pharmaceutical industry.[16] PMI comparison between the D-serine and 2-CAN routes revealed a 14.5% reduction for the serine process (Figure 1).

GWP contributions from solvent usage were calculated using Ecoinvent LCA data.[17] Overall, the GWP from solvent usage is reduced 69% by the serine route. The largest GWP contributor in the new route is *tert*-amyl alcohol (43%). Future modifications to the serine route that would reduce the GWP further include reduction of *tert*-amyl alcohol use and further incorporation of 2-MeTHF, which has a GWP of 0.2.[18] It is noteworthy that the solvents used in the serine process are all considered pharmaceutically acceptable solvents, whereas the 2-CAN process uses the suspected carcinogen dichloromethane as one of the primary process solvents. While it was difficult to access the GWP data directly for the key raw materials D-serine and 2-CAN, assessment of the routes to manufacture indicates a clear environmental advantage for the D-serine raw material. For example, D-serine is likely produced directly from D,L-serine by an enzymatic process that selectively degrades the L isomer.[19] In contrast, 2-CAN is produced by chlorination of acrylonitrile followed by dehydrohalogenation, both of which are highly hazardous unit operations.[20] The overall yields of **1** obtained by the two processes are similar; 27.5% for the D-serine process versus 22% for the 2-CAN process. However, the 2-CAN process has been run for eight API manufacturing

DOI: 10.1021/acs.oprd.5b00014
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

campaigns with the process yields optimized. On the other hand, the D-serine process has greater opportunities for further yield improvement (25−35% estimated), which could translate into significant long-term environmental and economic gains. For these reasons, and because of the inherent hazards associated with 2-chloroacrylonitrile, we expect that the serine-based approach will completely replace the 2-CAN route as the preferred route for commercial manufacture of intermediate **1**.

CONCLUSIONS

A second-generation asymmetric synthesis to produce **1**, the API starting material for edivoxetine·HCl, was developed and piloted to produce the target compound with >99.9% ee in 27.5% overall yield from D-serine. This novel approach features the development of a scalable diazotization reaction and highly chemoselective transformations to cyclize and install the morpholine ring. The D-serine process replaces the prior production process, which utilized highly hazardous 2-chloroacrylonitrile and an inefficient resolution operated on a tonnage scale.

EXPERIMENTAL SECTION

Reaction solvents and reagents were used as purchased, and no special precautions were used to further dry them, unless otherwise noted. Reactions were carried out under a dry nitrogen atmosphere. ^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded in $CDCl_3$ unless otherwise specified. Achiral and chiral HPLC area % purities are reported, unless otherwise noted. The achiral and chiral HPLC methods used to analyze compounds **1** and **11** are described in the Supporting Information.

Potassium (*S*)-(−)-2,3-Epoxypropanoate (Potassium (*S*)-Oxirane-2-carboxylate, 7). *Stage 1: Formation of Bromohydrin **6**.* D-Serine (7.2 kg, 68.5 mol) and potassium bromide (23.4 kg, 196.6 mol) were dissolved in water (24.8 L) in a 50 gallon reactor. Hydrobromic acid (48%, 25.3 kg, 150 mol) was added with agitation, and the reaction mixture was subsequently cooled to an internal temperature of 0 °C. A solution of sodium nitrite (5.9 kg, 85.5 mol) in water (11.2 L) was added to the above solution at a controlled rate, such that the internal temperature remained <5 °C. The reaction vessel was well-vented during the addition to prevent pressure buildup. The reaction mixture was then agitated for 1 h, during which it was repeatedly pressurized to 20 psia and vented to purge byproduct gases. The mixture was warmed to 20−25 °C, and the aqueous layer was extracted three times sequentially with 2-MeTHF (43, 29, and 14.5 L). The 2-MeTHF layers were combined and vacuum-distilled (1.5 psia, 20−25 °C internal temperature) to a final volume of 29 L. 2-MeTHF (39 L) was added to the reaction vessel, and the vacuum distillation was repeated to a final volume of 29 L to ensure that residual hydrobromic acid was removed. This solution of bromohydrin **6** was used directly in the next stage.

*Stage 2: Formation of Epoxide **7**.* The stirred solution of bromohydrin **6** from the first stage was diluted with ethanol (denatured with 5% methanol) (14.4 L) and cooled to an internal temperature of −5 °C. Potassium hydroxide (8.5 kg, 128.7 mol) was charged into a separate vessel containing ethanol (denatured with 5% methanol) (43 L), which was agitated and cooled at 0 °C. At the completion of the charge, the internal temperature was raised to 20 °C, and the contents were agitated until complete dissolution was achieved. The potassium hydroxide solution was then charged into the reactor containing the chilled stage 1 solution. The internal temperature of the reactor containing the stage 1 solution was maintained between −5 and 0 °C during the addition of the potassium hydroxide solution. The reaction mixture, which was now a suspension, was stirred for an additional hour at −5 to 5 °C. The suspension was filtered, washed with 2-MeTHF (29 L), and dried in vacuo at 40 °C to produce 14.7 kg of compound **7** as a white solid (82% yield, 48.1% purity).[21] ^{1}H NMR (400 MHz, D_2O) δ 2.64−2.66 (m, 1H), 2.79−2.82 (m, 1H), 3.22−3.24 (m, 1H).

2-(Benzylamino)ethyl Hydrogen Sulfate (9). *N*-Benzylethanolamine (14.0 kg, 92.6 mol) and toluene (84.6 L) were charged into a 50 gallon reactor. The agitated mixture was inerted with nitrogen and heated to 35−40 °C. Sulfuric acid (96%, 9.74 kg, 95.37 mol) was added over 20 min, leading to an exotherm of 54 °C. The mixture was heated to reflux, and water was removed by azeotropic distillation to decrease the water level to <100 ppm. The mixture was cooled to 20−30 °C, and isopropyl alcohol (33.5 L) was added. The mixture was cooled to 10−20 °C, stirred for 30 min, and filtered, and the wet cake washed with a solution prepared from toluene (26.6 L) and isopropyl alcohol (15.4 L). The solids were dried in vacuo at 40 °C to afford 19.71 kg of compound **9** in 93% yield with >99% purity. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.11 (s, 2H), 4.00−4.03 (m, 2H), 4.15 (s, 2H), 7.40−7.48 (m, 5H), 8.90 (s, 2H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 132.2, 130.5, 129.4, 129.1, 61.7, 50.5, 46.7; MS (ESI) m/z 232.0627 (232.0638 calcd for $C_9H_{14}NO_4$, MH), mp (DSC) 234 °C.

Potassium (*S*)-3-(Benzyl(2-(sulfonatooxy)ethyl)-amino)-2-hydroxypropanoate (10). *Stage 1: Purification of Epoxide **7**.* Potassium (*S*)-(−)-2,3-epoxypropanoate (46.6%, 12.68 kg, 46.85 mol) and methanol (59 L) were charged into a 50 gallon reactor. The mixture was agitated for 2 h at 20−30 °C and then filtered. The filtered solution of purified epoxide **7** was used in the next stage. The solution was analyzed by quantitative NMR spectroscopy to measure the amount of **7** (42.6 mol, 91% recovery).

Stage 2: Epoxide Opening. Compound **9** (9.85 kg, 42.6 mol) and methanol (19.7 L) were charged into a 50 gallon reactor. Potassium methoxide (25 wt % in methanol, 11.95 kg, 42.59 mol) was added while maintaining the temperature below 35 °C. Then the epoxide solution from stage 1 was added to the reactor. The volume was reduced to 49 L by vacuum distillation (4 psia, 30−40 °C). After the completion of the distillation, the mixture was agitated at 50 °C until at least 80% conversion had been achieved (ca. 8 h). Once the target conversion was achieved, the reactor contents were cooled to 20−25 °C, and the thick suspension was diluted with 49 L of methanol to aid with the isolation. The product was filtered, and the solids were washed with 20 L of methanol and dried in vacuo at 60 °C to afford 13.4 kg of compound **10** in 80% yield with 90% purity and 99.5% ee. ^{1}H NMR (400 MHz, D_2O) δ 2.63−2.87 (m, 4H), 3.64−3.67 (m, 1H), 3.75−3.78 (m, 1H), 4.02−4.05 (m, 3 H), 7.22−7.33 (m, 5H); ^{13}C NMR (75.5 MHz, D_2O) δ 137.6, 129.8, 128.5, 127.5, 70.1, 66.2, 57.8, 57.7, 51.8; MS (ESI) m/z 320.0788 (320.0798 calcd for $C_{12}H_{18}NO_7S$, MH).

(*S*)-4-Benzylmorpholine-2-carboxylic Acid *p*-Toluenesulfonate (11). Compound **10** (7.9 kg, 90.5% potency, 18.0 mol) and *tert*-amyl alcohol (95 kg) were charged into a 50 gallon reactor. Sodium hydroxide (50 wt %, 3 kg, 37.5 mol of

DOI: 10.1021/acs.oprd.5b00014
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

base, 83.3 mol of water) was added while the mixture was agitated. The mixture was heated to an internal temperature of 80 °C, and after 45−90 min, water (4 kg, 222 mol) was added. After the addition of the water, the mixture was agitated at 80 °C until reaction completion (≤2% starting material remaining, ca. 3 h). The reaction mixture was cooled to 30 °C, and water (35.7 kg) was added. The mixture was agitated, and the pH was adjusted to 5.0 using HCl (37%, ca. 3.6 kg). The layers were separated, and the aqueous layer was charged into a separate 50 gallon reactor. *n*-Heptane (5.4 kg) and water (23.7 kg) were added to the organic layer, and the mixture was agitated for 0.5 h at 30 °C. The layers were separated, and the aqueous phase was combined with the first aqueous layer. The combined aqueous layers were cooled to an internal temperature of 25 °C, and a solution of *p*-toluenesulfonic acid monohydrate (96%, 8.0 kg, 40.38 mol) dissolved in water (6.2 kg) was slowly added to form the acid salt. The suspension was cooled to 5 °C, agitated for 1 h, and then filtered. The filtered solids were washed with water (15.8 kg) and dried at 20 mm vacuum at a jacket set point of 80 °C to afford 4.4 kg of compound **11** in 56% yield with >99.9% HPLC purity and >99.9% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51−7.40 (m, 7H), 7.10 (d, J = 7.9 Hz, 2H), 4.37 (m, 3H), 4.02 (d, J = 11.3 Hz, 1H), 3.73 (m, 1H), 3.44 (d, J = 11.4 Hz, 1H), 3.10−3.25 (m, 3H), 2.26 (s, 3H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 168.8, 145.6, 138.4, 131.7, 130.2, 129.5, 129.3, 128.6, 125.9, 71.6, 63.3, 59.8, 51.5, 50.5, 21.2; MS (ESI) m/z 222.1112 (222.1125 calcd for $C_{12}H_{16}NO_3$, MH); mp (DSC) 212 °C.

(*S*)-(4-Benzylmorpholin-2-yl)(morpholino)methanone Methanesulfonate (1). PTSA salt **11** (6.5 kg, 16.52 mol) and toluene (65 L) were charged into a 50 gallon reactor that was kept under a nitrogen atmosphere. *N*,*N*-Diisopropylethylamine (4.3 kg, 33.26 mol) was added to the mixture, which was agitated for 0.5 h at 25 °C. The reactor was cooled to 0 °C, and 1-propanephosphonic acid cyclic anhydride (T3P, 52.1 wt % in toluene, 12.7 kg, 20.79 mol) was added. The reaction mixture was stirred for 1 h at 0 °C, and then morpholine (2.2 kg, 25.25 mol) was charged into the mixture at a rate such that the reaction temperature remained at ≤5 °C. The reaction mixture was stirred for 1.5 h at 0 °C and then quenched by the addition of a chilled (0 to 5 °C) aqueous sodium carbonate solution (0.5 M, 40 L). The mixture was agitated while being warmed to 25 °C, and then the layers were separated. The organic layer was washed two more times at 25 °C with aqueous sodium carbonate (0.5 M, 2 × 40 L). The organic layer was reduced to a volume of 40 L by vacuum distillation (0.5 psia, 50 to 55 °C). Isopropyl alcohol (6.3 L) was added to the organic layer, and the solution was cooled to 0 °C. A solution of methanesulfonic acid (1.6 kg, 16.64 mol) dissolved in isopropyl alcohol (4.35 L) was added to the reaction mixture over 20 min to form the acid salt. The suspension of crystals that formed was stirred for 1 h at 0 °C and filtered, and the filtered solids were washed with isopropyl alcohol (12.5 L) and dried under full vacuum at a jacket set point of 80 °C to afford 4.77 kg of compound **1** in 75% yield with >99.9% HPLC purity and >99.9% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.49 (m, 2H), 7.47−7.41 (m, 3H), 5.02 (dd, J = 2.4 Hz, J = 10.8 Hz, 1H), 4.36 (ddd, J = 2.2 Hz, J = 13 Hz, J = 13 Hz, 1H), 4.26−4.18 (m, 2H), 4.01 (dd, J = 3.4 Hz, J = 13 Hz, 1H), 3.71−3.38 (m, 10H), 3.17−3.09 (m, 1H), 2.91−2.83 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.5, 131.3, 130.5, 129.5, 127.2, 69.6, 66.8, 66.5, 63.5, 61.7, 52.2, 50.8, 46.1, 42.4, 39.5; MS (ESI) m/z 291.1687 (291.1703 calcd for $C_{16}H_{23}N_2O_3$, MH); mp (DSC) 176 °C.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Chiral and achiral HPLC methods for compounds **1** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kopach_michael@lilly.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge the management at Eli Lilly and Company for past and present support of the edivoxetine project. In addition, we acknowledge the contributions of Evonik Industries for the use of their facilities and personnel to implement pilot-plant runs for the D-serine process. Finally, we acknowledge the contributions of Prof. A. I. Meyers, one of the founding fathers of asymmetric synthesis.

■ REFERENCES

(1) (a) Kopach, M. E.; Singh, U. K.; Kobierski, M. E.; Trankle, W. G.; Murray, M. M.; Pietz, M. A.; Forst, M. B.; Stephenson, G. A.; Mancuso, V.; Giard, T.; Vanmarsenille, M.; DeFrance, T. *Org. Process Res. Dev.* **2009**, *13*, 209. (b) Kopach, M. E.; Roberts, D. J.; Johnson, M. D.; McClary-Groh, J.; Adler, J. J.; Schafer, J. P.; Kobierski, M. E.; Trankle, W. G. *Green Chem.* **2012**, *14*, 1524. (c) King, F. D.; Martin, R. T. *Tetrahedron Lett.* **1991**, *32*, 2281. (d) Cases-Thomas, M. J.; Masters, J. J.; Walter, M. W.; Campbell, G.; Haughton, L.; Gallagher, P. T.; Dobson, D. R.; Mancuso, V.; Bonnier, B.; Giard, T.; DeFrance, T.; Vanmarsenille, M.; Ledgard, A.; White, C.; Ouwerkerk-Mahdevan, S.; Brunelle, F. J.; Dezutter, N. A.; Herbots, C. A.; Lienard, J. Y.; Findley, J.; Hayhurst, L.; Boot, J.; Thompson, L. K.; Hemrick-Luecke, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2022.

(2) (a) Gizhlaryan, M. S.; Khechumov, S. A. Toxikologische Charakterisierung von α-Chloracrylnitril (German translation from the Russian). *Gig. Tr. Prof. Zabol.* Heft 2, **1983**, 53. (b) Saillenfait, A. M.; Bonnet, P.; Guenier, J. P.; De Ceaurriz, J. *Fundam. Appl. Toxicol.* **1993**, *20*, 365. (c) Eastman Kodak Company, Laboratory of Industrial Medicine Toxicity report-2-chloroacrylonitrile Report (1971) NTIS/OTS 0555346. (d) BG Chemie, Toxicological Evaluation of 2-chloroacrylonitrile. http://www.bgrci.de/fileadmin/BGRCI/Downloads/DL_Praevention/Fachwissen/Gefahrstoffe/TOXIKOLOGISCHE_BEWERTUNGEN/Bewertungen/ToxBew038-E.pdf (accessed Jan 9, 2015).

(3) (a) Petit, Y.; Larcheveque, M. In *Organic Syntheses*; Wiley & Sons: New York, 2004; Collect. Vol. *X*, p 401. (b) Koppenhoefer, B.; Schurig, V. In *Organic Syntheses*, Wiley & Sons: New York, 1993; Collect. Vol. *VIII*, p 119.

(4) Bunegar, M. J.; Dyer, U. C.; Green, A. P.; Gott, G. G.; Jaggs, C. M.; Lock, C. J.; Mead, B. J. V.; Spearing, W. R.; Tiffin, P. D.; Tremayne, N.; Woods, M. *Org. Process Res. Dev.* **1998**, *2*, 334.

(5) Prat, D.; Hayler, J.; Wells, A. *Green Chem.* **2014**, *16*, 4546.

(6) Savelski, M.; Slater, S. C.; Aycock, D.; Comanita, B.; Prescott, S.; Shifflette, J. Life Cycle Analysis of Biobased Pennakem's ecoMeTHF: Green Solvents for the Pharmaceutical and Fine Chemical Industry. Presented at the 16th Annual Green Chemistry and Engineering Conference, June 18−20, 2012. https://pharmahub.org/resources/585/download/PennAKem_MeTHF_LCA_-_Green_Chemistry_and_Engineering_Conference_2012.pps (accessed Jan 9, 2015).

(7) Solubility data of epoxide **7** in methanol: 110 mg/mL at 22 °C; 146 mg/mL at 40 °C. Solubility of KBr in methanol: 17 mg/mL at 20 °C; 18.0 mg/mL at 40 °C; 22 mg/mL at 60 °C. See: Zeitlin, S. *Ukr. Khim. (Russ. Ed.)* **1925**, *1*, 581.

DOI: 10.1021/acs.oprd.5b00014
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

(8) (a) Stenlake, J. B.; Dhar, N. C.; Haddow, J.; McDonald, I. M.; Maehr, R. B.; Wastila, W. B. *Eur. J. Med. Chem.* **1992**, *27*, 463. (b) Hirschbein, B. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1982**, *104*, 4458. (c) Bihovsky, R. *J. Org. Chem.* **1992**, *57*, 1029. (d) Grosjean, F.; Huche, M.; Larcheveque, M.; Legendre, J. J.; Petit, Y. *Tetrahedron* **1994**, *50*, 9325.
(9) Buckley, B. R.; Patel, A. P.; Wijayantha, K. G. U. *J. Org. Chem.* **2013**, *78*, 1289.
(10) Other acids that were used to prepare acid salts of **8a** were trifluoroacetic acid, hydrochloric acid, methanesulfonic acid, maleic acid, and (+)-10-camphorsulfonic acid.
(11) Three batches of compound **11** were prepared with a total weight of 13.3 kg.
(12) Dunetz, J. R.; Xiang, Y.; Baldwin, A.; Ringling, J. *Org. Lett.* **2011**, *13*, 5048.
(13) Cope, A. C; Trumbull, E. R. *Org. React.* **1960**, *11*, 317−493.
(14) Diethylamine contamination of the triethylamine reagent cannot be ruled out as the source of diethylamide impurity **20**.
(15) T3P as a 50% ethyl acetate solution is the most commonly available formulation. However, T3P is now commercially available in several solvents, and the toluene composition was selected for purposes of process simplification.
(16) Jimenez-Gonzalez, C.; Ponder, C. S.; Broxterman, Q. B.; Manley, J. B. *Org. Process Res. Dev.* **2011**, *15*, 912.
(17) (a) Wernet, G.; Conradt, S.; Isenring, H. P.; Jiminez- Gonzalez, C.; Hungerbuhler, K. *Int. J. Life Cycle Assess.* **2010**, *15*, 294. (b) Raymond, M. J.; Slater, C. S.; Savelski, M. J. *Green Chem.* **2010**, *12*, 1826.
(18) Rowan University GWP for 2-MeTHF was used to supplement Ecoinvent data (see ref 6).
(19) May, O.; Bucholz, S.; Drauz, K.; Schwarm, M.; Turner, R. J.; Fotheringham, G. Mutants for the Preparation of D-Amino Acids. U.S. Patent 20060228787 A1.
(20) (a) Matsuda, H.; Hashimoto, H.; Sadashima, C. Preparation of 2-Cyanopiperazine. Japanese Patent JP2001354662, A1. (b) Li, W.; Li, J.; Wan, Z.; Wu, J.; Massetski, W. *Org. Lett.* **2007**, *9*, 4607.
(21) The potency was determined by quantitative ^{1}H NMR spectroscopy (300 MHz, D_2O). Sodium acetate was used as the internal standard.

DOI: 10.1021/acs.oprd.5b00014
Org. Process Res. Dev. XXXX, XXX, XXX−XXX