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Efficient synthesis of the κ-opioid receptor agonist CJ-15,161: four stereospecific inversions at a single aziridinium stereogenic center

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Abstract—An efficient four-step sequence has been developed for the synthesis of the κ-opioid receptor agonist CJ-15,161. The process features four consecutive regioselective and stereospecific inversions at a single aziridinium stereogenic center, which leads to overall retention of stereochemistry, in a single operation. The chemistry is straightforward, practical and amenable to large-scale synthesis.

1. Introduction

It is well established that opioid analgesics such as morphine are therapeutically useful, but their usage is limited due to adverse side effects, such as physical addictiveness, withdrawal properties, and respiratory depression, amongst others. Since opiates exert their effects by interacting with opioid receptors, considerable research has been directed towards determining the distinct pharmacological profiles of the μ (OP_3), δ (OP_1) and κ (OP_2) sub-types of receptors.[1] While μ opioid receptors mediate opiate phenomena associated with morphine, including analgesia, euphoria, respiratory functions and physical dependence,[2] stimulation of the κ receptors has been shown to produce analgesia.[3] Separating the action based on the former receptor from the latter has been investigated to develop potent, non-addictive analgesics with reduced tendency to cause dependence.

In a recent development program of the κ-opioid receptor agonist drug candidate CJ-15,161 **1**,[4] we required large scale production of the drug substance to support toxicological screening and clinical trials. The original discovery route was straightforward from a synthetic point of view, but was not amenable to large-scale preparation and long-term manufacturing (Scheme 1). More specifically, there were no crystalline intermediates throughout the synthesis, the styrene oxide **2** ring opening by pyrrolidine **3** lacked regioselectivity, the reactions did not lend themselves to easy manipulations, and the actual drug substance was an amorphous hydrochloride salt. While we sought alternate routes to CJ-15,161 **1**,[5] we improved upon the current synthesis to enable the production of drug substance.

The initial goal was to identify a final crystalline form for the drug substance: Salt screens showed that the benzoic acid salt mono-hydrate was a stable polymorph suitable for formulation (Fig. 1).

As mentioned above, the penultimate MOM-protected intermediate **6** was non-crystalline, and purification of this oil required silica gel chromatography. We therefore sought an alternative protecting group that would impart crystallinity and would allow purification by simple crystallization. Using the bottoms-up approach,[6] we derivatized the alcohol group of **1** in various protected forms compatible with the previous chemistry, and identified the benzoate ester **7** as a stable crystalline intermediate. Based on this, we protected pyrrodinol **3** as the benzoate ester **8** (Scheme 2). By performing the

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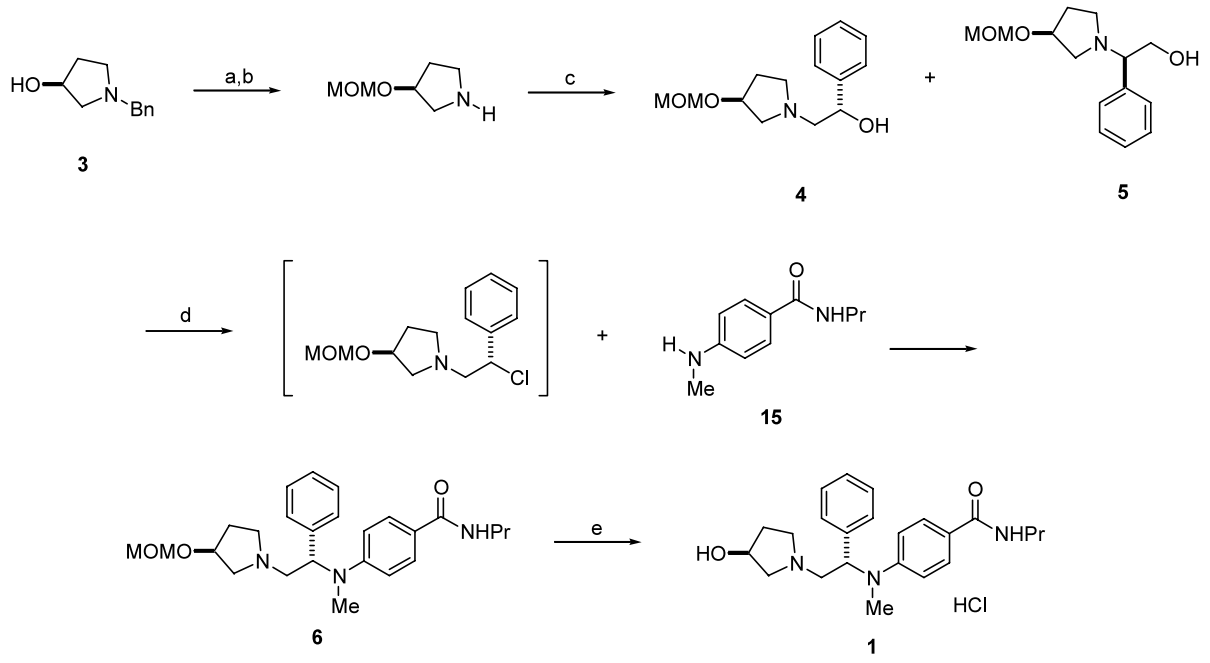


Scheme 1. Original discovery route. *Reagents and conditions*: (a) MOMCl, NaH, DMF, 70°C, 3 h, SiO_2 chromatography, 97%; (b) H_2, $Pd(OH)_2/C$, EtOH, rt, 40 h, quant.; (c) (*S*)-styrene oxide, EtOH, reflux, 2 h, SiO_2 chromatography, 59%, **4**:**5** = 0.65:0.35; (d) MsCl, TEA, CH_2Cl_2, rt, 12 h then **15**, EtOH, reflux, 2 h, SiO_2 chromatography, 88%; (e) HCl, MeOH, rt, 6 h, 89%.

reaction in the absence of base, the hydrogen chloride generated in the process provided the hydrochloride salt, which was conveniently isolated as a crystalline solid by addition of MTBE upon reaction completion. In addition to the hydrochloride's crystallinity, the subsequent *N*-benzyl hydrogenolysis with 10% Pd/C in isopropanol was accelerated when compared to the corresponding oily free-base, which actually stalled at some point.[7] Upon reaction completion and filtration of the catalyst, the solvent was concentrated with concomitant azeotropic removal of water originating from the wet catalyst. The resulting solution was then diluted with diisopropyl ether, from which pyrrolidine **9** crystallized out of solution. When performed on a multikilo scale, the reactions yielded 97 and 87%, respectively, of easily filterable crystalline solids.

With the requisite pyrrolidine **9** in hand, the key coupling with (*S*)-styrene oxide was investigated. To that effect, the preparation of β-substituted amines from mixtures of styrene oxide opening products via a common aziridinium ion intermediate was recently communicated.[8] In essence, the production of the two regioisomers **10** and **11** is not problematic since they both independently lead to the desired diamine **7**. As evidenced by the X-ray of CJ-15,161 **1** (Fig. 1), the overall transformation proceeds with net retention of configuration at the benzylic site. More specifically, we have found that the two isomers **10** and **11** initially produce a single common intermediate isolated and characterized as the benzylic chloride **12** (Scheme 3).

From a mechanistic viewpoint, formation of chloride **12** from both regioisomers **10** and **11** can be explained by the common intermediacy of the aziridinium intermediate **13**. Thus, the isolation of the benzyl chloride **12** further substantiates that the reaction leading to diamine **7** proceeds with anchimeric assistance on two successive occasions in order to account for the overall net retention of configuration at the benzylic site.[9] The foregoing argument that a total of four stereospecific inversions occurred at the benzylic position adds further insight to earlier reports that consider the net retention a result of two successive inversions.[10]

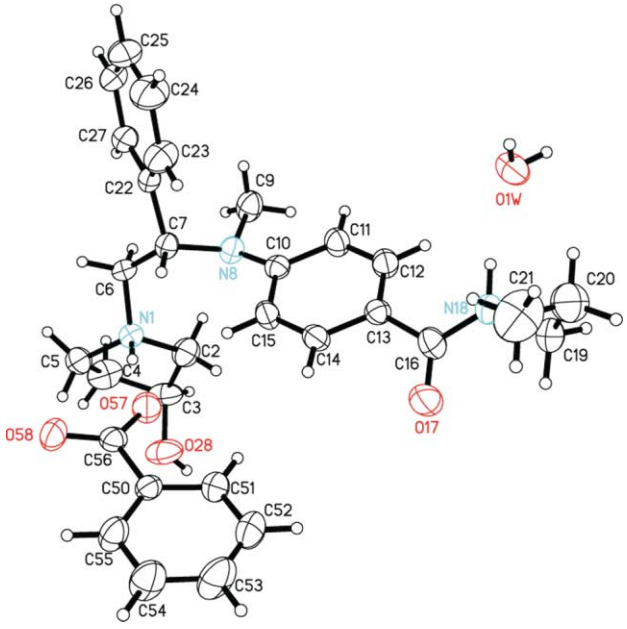
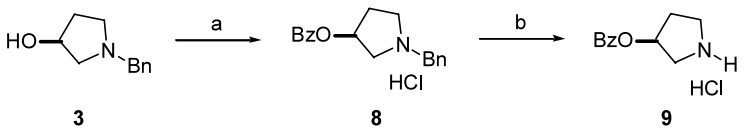
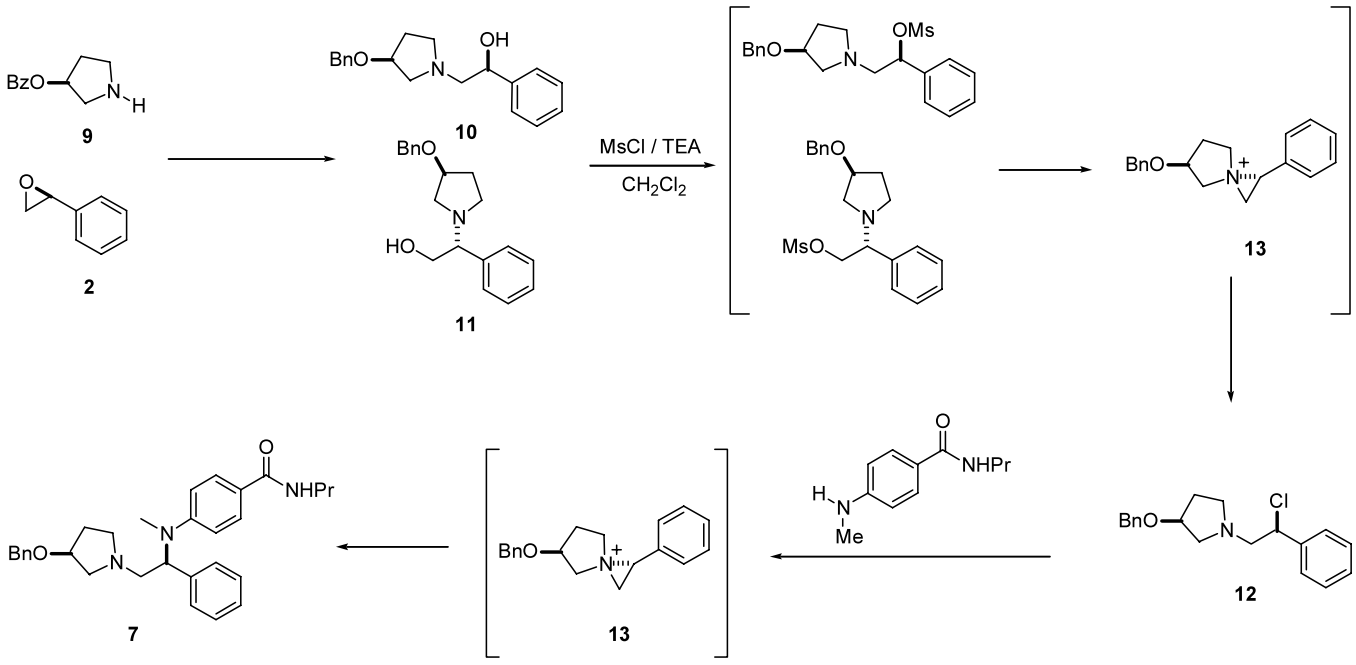


Figure 1. ORTEP representation of **1**·BzOH·H_2O.



Scheme 2. *Reagents and conditions*: (a) BzCl, CH_2Cl_2 then MTBE, 97%; (b) H_2, 10% Pd/C, *i*-PrOH then IPE, 87%.



Scheme 3.

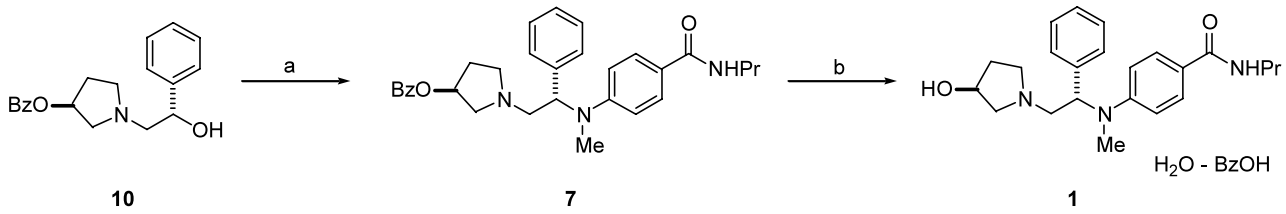
From a process chemistry perspective, the regioisomeric mixture of **10** and **11** was an oil, whereas the isolated benzylic alcohol **10** is a stable, crystalline intermediate. Therefore, it would be desirable to identify a regioselective synthesis of **10**, which could be purified by simple crystallization, and thus provide an additional point of purity control in the synthesis. We initially attempted to perform the coupling reaction directly with the pyrrolidinium salt **9** by free-basing in situ. Unfortunately, even after an exhaustive screen of bases, we were not able to effect the reaction starting from the hydrochloride salt with an acceptable rate and complete conversion.

The preferred solvent utilized for the free-basing procedure was methyl-THF, which provided good solubility for the free base, and excellent separation from water, as compared to THF. It was later observed that while residual amounts of up to 10% MeTHF left behind after displacement in the reaction solvent slowed the reaction slightly, it did not adversely affect the isomer ratio or impurity profile.[11] Solvent screening was performed to optimize the 65:35 regioselectivity (**10**:**11**) observed in the original coupling reaction when performed in ethanol (Table 1). In general, higher boiling, more polar solvents both increased the reaction rate and the ratio of **10**:**11**. Performing the coupling in *N*-methylpyrrolidinone at 100°C offered the best regioselectivity (12:1), with reaction completion after 12 h.

Isolations from polar, high boiling solvents can be difficult. In the course of our experiments, however, we found that the combination of NMP with water as an anti-solvent selectively crystallized the predominant regioisomer **10**. Fortunately, the resulting slurry filters relatively quickly despite the aqueous solvent mixture. The optimized procedure for coupling was to free-base pyrrolidinium **9** with MeTHF, displace into NMP, add

Table 1. Regioselective styrene oxide opening

Entry	Solvent	**10**:**11** ratio	Conversion (%)
1	THF	82:18	97
2	2-Me-THF	80:20	94
3	NMP	92:8	98
4	MeCN	74:26	90
5	DMF	84:16	95
6	DMAC	86:14	77
7	DMSO	88:12	89
8	MTBE	73:27	95
9	Diisopropyl ether	64:36	95
10	*n*-BuOAc	80:20	75
11	MeOPiv	79:21	26
12	EtOH	65:35	70
13	*i*-PrOH	78:22	50
14	1,2-Dichloroethane	58:42	79



10 7 1

Scheme 4. *Reagents and conditions*: (a) MsCl, TEA, CH_2Cl_2 then **14**, 80% (b) aq. NaOH, *i*-PrOH then BzOH, *i*-PrOH, 81%.

styrene oxide, heat to 100°C for 12 h, cool, add water, and filter. This procedure was exemplified in the kilo-lab facility[12] on a 7.2 kg scale, resulting in the isolation of 5.9 kg (60%) of the crystalline aminoalcohol **10**.[13]

With alcohol **10** in hand, we proceeded with the key aziridinium formation and coupling (Scheme 4). We found that methylene chloride was an ideal solvent for the mesylation/chloride displacement reaction, and that trimethylamine, required for both the activation and coupling steps, could be added in one initial charge. We also found that dichloromethane could advantageously be used in the coupling step instead of ethanol. Exclusion of the latter offered a single solvent process, eliminating a reaction quench and solvent swap. Additionally, the coupling occurred at a lower temperature, and there was no longer the need to remove the ethanol prior to the aqueous quench. Furthermore, any residual pyrrolidine **9** was purged with two 1 M hydrochloric acid washes.[14] Methylene chloride, with its low boiling point, made for easy displacement with ethyl acetate, and subsequent crystallization of the product via hexane addition and seeding. The penultimate intermediate was isolated in 87% yield (>99% purity) as a crystalline free-base. The process was exemplified on a 5.9 kg scale providing 7.2 kg of pure (99%), crystalline material.

The final transformation leading to the drug substance entails a saponification, followed by salt formation using benzoic acid in the presence of water to produce the mono-hydrated salt. Since the conjugate acid of the sodium benzoate produced in the saponification is the actual acid used to produce the final salt form, there lies an opportunity to neutralize the saponification reaction mixture with benzoic acid, in which case there cannot be scrambling between different counter-ions. Accordingly, instead of going through the usual series of pH adjustments and biphasic extractions, we devised a simple one-pot, one-isolation process. Following treatment of benzoate **7** with 1.2 equiv. of 1 M sodium hydroxide for 4 h at 50°C in 5 volumes (L of solvent per kg of substrate) of isopropanol, 2.3 equiv. of benzoic acid were added[15] to neutralize the excess sodium hydroxide and form the desired benzoate salt. The procedure was tailored such that when the clear solution was cooled to room temperature, the product crystallized out while the sodium benzoate by-product remained soluble. Following this simple process, the crystalline material was isolated by filtration to provide an 83% yield of drug substance, in the correct polymorphic state.

This work demonstrates an efficient and practical large-scale synthesis of CJ-15,161, where all the intermediates are crystalline solids and only one biphasic extraction is utilized throughout the synthesis. The end-game features a saponification quench with benzoic acid, which concomitantly produces the desired final benzoate salt form directly in the correct polymorphic state. The chemistry was exemplified on a multi-kilogram scale and the operations lend themselves to simple manipulations.

2. Experimental

2.1. General methods

Unless otherwise noted, all operations were performed in Clean-By-Test nitrogen purged vessels. Charges and transfers were performed using an isolated vacuum whenever possible. The ^1H and ^{13}C NMR spectra were recorded on a Varian Innova 400 spectrometer. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Inc. (Woodside, NY). Melting points were obtained from a Thomas Hoover Uni-Melt capillary apparatus and are uncorrected.

2.2. 4-*N*′-Methylamino-*N*-propylbenzamide 14

To a suspension of 4-*N*-methylaminobenzoic acid (34.5 kg, 229 mol) in dichloromethane (455 L) was added propylamine (22 L, 267 mol) followed by EDC (52.6 kg, 274 mol). The resulting suspension was stirred at rt for 17 h, then water (150 L) added and the biphasic mixture stirred for 15 min. The layers were allowed to settle, and then the aqueous phase extracted with dichloromethane (50 L). The combined organic layers were washed twice with aqueous citric acid (10%, 2×115 L) and then concentrated down to a crude solid (37.76 kg, 85%). The crude material (30.11 kg) was purified by dissolution in ethyl acetate (45 L) and toluene (45 L) at 70°C, followed by cooling to rt whereupon additional toluene (90 L) was added to the resulting slurry. The mixture was further cooled to 0°C and stirred for an additional 2 h. The crystalline material was collected by filtration and rinsed with ice-cold toluene (10 L) to provide the title compound (26.3 kg, 87%) as a colorless solid, mp 94–95°C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, $J=3.5$ Hz, 2H), 6.58 (d, $J=3.5$ Hz, 2H), 6.09 (brs, 1H), 3.36 (q, $J=6.5$ Hz, 2H), 2.85 (s, 3H), 1.60 (m, 2H), 0.95 (t, $J=7.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 151.5, 128.7, 123.5, 112.0, 41.8, 30.8, 23.3, 11.7. Anal. calcd for $C_{11}H_{15}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.70; H, 8.59; N, 14.50.

2.3. (*S*)-3-Benzoyloxy-*N*-benzylpyrrolidine hydrochloride 8

To an ice cold, stirred solution of (*S*)-*N*-benzyl-3-pyrrolidinol (6.90 kg, 38.9 mol) in dichloromethane (21 L), was slowly added a solution of benzoyl chloride (5.75 kg, 40.8 mol) in dichloromethane (5 L). The reaction mixture was warmed to rt and stirred for an additional 2 h. Upon confirmation of reaction completion, methyl *t*-butyl ether (26 L) was added, and the resulting slurry stirred for 2 h at −10°C. The solids were isolated by filtration, washed with methyl *t*-butyl ether (14 L) and dried under vacuum at 40°C to provide the title pyrrolidine (11.8 kg, 96.6%) as a colorless crystalline material, mp 203–204°C; ^{1}H NMR (400 MHz, $CDCl_3$) (major isomer) δ 8.14–7.90 (m, 2H), 7.70–7.39 (m, 8H), 5.59–5.58 (m, 1H), 4.30 (d, $J=5.5$ Hz, 2H), 4.14–4.08 (m, 1H), 3.80–3.76 (m, 1H), 3.24–3.17 (m, 2H), 2.66–2.61 (m, 1H), 2.37–2.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 165.6, 134.0, 133.7, 131.1, 130.9, 130.3, 130.2, 130.1, 130.0, 129.8, 129.6, 129.5, 129.4, 129.1, 129.0, 128.8, 128.6, 73.0, 71.9, 59.1, 58.5, 57.5, 57.2, 52.1, 52.0, 31.3, 30.6; MS [(*m*+1)/*z*] 282.2. Anal. calcd for $C_{18}H_{20}ClNO_2$: C, 68.03; H, 6.34; N, 4.41. Found: C, 67.81; H, 6.28; N, 4.44.

2.4. (*S*)-3-Benzoyloxypyrrolidine hydrochloride 9

A warm suspension of (*S*)-3-benzoyloxy-*N*-benzylpyrrolidine hydrochloride (11.8 kg, 37.0 mol) in 2-propanol (118 L) at 40°C was hydrogenated over 10% palladium on carbon (2.35 kg, 50% water wet) under 50 psig for 12 h. Upon confirmation of reaction completion, the mixture was filtered over Celite and the latter rinsed with additional 2-propanol (38 L). The combined filtrate and rinse solutions were concentrated by atmospheric distillation (to a total volume of 35 L). At this stage, diisopropyl ether (105 L) was slowly added over 15 min, and the resulting slurry was further stirred at 55°C for a further 15 min. The reaction mixture was gradually cooled to −10°C, and stirred for an additional 2 h. The solids were isolated by filtration, washed with diisopropyl ether (30 L) and dried under vacuum at 40°C to provide the title pyrrolidine (7.3 kg, 86.6%) as a colorless crystalline material, mp 140–141°C; ^{1}H NMR (400 MHz, d_6 DMSO) δ 9.65 (bs, s, 2H), 8.04–8.01 (m, 2H), 7.68–7.64 (m, 1H), 7.53–7.49 (m, 2H), 5.53–5.51 (m, 1H), 3.42–3.41 (m, 2H), 3.33–3.28 (m, 2H), 2.25–2.15 (m, 2H); ^{13}C NMR (100 MHz, d_6 DMSO) δ 165.8, 134.3, 130.2, 130.0, 129.3, 74.2, 50.4, 43.7, 31.3; MS [(*m*+1)/*z*] 192.2. Anal. calcd for $C_{11}H_{14}ClNO_2$: C, 58.03; H, 6.20; N, 6.15. Found: C, 58.00; H, 6.07; N, 6.30.

2.5. (2′*S*,3*S*)-3-Benzoyloxy-*N*-(2-hydroxy-2-phenyl)-ethylpyrrolidine 10

To a stirred solution of sodium hydroxide (1.52 kg, 38.0 mol) in water (35 L), was added (*S*)-3-benzoyloxypyrrolidine hydrochloride (7.20 kg, 33.0 mol) and 2-methyltetrahydrofuran (14 L).[11] The mixture was allowed to settle and the layers separated. The aqueous phase was extracted with an additional 2-methyltetrahydrofuran (14 L). The combined organic solutions were washed with brine (7 L), dried over magnesium sulfate (3.7 kg), filtered over Celite, and the latter rinsed with additional 2-methyltetrahydrofuran (18 L). The combined filtrate and rinse solutions were concentrated by vacuum distillation (to a total volume of 22 L). At this stage, 1-methyl-2-pyrrolidinone (15 L) was added and the resulting solution was further vacuum distilled to remove residual 2-methyltetrahydrofuran. A solution of (*S*)-styrene oxide (4.0 kg, 33 mol) in 1-methyl-2-pyrrolidinone (36 L) was then added and the resulting mixture was heated to 100°C for 12 h. Once the reaction was deemed complete, the solution was cooled to 25°C and water (22 L) added portion-wise over 30 min. After the addition of seed crystals, additional water (29 L) was added portion-wise over 1 h, and the resulting slurry stirred for a further 4 h. The solids were isolated by filtration, washed with water (22 L) and dried under vacuum at 45°C to provide the title pyrrolidine (5.9 kg, 58%) as a colorless crystalline material, mp 103–104°C; $[\alpha]_D^{22}=+44.8$ (*c* 1.1, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06–8.03 (m, 2H), 7.59–7.55 (m, 1H), 7.47–7.43 (m, 2H), 7.40–7.32 (m, 4H), 7.29–7.25 (m, 1H), 5.47–5.43 (m, 1H), 4.80 (dd, $J=3.2$, 10.4 Hz, 1H), 3.29–3.24 (m, 1H), 3.17–3.11 (m, 1H), 2.93–2.83 (m, 2H), 2.72–2.62 (m, 2H), 2.43–2.36 (m, 1H), 2.10–2.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 142.0, 133.4, 130.3, 129.8, 128.6, 127.9, 126.1, 74.6, 70.8, 64.1, 60.3, 52.9, 32.2; MS [(*m*+1)/*z*] 312.2. Anal. calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.49; H, 6.74; N, 4.59.

2.6. (2′*S*,3*S*)-3-Benzoyloxy-*N*-(2-chloro-2-phenyl)-ethylpyrrolidine 12

A solution of (2′*S*,3*S*)-3-benzoyloxy-*N*-(2-hydroxy-2-phenyl)ethyl-pyrrolidine (350 mg, 1.10 mmol) in dichloromethane (3.5 mL) was treated with triethylamine (157 μL, 1.20 mmol) followed by a dropwise addition of methanesulfonyl chloride (96 μL, 1.10 mmol). The reaction mixture was stirred for 30 min, and then diluted with additional dichloromethane (10 mL) and quenched with water (5 mL). The organic layer was separated, dried over sodium sulfate, concentrated and the residual material purified by silica gel chromatography (20% ethyl acetate in hexane) to provide the title compound (236 mg, 64%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06–8.04 (m, 2H), 7.57–7.55 (m, 1H), 7.45–7.30 (m, 7H), 5.42–5.38 (m, 1H), 4.97 (dd, $J=6.4$, 7.9 Hz, 1H), 3.21 (dd, $J=7.9$, 13.1 Hz, 1H), 3.11–3.01 (m, 2H), 2.85–2.79 (m, 2H), 2.70–2.65 (m, H), 2.32–2.27 (m, 1H), 2.00–1.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 140.7, 133.3, 130.5, 129.9, 128.9, 128.7, 128.6, 127.5, 74.9, 64.1, 61.7, 60.3, 53.3, 32.1; HRMS calcd for $C_{19}H_{21}ClNO_2$ (M^++1) 330.1261, found 330.1267.

2.7. (2′*S*,3*S*)-3-Benzoyloxy-*N*-{2-[*N*-methyl-*N*-4-(*N*-propylaminocarbonyl)phenyl]amino-2-phenyl}ethyl-pyrrolidine 7

A solution of (2′*S*,3*S*)-3-benzoyloxy-*N*-(2-hydroxy-2-phenyl)ethyl-pyrrolidine (5.82 kg, 18.7 mol) in dichloromethane (70 L) was distilled to a total volume of 64 L. The resulting solution was cooled to 0°C and treated with triethylamine (6.25 L, 44.9 mol) followed by the slow addition of methanesulfonyl chloride (1.74 L, 22.4 mol) over 30 min. The solution was then warmed to 20°C and stirred for a further 30 min. Once the reaction was deemed complete, 4-(*N*-methylamino)-*N*-propylbenzamide (3.59 kg, 18.7 mol) was added and the resulting solution heated to reflux for 12 h. Upon confirmation of reaction completion, the reaction mixture was cooled to 20°C, and successively washed with water (20 L), hydrochloric acid (1 M, 20 L), hydrochloric acid (1 M, 10 L), brine (10 L), aqueous sodium hydroxide (29 L) and water (20 L). The organic phase was concentrated by atmospheric distillation to a total volume of 12 L. The solution was cooled to 25°C after which ethyl acetate (29 L) was added and the mixture concentrated further by atmospheric distillation to a total volume of 12 L. The solution was cooled to 25°C and hexane (2 L) was added portion-wise over 30 min. After the addition of seed crystals, additional hexane (12.5 L) was slowly added over an hour, and the resulting slurry was further stirred for 12 h. The solids were isolated by filtration, washed with hexane (17.5 L) and dried under vacuum at 45°C to provide the title pyrrolidine (7.24 kg, 80%) as a colorless crystalline material, mp 105–107°C; $[\alpha]_D^{22}=+161.9$ (*c* 1.1, MeOH); ^{1}H NMR (400 MHz, d_6 DMSO) δ 8.06–8.03 (m, 1H), 7.86 (d, $J=7.6$, 2H), 7.66 (d, $J=9.2$ Hz, 2H), 7.64–7.60 (m, 1H), 7.51–7.47 (m, 2H), 7.32–7.19 (m, 4H), 6.82 (d, $J=9.2$, 2H), 5.23–5.19 (m, 2H), 3.17–3.06 (m, 3H), 3.00–2.95 (m, 1H), 2.86–2.76 (m, 6H), 2.52 (dd, $J=8.0$ Hz, 14.4, 1H), 2.21–2.13 (m, 1H), 1.79–1.75 (m, 1H), 1.51–1.42 (m, 2H), 0.083 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 166.6, 152.7, 133.2, 129.8, 128.8, 128.7, 128.6, 127.6, 127.2, 112.1, 74.8, 60.5, 60.4, 57.5, 53.1, 41.8, 32.7, 32.1, 23.3, 11.7; MS [(*m*+1)/*z*] 486.2. Anal. calcd for $C_{30}H_{35}N_3O_3$: C, 74.20; H, 7.26; N, 8.65. Found: C, 73.94; H, 7.12; N, 8.68.

2.8. (2′*S*,3*S*)-3-Hydroxy-*N*-{2-[*N*-methyl-*N*-4-(*N*-propyl-aminocarbonyl)phenyl]amino-2-phenyl}-ethylpyrrolidine 1

To a stirred solution of (2′*S*,3*S*)-3-benzoyloxy-*N*-{2-[*N*-methyl-*N*-4-(*N*-propylaminocarbonyl)phenyl]amino-2-phenyl}ethylpyrrolidine (7.24 kg, 14.9 mol) in 2-propanol (22 L) was added an aqueous solution of sodium hydroxide (1 M, 18.2 L). The resulting slurry was warmed to 55°C and stirred for 4 h. Upon confirmation of reaction completion, the solution was cooled to 40°C and spec-free filtered. A warm solution of benzoic acid (4.37 kg, 35.8 mol) in 2-propanol (14.5 L) at 55°C was then added to the reaction mixture. The resulting slurry was gradually cooled to 20°C over 2 h and stirred for an additional 12 h at the same temperature. The solids were then isolated by filtration, washed with 2-propanol (7.2 L) and dried under vacuum at 45°C to provide the title pyrrolidine (6.30 kg, 81%) as a colorless crystalline material. Mp 110–111°C; $[\alpha]_D^{22}=+168.4$ (*c* 1.1, MeOH); ^{1}H NMR (400 MHz, d_6 DMSO) δ 8.043 (t, $J=5.6$, 1H), 7.93–7.91 (m, 2H), 7.65 (d, $J=9.2$ Hz, 2H), 7.60–7.56 (m, 1H), 7.48–7.44 (m, 2H), 7.29–7.28 (m, 3H), 7.26–7.19 (m, 1H), 6.79 (d, $J=9.2$), 5.16–5.13 (m, 1H), 4.12–4.07 (m, 1H), 3.16–3.11 (m, 2H), 3.05–3.00 (m, 1H), 2.93–2.89 (m, 1H), 2.76–2.74 (m, 1H), 2.60–2.56 (m, 2H), 2.48–2.46 (m, 2H), 2.73 (dd, $J=4$, 9.6 Hz, 1H), 1.93–1.84 (m, 1H), 1.51–1.42 (m, 3H), 0.83 (t, $J=7.6$, 3H); ^{13}C NMR (100 MHz, d_6 DMSO) δ 168.5, 166.7, 152.3, 140.8, 133.0, 132.6, 129.9, 129.3, 129.2, 129.0, 127.8, 122.5, 111.8, 70.0, 63.1, 59.5, 58.1, 53.3, 41.5, 34.9, 32.7, 23.3, 12.2; MS [(*m*+1)/*z*] 382.2. Anal. calcd for $C_{30}H_{39}N_3O_4$: C, 69.07; H, 7.54; N, 8.06. Found: C, 69.07; H, 7.43; N, 8.15.

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11. Trace amounts of methylene chloride, as low as 0.1% (v/v), were absolutely detrimental to the reaction. Reaction completion was decreased, the ratio of product isomers was negatively affected, and unknown impurities in the range of 10% surfaced. Interestingly, it was noted that the addition of methyl-THF to the reaction mixture where the pyrrolidine had previously been extracted in dichloromethane led to a cleaner reaction profile. This could be attributed to the presence of BHT originating from the methyl-THF.
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13. The yield on scale was lower than the 75% typically observed in laboratory pilots, owing to the fact that less water than expected was added as anti-solvent.
14. In a control experiment, 98% of free-base was recovered after dissolution in dichloromethane and vigorous stirring with 1 M aqueous HCl.
15. At 2 volumes of isopropanol, the benzoic acid would not come out of solution if kept above 30°C. To be certain that no crystallization occurred in the lines during speck-free filtration, the solution was heated to 50–60°C and transferred through an insulated stainless steel line.