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ARTICLE

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The First Large-Scale Synthesis of MK-4305: A Dual Orexin Receptor Antagonist for the Treatment of Sleep Disorder

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ABSTRACT: A new synthetic route to drug candidate **1**, a potent and selective dual orexin antagonist for the treatment of sleep disorders, has been developed. The key acyclic precursor **10** was prepared in a one-step process in 75% isolated yield from commercially available starting materials using novel chemistry to synthesize 2-substituted benzoxazoles. A reductive amination was followed by a classical resolution to afford chiral diazepane (*R*)-**11**. Finally, coupling of (*R*)-**11** with acid **5** furnished the desired drug candidate **1**.

INTRODUCTION

Insomnia is characterized by difficulty initiating or maintaining sleep, waking early, or finding sleep nonrestorative. In a recent poll of American adults, over 50% reported having at least one symptom of insomnia during the previous year, and a third reported symptoms almost every night.[1] The direct and indirect costs to the U.S. economy related to insomnia have been estimated to be well in excess of $100 billion per year.[2] Recently, orexin receptor antagonists have emerged as a new class of therapeutic agents for the treatment of primary insomnia and potentially offer several advantages over other classes of sleep medication such as the benzodiazepines.[3] Merck & Co. have just disclosed a novel orexin antagonist **1** (MK-4305) that has entered phase III clinical trials for the treatment of primary insomnia.[4] Key structural features of **1** include a 1,4-diazepane ring system with a chiral methyl substituent in the 7-position, with the ring nitrogen atoms bearing benzoxazole and aromatic amide moieties. The requirement to synthesize the diazepane ring led to the development of a challenging intramolecular reductive amination and classical resolution protocol. The preparation of the cyclization precursor also demanded the exploration of new chemistry towards the synthesis of 2-aminated benzoxazoles. This article describes the successful realization of a suitable route to MK-4305 that successfully supplied the first kilogram quantities of drug substance to support ongoing studies.

Medicinal Chemistry Approach To 1. The route identified by the Medicinal Chemistry team to prepare **1** is outlined in Scheme 1.[4] Central to this approach was the synthesis of the core diazepane (*R*)-**4**, which was afforded by a preparative chiral HPLC separation on the orthogonally protected rac-**4**. A further four steps were used to generate **1** after this chiral resolution step. After Boc removal, the amine (*R*)-**3** was coupled with acid **5** to afford **6**, which upon hydrogenolysis of the CBz group generated compound **7**. Finally, treatment of **7** with chloride **8** in the presence of potassium carbonate completed the synthesis of **1**. The overall sequence required nine steps in the longest linear sequence and afforded **1** in 12% overall yield.

While this route was successful for the production of multigram quantities of **1** routinely required during early compound development, a number of issues needed to be addressed with this route if it was to be successfully applied to prepare the multikilogram quantities subsequently needed as **1** moved through the development phases. The aza-Michael reaction to prepare **2** was low yielding due to the formation of the double methyl vinyl ketone (MVK) adduct and various byproducts, requiring chromatographic purification. Next, the extensive use of protecting group chemistry significantly protracted the synthetic sequence, with five protecting group manipulations required out of a total of nine steps to ensure selectivity during the *N*-functionalization. Finally, the preparative chiral HPLC separation would prove difficult and costly on scale. With these points in mind work began to identify a new route to **1** which addressed these concerns.

Proposed Process Chemistry Approach to 1. The medicinal chemistry approach allowed for selective *N*-functionalization of either amine of the diazepane ring during lead optimization. The synthesis of orthogonally protected **4** gave a synthetic handle for the exploration of the structure activity relationships around this diazepane ring, and hence a large library of structural analogues could be synthesized in short order. However, once the desired structure is identified and moves into development an optimized route to that specific compound is required. This differentiation in desired project outcomes lends itself to the possibility of an alternative disconnection strategy which could potentially lead to a more efficient route to construct the desired target **1**. To this end a redesigned route to **1** was identified and is highlighted in Scheme 2.

The main objective was to remove unnecessary protecting group manipulations from the original Medicinal Chemistry route, leading to a significantly shorter sequence. In addition, an efficient solution to install the chiral center and to circumvent

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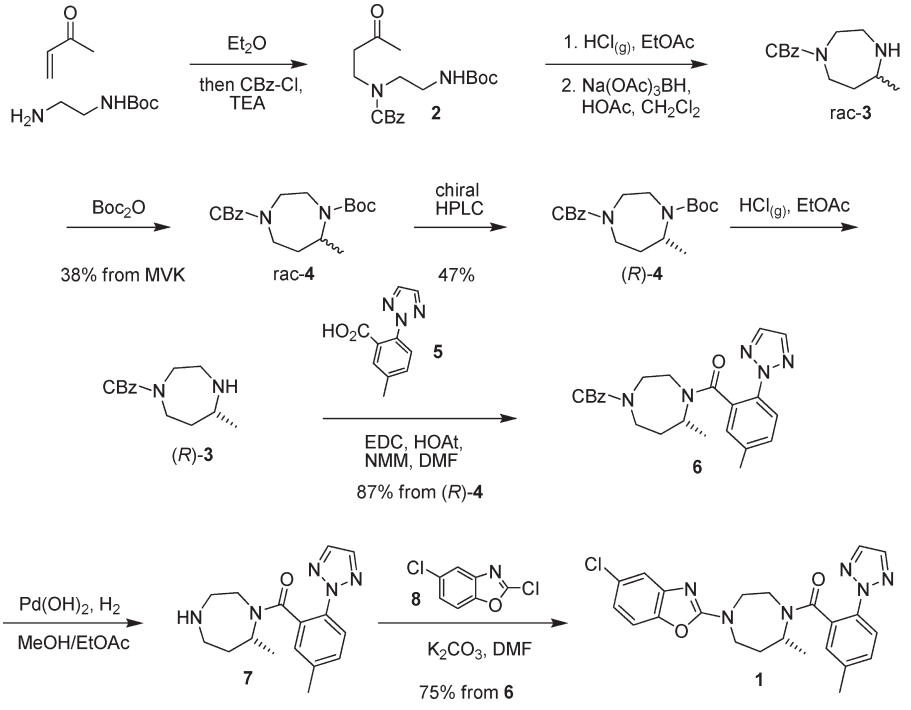
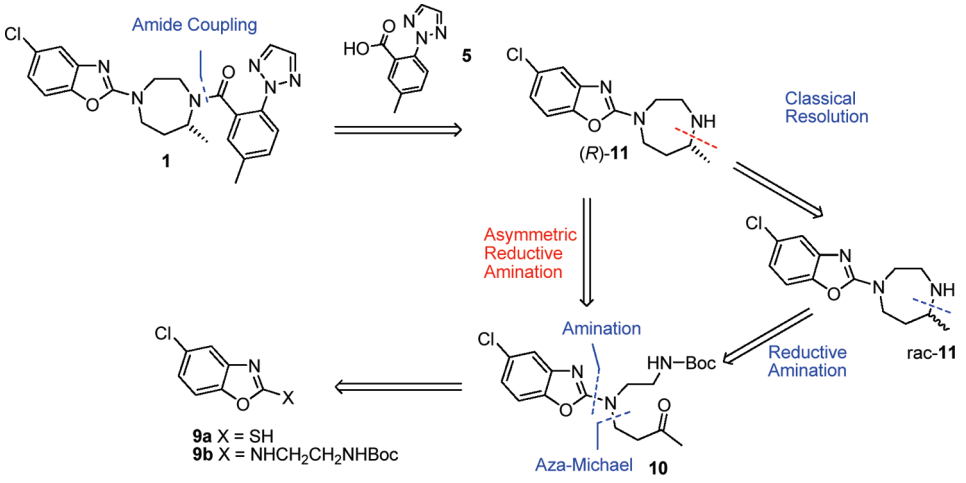
Scheme 1. Medicinal chemistry route to 1



Scheme 2. Proposed process research route to 1



the problems of the nonselective aza-Michael reaction was sought. We reasoned that the benzoxazole functionality could replace the CBz protecting group and act as a surrogate protecting group during the aza-Michael reaction. This would remove the requirement for both the CBz-deprotection and the final coupling steps, hence establishing a shorter and more efficient synthesis. Analyzing the disconnection, the final step to **1** would be a coupling between **5** and (*R*)-**11**, which in turn could be a candidate for classical resolution from rac-**11**. The diazepane ring rac-**11** could be prepared by Boc-removal and reductive amination from **10**. Whilst a classical resolution would provide the quickest route to chiral **1** and would form the basis for the first kilogram-scale delivery reported herein, this disconnection strategy would also lend itself to the ultimate synthetic long-term goal, namely to develop a synthetically challenging asymmetric reductive amination to provide (*R*)-**11** directly from deprotected **10**.

RESULTS AND DISCUSSION

Synthesis of Intermediate 10. The synthesis began with the production of the ketone **10**. While the required starting material **9a** is commercially available on small scale, cost and lead times associated with obtaining bulk quantities were excessive. Therefore, an efficient synthesis of **9a** from the cheap and readily available starting materials, 2-amino-4-chlorophenol and thiophosgene, was developed (Scheme 3).[5] Reaction of the two components in a water/methanol mixture led to precipitation of

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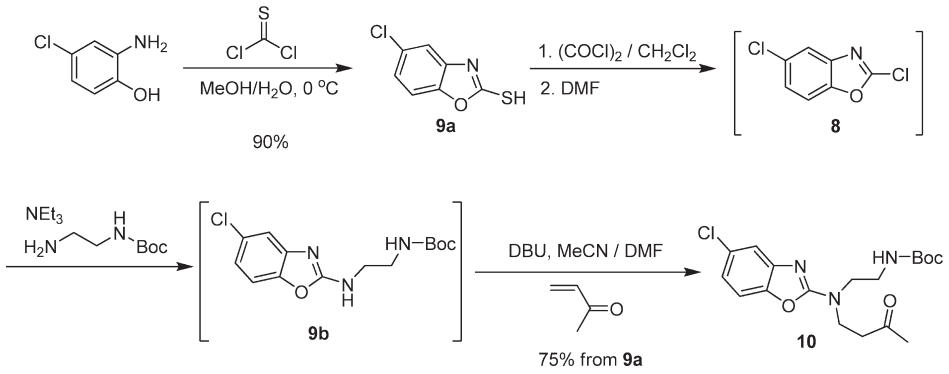
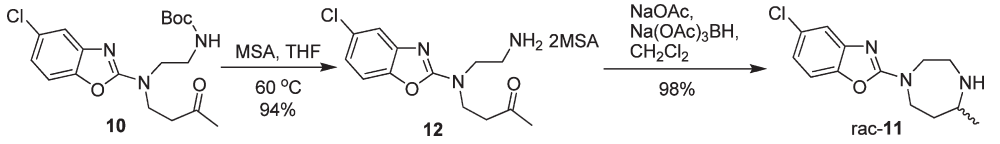
Scheme 3. Preparation of key cyclization precursor 10



Scheme 4. Formation of the diazepane ring system



the desired compound **9a** which could be isolated by filtration, in 90% yield.

With **9a** in hand, its conversion to the key ketone intermediate **10** was addressed. Direct displacement of the thiol moiety of **9a** with the Boc-diamine would provide the most direct way to prepare the desired intermediate **9b**. While this methodology proved successful, forcing conditions were required and led to production of the highly toxic and flammable hydrogen sulfide as a byproduct. Alternative approaches for this process were therefore considered. The corresponding 2-chlorobenzoxazole **8** was an attractive alternative, which we envisaged would be a suitable precursor in the preparation of the desired 2-aminobenzoxazole **9b**. Literature procedures for the preparation of 2-chlorobenzoxazoles from 2-thiobenzoxazoles typically rely on the use of PCl_5 at elevated temperatures, which necessitate purification of the chloride intermediate prior to use in subsequent steps.[6] Unfortunately, these chlorides are generally unstable, and we therefore sought to identify a milder chlorination to prepare **8.**

A screen of chlorinating reagents identified an oxalyl chloride/DMF mixture as the most promising candidate for this process. After consumption of the starting material, the reaction mixture was quenched with 3 equiv of triethylamine before treatment with 1 equiv of *N*-Boc-ethylenediamine. This led to complete conversion to the desired 2-aminobenzoxazole **9b** in an 82% isolated yield over the two steps. Reaction of **9b** with MVK in the presence of 1,8-diazabicycloundec-7-ene (DBU)[7] cleanly formed ketone **10**, with the desired product crystallizing directly from the reaction medium acetonitrile (MeCN) as the reaction progressed. On the basis of this encouraging result, a through process for the conversion of thiol **9a** to ketone **10** was considered. After completion of the amination to **9b**, an aqueous workup was performed prior to a solvent switch to MeCN, then MVK was added, followed by DBU. Once again, **10** crystallized directly from the reaction mixture, and the liquor loss was minimized by the addition of water as antisolvent. This three-step through process of chlorination, amination, and MVK aza-Michael reaction became the method of choice to prepare **10** in an 83% assay yield. The isolated yield of the desired product **10** was 75% over the three steps from **9a**; the losses to the liquors were determined to be 8%. This chemistry has subsequently been expanded as a mild and efficient one-pot synthesis of 2-aminated benzoxazoles and benzothiazoles from the corresponding thiobenzoxazoles.[8]

Synthesis of the Diazepane Ring System. We were now in position to evaluate the preparation of the diazepane ring. In the Medicinal Chemistry route, this was accomplished by a Boc deprotection with gaseous HCl in EtOAc, followed by reductive amination with sodium triacetoxyborohydride (STAB) (Scheme 1). The Boc-deprotection of **10** using either HCl·dioxane or TFA in CH_2Cl_2 (DCM) was initially explored; however, extensive investigations concluded that these procedures, while effective for removal of the Boc group, led to multiple impurities being formed.

Our attention was then turned to the use of sulfonic acid derivatives for this deprotection, with *p*-toluenesulfonic acid monohydrate ($TsOH·H_2O$) initially investigated. Heating a tetrahydrofuran (THF) solution of **10** containing 2 equiv of $TsOH·H_2O$ for 48 h at 60 °C led to the desired deprotection. Alternatively, methanesulfonic acid (MSA) was able to effect the same transformation in THF after an overnight age at 60 °C (Scheme 4). As the reaction progressed, a generous seed bed of the desired product was generated, and once the reaction was complete, the mixture was cooled, and the desired bis-MSA salt **12** could be simply filtered from the reaction mixture with minimal losses to the liquors (2%) in an isolated 94% yield.

The scene was now set for the reductive amination to prepare rac-**11**. This required a number of synthetic challenges to be overcome; namely the requirement for preferential reduction of an intermediate cyclic imine over the acyclic ketone, combined with a challenging 7-membered ring formation, and the need for preferential intra- vs intermolecular reactivity.

Originally the racemic reductive amination of **12** was effected by STAB in DCM and was found to be moderately effective; however, in addition to the desired product rac-**11** it was found

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that impurities **13** and **14** were generated (see Figure 1). This was thought to be due to the sensitive nature of the bis-MSA salt product to water, leading to cleavage of the benzoxazole moiety under the conditions of the reductive amination. It was therefore apparent that removal of the most acidic proton (presumably that of the protonated benzoxazole nitrogen) would eliminate these impurities from the subsequent reductive amination. We found that the addition of 1 equiv of NaOAc was suitable, with the addition of acetic acid to aid dissolution. Hence, treatment of a slurry of **12** in DCM containing acetic acid with NaOAc (1 equiv) led to a solution of the mono-MSA salt of **12**, which when treated with STAB (1.2 equiv) smoothly converted to rac-**11**. Finally, after workup the stream was solvent switched to 4:1 THF/DCM. This provided a stream of rac-**11**, which could be used directly in the classical resolution. Analysis of the final reaction stream showed the desired product had been formed in a 98% yield.

Classical Resolution. Screening has become a major tool in defining classical resolution; thus, the initial focus in the development of the classical resolution of rac-**11** was to treat the amine with a range of common resolving chiral acids in a variety of solvents. Somewhat surprisingly, the results of this screen showed that the majority of salts were either very low ee or racemic.[9] Fortunately, one salt proved to be the exception; when rac-**11** was treated with dibenzoyl-L-tartaric acid in THF, an initial hit was discovered with the isolated salt found to have a 76% ee.

We therefore concentrated our efforts on improving the resolution process. Early work determined that dibenzoyl-D-tartaric acid **15** (DBT) was required to afford the desired (*R*)-configuration of the amine in **16**. Analysis of the ^{1}H NMR spectrum of the salt **16** derived from rac-**11** and **15** showed the salt to be a 1:1 mixture of acid/amine. Conversely in some solvents a 2:1 amine/acid salt was isolated, which was found to be racemic. This obviously added a complication; in order to obtain the scalemic salt **16**, control of the salt form was required in the resolution process.

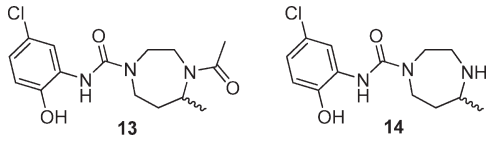


Figure 1. Impurities identified during the reductive amination optimization.

Extensive loading studies showed that 1.85 equiv of the chiral acid **15** was optimal in affording the desired 1:1 salt and hence enantioenriched salt. In addition ee and yields were maximized after shorter crystallization times (Table 1, entries 2 and 5), with prolonged aging of the reaction mixtures leading to turnover of the 1:1 salt **16** to racemic salts (Table 1, entry 4).

Despite extensive efforts the maximum ee obtained from this protocol was 76%. Attention was therefore switched to devising an upgrade of the initially formed salt. To this end a solubility study of the pure diastereomers of the 1:1 salts **16** and **17** and the racemic 2:1 salt **18** was performed, (Table 2).

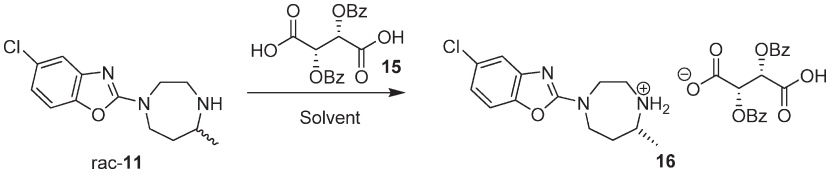
This study highlighted THF as a good solvent for a potential upgrade with the undesired 1:1 salt **17** three times more soluble in this solvent than our desired salt **16**, (Table 2, entry 1). It was therefore surprising that this system offered no upgrade. This led us to reason that this may be due to the fact that the upgrade was being performed on a mixture of the desired 1:1 salt **16** and the racemic 2:1 salt **18**. If this was indeed the case, then the higher solubility of the 2:1 salt in methanol (Table 2, entry 2) would be expected to upgrade our initially formed salt **16**.

Subjecting the salt to a rework in pure methanol confirmed this and was found to upgrade the salt to 97% ee albeit in low yield (Table 3, entry 1). Fortunately, a screen of antisolvents identified isopropyl acetate (iPAc) as a suitable candidate to reduce product loss to the liquors while maintaining high ee.

With these results in hand, the resolution was scaled up, and the ee was monitored as a function of time (Table 4). After 3.5 h an acceptable level of mother liquor loss (MLL) versus ee was attained (Table 4, entry 4), and the reaction mixture was filtered to afford the desired salt **16** in 39% yield with the ee measured at 74%.

After further refinement the large-scale upgrade was run in a 4:1 mixture of iPAc/methanol (25 volumes). After aging for 16 h at room temperature, a 74% yield of **16** was achieved with an ee of 96%. Evaluation of downstream chemistry showed this ee was suitable to prepare the desired drug substance of acceptable quality.

Table 1. Resolution of rac-11[a]



entry	acid **15** (equiv)	solvent (volumes)	age	yield (%)[b]	ee (%)[c]
1	1	THF (15)	40 h	29	76[d]
2	1.85	THF (15)	7 h[e]	41	73
3	1.85	THF (15), DCM (5)	90 min	–	69
4	1.85	THF (15), DCM (5)	16 h	–	rac
5	1.85	THF (15), DCM (1)	4 h	43	71

[a] The acid was dissolved in half the volume of THF, and the amine in half the volume of THF (with DCM if required) was added dropwise. The solution was then seeded and monitored over a period of time. [b] Isolated salt after filtration and drying. [c] Determined by chiral HPLC analysis. [d] Ee of salt deteriorated if aged for more than 40 h. [e] Ee was 75% after 3 h.

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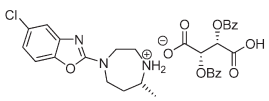
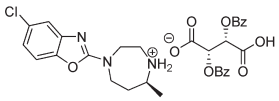
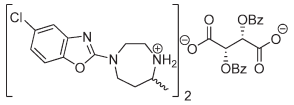
Table 2. Solubility data for the 1:1 and 2:1 DBT salts



>99% ee **16**



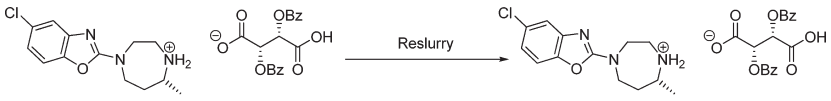
>99% ee **17**



racemic **18**

solvent	solubility **16** (mg/mL)	solubility **17** (mg/mL)	solubility **18** (mg/mL)
THF	3.25	9.6	4.1
MeOH	15.1	17.2	26.6
EtOH	2.6	2.6	4.05
IPA	0.5	0.58	1.4
DME	0.74	1.4	1.5
acetone	0.4	0.76	<0.5
MeCN	0.3	0.34	1.0
EtOAc	0.15	0.24	<0.5

Table 3. Investigation for the potential upgrade of the DBT salt 16



16 74% ee **16** up to 97 % ee

entry	solvent (vol)	temp (°C); time (h)	upgrade ee (%);[a] yield (%)[b]	liquor loss (mg/mL)
1	MeOH (15)	RT; 16	>97; 35	—
2	MeOH/iPAc 1:3 (20)	RT; —	94; —	16
3	MeOH/iPAc 1:4 (40)	RT; 16	94; 59	3.8
4	MeOH/iPAc 1:3 (20)	50; 18[c]	94; 71	5.8
5	MeOH/iPAc 1:3 (20)	RT; 16	95; 74	5.9
6	MeOH/iPAc 1:3 (25)	RT; 16	96; 74	4.8

[a] Determined by chiral HPLC analysis. [b] Isolated salt after filtration and drying. [c] Slurries were heated at 50 °C for 30 min, then cooled; time indicates total time from start of heating.

Synthesis of Triazole Acid 5. The Medicinal Chemistry route to triazole acid **5** involved a microwave-promoted amination of iodide **19** in NMP at 120 °C, which proceeded to give a 55:45 ratio of regioisomers **5** and **20**, and required a lengthy extraction and chromatographic separation to afford the desired isomer. For large-scale processing, both the use of microwave and the chromatographic purification needed to be addressed.

After a thorough screen of all reaction variables, it was found that complete reaction and higher selectivity could be achieved thermally in THF/DMF at 65 °C, with potassium carbonate as base (Scheme 5). An excess of triazole was optimum to ensure complete conversion and minimize formation of a homodimer impurity **21** formed from two acid units. Under these conditions the reaction typically reached >98% conversion and afforded an 81:19 ratio of regioisomers with <0.2% of homodimer **21** formed. At the end of reaction *N*,*N*-dimethylethylenediamine was added to aid copper removal, and the mixture was acidified to allow for extraction into an organic solvent. Attempts to reject the regioisomer **20** by crystallization under a number of conditions was not successful due to the lower solubility of this compound compared to that of **5**. On this basis purification via salt formation was explored. The cesium and potassium salts did not give significant upgrades; however, formation of the sodium salt in THF with adjustment of solvent volume led to the undesired isomer being rejected at the expense of around 15% of the desired isomer. In this way the sodium salt of **5** could be isolated in 65% yield, typically containing approximately 1% of the isomer **20**. Following salt break and crystallization from either ethyl acetate/heptane or iPAc/heptane the acid **5** was isolated in 60% yield from **19**.

Amide Coupling: The Synthesis of Drug Candidate 1. Moving onto the final step in the synthesis of drug candidate **1**, traditional amide coupling reagents were explored during the development of the final coupling between **5** and (*R*)-**11**. Unfortunately, the increased steric hindrance of the activated esters appeared to reduce the rate of the reaction considerably, prolonged heating was necessary to obtain a good conversion to **1**, and reaction profiles were poor. In addition, an isomeric byproduct **24** of the desired **1** was observed (up to 5 LCAP). This was thought to be a consequence of the instability of amine **11** under the reaction conditions. The formation of the isomeric impurity is believed to be the result of **11** undergoing an intramolecular ring flip via intermediate **22**. The ring flip amine isomer **23** could then couple with **5** to give rise to the observed impurity **24**, (Scheme 6).

It was subsequently found that converting **5** to the acid chloride and treating with amine (*R*)-**11** led to **1** with good yield

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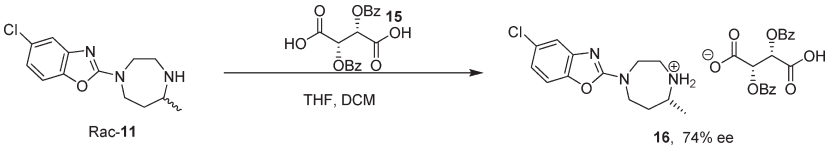
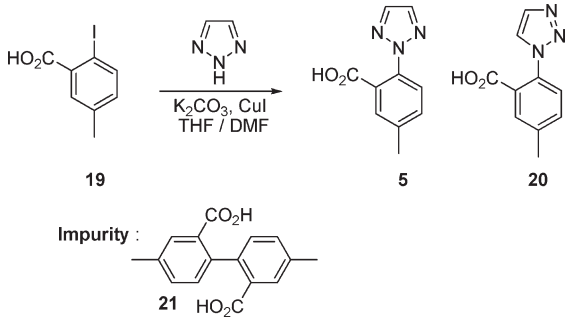
Table 4. Resolution of rac-11



entry	age (h)	salt ee (%)[a]	MLL (mg/mL)[b]
1	1	77	50.5
2	2	77	47.2
3	3	77	40.0
4	3.5[c]	72	35.8
5	5[d]	71	33.4
6	wet cake	71	—
7	liquors after filtration	53	32.2
8	isolated salt	74	—

[a] Determined by chiral HPLC analysis. [b] Mother liquor loss. (MLL). [c] Filtered after analysis of this time point, although filtration commenced after 4 h. [d] Sample taken 1 h into filtration.

Scheme 5. Preparation of acid 5



and purity. The acid chloride was prepared by treatment of acid **5** with oxalyl chloride and DMF in DCM. The formation of the less reactive anhydride was minimized by ensuring that the internal temperature of the reaction was maintained between 5 and 10 °C. Triethylamine was then premixed with the solution of amine (*R*)-**11**, and the mixture was then charged to the cold acid chloride solution. Conversion to **1** was typically complete within 30 min. After an extractive workup and concentration of the DCM solution, a solvent switch to MeCN was performed, and **1** could then be crystallized by the slow addition of water. Upon filtration **1** was isolated in a 95% yield, (Scheme 7).

SUMMARY

A new, robust and scalable synthesis of drug candidate **1**, a potent and selective orexin antagonist for the treatment of sleep disorders, has been developed and demonstrated on scale. The synthetic improvements described herein led to the synthesis of **1** in an improved 19% overall yield with five steps and one upgrade in the longest linear sequence. No chromatography was required in preparing **1**. Future work as compound **1** progresses through the development phases will focus on understanding the conditions that promote the isomerization of **11** and the potential development of an asymmetric reductive amination on intermediate **12** to further increase the efficiency and overall effectiveness of this synthesis. The results of these long-term project goals will be reported in due course.

EXPERIMENTAL SECTION

General. All materials were purchased from commercial suppliers and used without further purification. All reactions were conducted under an atmosphere of nitrogen unless noted otherwise. All reactors were glass-lined steel vessels. Unless reported otherwise, all reaction temperatures refer to the measured temperature of reaction mixtures not to the cooling or heating bath temperatures. Reactions were monitored for completion by removing a small sample from the reaction mixture and analyzing the sample by HPLC. HPLC analyses were performed using one of the following systems: Phenomenex Luna C18(2), 3.5 μm, 150 mm × 4.6 mm column, Zorbax Eclipse XDB-C8, 5 μm, 250 mm × 4.60 mm i.d. column, Zorbax eclipse XDB, 3.5 μm, 150 mm × 3.0 mm column, Zorbax Eclipse XDB, 5.0 μm, 250 mm × 3.0 mm column, and a mobile phase consisting of MeCN and 0.1% phosphoric acid. Enantiomer ratios for the classical resolution were determined by chiral HPLC analysis: ChiralPak AD-H, 5.0 μm, 250 mm × 4.6 mm column, and a mobile phase consisting of 60% hexane, 40% ethanol, 0.1% *i*-$BuNH_2$. Melting points were obtained by DSC studies conducted using a TA Instruments MDSC 2920 with refrigerated cooling system (RCS) (TA Instruments, Leatherhead, UK). NMR spectra were recorded on a Bruker Avance DPX or DRX 400 (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz) spectrometer. ^{1}H NMR data are reported as follows: chemical shifts are reported in ppm with the solvent resonance resulting from incomplete deuteration as the internal standard ($CDCl_3$: 7.26, d_6-DMSO: 2.50), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet or combinations thereof), integration, and coupling constants. ^{13}C NMR data are reported as follows: chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.16, d_6-DMSO: 39.51). High-resolution mass spectrometry was performed on a Micromass LCT . Optical rotation values were recorded on a PE 341 Polarimeter. LCWP refers to liquid chromatography weight percent and LCAP refers to liquid chromatography area percent.

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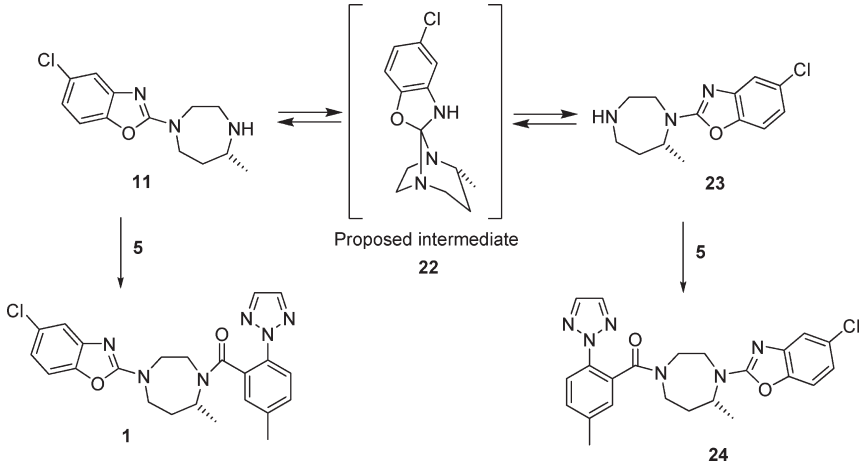
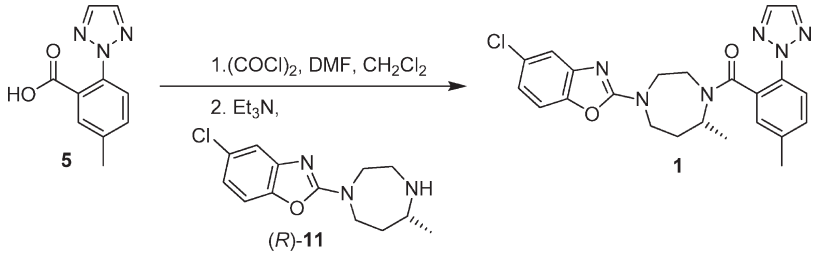
Scheme 6. Possible pathway for the formation of isomerization impurity 24 from 11



Scheme 7. Final coupling to prepare 1



5-Chloro-1,3-benzoxazole-2-thiol (***9a***). 2-Amino-4-chlorophenol (2.50 kg, 17.4 mol) was charged to a vessel and suspended in water (52 L) and methanol (10.4 L). *High dilution was required to prevent slow and difficult filtration of the product!* The mixture was stirred, cooled to 0 °C, and then thiophosgene (2.00 kg, 17.4 mol) was added to the suspension, ensuring that the internal temperature remained at 5 °C throughout the addition. Water (8 L) and methanol (2 L) were added to aid stirring, and the slurry was warmed to 13 °C for 1 h, followed by aging at 20 °C for a further 1 h. The slurry was then filtered and the solid washed with water (5 L). The batch was repeated and combined to dry in a vacuum oven (T = 40 °C) for 15 h to give **9a** (5.81 kg, 31.3 mol, 90% [corrected] yield, 98 LCWP, 98 LCAP). The loss to the liquors was 3%. The data corresponds to the commercially available material. ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.51 (d, 1 H, J = 9.2 Hz), 7.30−7.26 (m, 2 H). ^{13}C NMR (100.6 MHz, d_6-DMSO): δ 181.2, 147.4, 133.1, 129.7, 123.9, 111.6, 110.8. HRMS (ESI): m/z [M^+ + H] calcd for C_7H_4ClNOS: 185.9780; found: 185.9785.

{2-[(5-Chlorobenzoxazol-2-yl)-(3-oxo-butyl)-amino]ethyl}-carbamic Acid tert-Butyl Ester (***10***). Thiol **9a** (10.5 kg, 54.6 mol) was added to a vessel and suspended in DCM (141 kg). Oxalyl chloride (10.4 kg, 82.3 mol) was added (slightly endothermic) followed by DMF (40.0 kg, 547 mol) over 1.25 h, such that the batch temperature was ≤25 °C. The batch was aged at 20 °C for approximately 30 min; HPLC analysis showed reaction to be complete. The batch was cooled to 10 °C, and then triethylamine (16.64 kg, 164.4 mol) was added via a subsurface sample line at such a rate as to maintain a batch temperature of ≤10 °C. *A subsurface addition protocol was required to prevent buildup of triethylamine hydrochloride solid on the walls of the vessel.* The batch was cooled to 0 °C, and then a solution of *N*-Boc-ethylenediamine (10.5 kg, 61.2 mol) in DCM (10 kg) was added such that the batch temperature was ≤10 °C. The reaction was warmed to 20 °C and stirred for 2.5 h; HPLC analysis showed the reaction to be complete. Water (63.6 kg) was charged to the batch and the mixture stirred for 5 min. The layers were separated, and the aqueous phase was re-extracted with DCM (42.2 kg). The organic solutions were then combined, and approximately half of the total DCM volume was distilled from the batch under vacuum while maintaining a temperature of ≤40 °C. MeCN (83.3 kg) was then added and the remaining DCM removed by distillation (0.5 mol % DCM left by ^{1}H NMR wrt MeCN). MVK (4.61 kg, 65.8 mol) was added to the batch followed by DBU (4.17 kg, 27.4 mol) such that the temperature was ≤20 °C. The batch was aged for 10 h at 20 °C and then analyzed by HPLC. The reaction was then diluted with water (42.4 kg) and aged for a further 30 min. The mixture was filtered and the slurry washed with MeCN (33.3 kg). The solid was washed with MeCN (∼10 L) and then dried in a vacuum oven (T = 60 °C) for 22 h. MVK adduct **10** (15.5 kg, 75%, 102 LCWP, 99.8 LCAP) was isolated as an off-white solid. Mp 145−148 °C. The loss to the liquors was 8%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, 1 H, J = 2.3 Hz), 7.09 (d, 1 H, J = 8.5 Hz), 6.91 (dd, 1 H, J = 8.5, 2.3 Hz), 5.06 (s, 1 H, br), 3.73 (t, 2 H, J = 6.7 Hz), 3.63 (t, 2 H, J = 6.1 Hz), 3.37 (d, 2 H, br), 2.89 (t, 2 H, J = 6.7 Hz), 2.14 (s, 3H), 1.33 (s, 9 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 206.7, 163.0, 156.0, 147.4, 144.6, 129.2, 120.3, 116.6, 109.2, 79.4, 49.3, 44.3, 41.9, 39.1, 30.2, 28.3. HRMS (ESI): m/z [M^+ + H] calcd for $C_{18}H_{24}ClN_3O_4$: 382.1534; found: 382.1544.

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*4-[(2-Amino-ethyl)-(5-chlorobenzoxazol-2-yl)amino]butan-2-one-bis-MSA Salt (**12**).* MVK adduct **10** (15.04 kg, 39.38 mol) was charged to a vessel, and THF (150.4 L) was added. The resulting slurry was cooled to 5 °C, and methane sulfonic acid (7.57 kg, 78.8 mol) was added via a diaphragm pump maintaining an internal temperature below 25 °C. The batch was heated to 60 °C and allowed to age overnight. After aging overnight HPLC showed the reaction to be 83% complete; thus, a further charge of methane sulfonic acid (3.78 kg, 39.3 mol) was added via a diaphragm pump, and heating was continued for a further 2 h. *It is important to note that charging 3 equiv of MSA directly to the reaction mixture led to the product oiling out during the course of the reaction. Initially charging 2 equiv of MSA allowed a seed bed to form which controlled the crystallization during the remainder of the reaction after the final equivalent of MSA had been added.* After 2 h HPLC confirmed complete consumption of the starting material. The batch was cooled to 20 °C and then filtered, and the cake was washed with THF (20 L). The resultant solid was dried in a vacuum oven (T = 60 °C) for 36 h, to give **12** (17.4 kg, 36.7 mol, 94%) as a pale, tan solid. Mp 126.4 °C; 2% was lost to the liquors. ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.86 (bs, 3H), 7.44 (d, 1H, J = 8.5 Hz), 7.35 (d, 1H, J = 1.1 Hz), 7.06 (dd, 1H, J = 8.5 Hz, 1.1 Hz), 3.75 (t, 2H, J = 5.6 Hz), 3.69 (t, 2H, J = 6.9 Hz), 3.15 (m, 2H), 2.93 (t, 2H, J = 5.6 Hz), 2.36 (s, 6H), 2.14 (s, 3H). ^{13}C NMR (100.6 MHz, d_6-DMSO): δ 207.8, 163.1, 147.7, 144.7, 128.6, 120.6, 115.7, 110.6, 46.7, 44.2, 41.3, 40.1 (identified by dept), 37.4, 30.5. HRMS (ESI): m/z [M$^+$ + H] calcd for $C_{13}H_{16}ClN_3O_2$: 282.1009; found: 282.1012.

*5-Chloro-2-(5-methyl-[1,4]diazepan-1-yl)-benzoxazole (rac-**11**).* Bis-MSA adduct **12** (17.19 kg, 36.27 mol), sodium acetate (2.97 kg, 36.3 mol), and DCM (152 kg, 115 L) were charged to a vessel. The resulting slurry was cooled to 15 °C ,and acetic acid (26.8 kg, this was the amount required for dissolution of the salt) was added, maintaining an internal temperature below 20 °C. The batch was cooled to 15 °C, and $Na(OAc)_3BH$ (9.25 kg, 43.6 mol) was charged via a glovebag over 30 min, maintaining an internal temperature below 20 °C. The resulting solution was aged for 30 min at 20 °C; HPLC analysis showed the reaction to be complete. The batch was then cooled to 10 °C, 2 N HCl (38.80 kg) was added, and the resulting solution was aged for 30 min at 10 °C. The mixture was then adjusted to pH 9 using 5 N NaOH, maintaining an internal temperature below 20 °C. Once at pH 9 the layers were allowed to separate, and the organic lower layer was run off into a clean drum. DCM (76.2 kg, 57.5 L) was then added to the aqueous phase; the layers were mixed and allowed to separate, and then the lower layer was combined with the previous organics (this step was repeated, but HPLC of the third DCM layer showed that this was unnecessary as it only contained 12.5 g of rac-**11** by assay). The combined DCM fractions were then charged to a 160-L vessel and were distilled to approximately 20 L (~1 volume of DCM). THF (44 kg) was charged to the vessel, and the resulting stream was discharged into a clean drum and stored in the cold room prior to the next step in the reaction sequence. The final solution was found to contain 9.4 kg of rac-**14** (98% yield, assay by weight). This stream was sufficiently pure to be used directly in the subsequent resolution.

*DBT Salt **16**.* Dibenzoyl-D-tartaric acid **15** (22.6 kg, 63.1 mol) was charged to a vessel. THF (80 kg) was added over 20 min and the suspension stirred (slight exotherm). The amine (9.37 kg, crude from previous step in DCM [~1 vol] and THF [44 kg, 50 L] (total weight 65.5 kg)) was added over 35 min (slight exotherm). The solution was seeded with enantiomerically pure **16** (crystallization had already started), and the batch was aged at 20 °C for 4 h, being analyzed over time by HPLC. *The batch showed 72% ee and 35.8 mg/mL liquor loss after 3.5 h.* The slurry was filtered (filtration from the vessel took 3 h) and the vessel washed with THF (25 kg), filtering and washing the solid (this filtration took a further 2 h). The solid in the filter was dried with a stream of nitrogen overnight, and then dried in a vacuum oven (T = 40 °C) for 48 h. The DBT salt **16** (8.47 kg, 13.6 mol, 38.5%, 74% ee, 99 LCWP based on amine) was isolated as a white solid. The liquors after filtration showed 53% ee.

*Upgrade of the DBT salt **16**.* The DBT salt **16** (8.35 kg, 13.4 mol, 74% ee) was charged to a vessel. iPAc (137 kg) was added over 10 min and the suspension stirred. MeOH (52 kg) was added over 5 min (slight endotherm), and the batch was aged at 20 °C for 22 h, analyzed over time by HPLC. *The batch showed 95% ee and 5.3 mg/mL liquor loss after 22 h.* The slurry was filtered and the vessel washed with iPAc (29 kg), filtering and washing the solid (total filtration took 1.5 h). The solid was dried in a vacuum oven (T = 40 °C) for 20 h. The DBT salt **16** (5.85 kg, 9.37 mol, 70%, 96% ee, 95 LCWP based on amine) was isolated as a white solid. Mp 164.2 °C. The liquors after filtration were 14% ee. ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.93 (d, 4H, J = 7.2 Hz), 7.62 (t, 2H, J = 7.4 Hz), 7.51−7.47 (m, 4H), (d, 1H, J = 8.0 Hz), 7.34 (d, 1H, J = 2.0 Hz), 7.03 (dd, 1H, J = 8.4, 2.0 Hz), 5.65 (s, 2H), 3.89−3.76 (m, 2H), 3.67−3.58 (m, 1H), 3.43−3.27 (m, 2H), 3.23−3.16 (m, 2H), 1.99−1.84 (m, 2H), 1.19−1.17 (d, 3H, J = 6.6 Hz). ^{13}C NMR (100 MHz, d_6-DMSO) δ 168.5, 165.0, 162.4, 147.3, 144.8, 133.4, 129.7, 129.3, 128.7, 128.1, 119.8, 115.3, 109.9, 73.1, 53.5, 44.5, 44.0, 43.8, 31.9, 19.0. HRMS (ESI): m/z [M$^+$ + H] calcd for $C_{13}H_{16}ClN_3O$: 266.1060; found: 266.1058.

*5-Methyl-2-[1,2,3]triazol-2-yl-benzoic Acid **5**.* The iodide **19** (6.04 kg, 23.0 mol), THF (45 L), and DMF (9.0 L) were charged to a vessel. Copper iodide (218 g, 1.15 mol) and potassium carbonate (7.94 kg, 57.4 mol) were added, and the mixture was heated to an internal temperature of 40 °C. 1,2,3-Triazole (3.16 kg, 4.60 mol) was added as a solution in THF (6.0 L) over half an hour (no exotherm), and heating continued to 65 °C (again no exotherm observed), and the reaction was monitored by HPLC. Once complete *N,N*-dimethylethylenediamine (244 mL, 2.30 mol) was added and mixture cooled to RT. Aqueous 3.6 M HCl (36 L) was added (exotherm) and the mixture extracted twice with ethyl acetate (2 × 30 L). The combined organics were washed with LiCl solution (2 × 20 L). The acid solution assayed for 3.79 kg of **5** (81%) and 4.64 kg of **5** and **20** combined (99%).

A solution of acids **5** and **20** (approximately 4.64 kg, 22.9 mol) in THF and EtOAc (approximately 110 L) was concentrated to low volume. THF (90 L) was added, and the solvent composition was checked by ^{1}H NMR to ensure most ethyl acetate had been removed. Sodium *tert*-butoxide (2.42 kg, 25.2 mol) was added slowly as a solid over 1−2 h (slight exotherm), allowing the sodium salt to form, and was stirred overnight at RT. The liquors showed a 45:55 ratio of **5**:**20**, and the solid was collected by filtration, washed with THF (2 × 20 L), and dried in a vacuum oven (T = 40 °C) for 15 h to afford 4.22 kg of crude sodium salt (72 wt %, corrected to 3.04 kg free acid equivalent, 65% from **19**, 95.8 LCAP).

The crude sodium salt (4.22 kg, 14.9 mol) was charged to a 50-L vessel, and 3.6 N HCl (21.2 L) was added with cooling. The slurry was then stirred at room temperature for 16 h and the off-white solid isolated by filtration. The cake was washed with water (11 L) and iPAc/heptane (2 × 5 L), and then was dried in a

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vacuum oven (T = 35 °C) for 15 h to give 3.10 kg of crude acid **5** (97.9 LCAP, 92 wt %, corrected weight 2.85 kg, 61% yield from **19**).

The acid **5** (2.85 kg corrected, 14.0 mol) was charged to a 50-L vessel, and EtOAc (28 L) and dilute 0.22 M HCl (14 L) were added, and the mixture was stirred until two clear phases resulted. The aqueous layer was removed and the organic layer filtered to remove any particulate matter. The ethyl acetate was reduced to about 8 L, and then heptane (15.6 L) was added over 1 h, and the liquors were sampled to check for appropriate losses. The solid was isolated by filtration, washed with heptane/ethyl acetate (3:1, 4 L), and dried on the filter under nitrogen to give 2.81 kg of acid **5** (60% from iodide **19**, 99.4 LCAP, 98 wt %). Mp 174−176 °C. ^{1}H NMR (400 MHz, d_6-DMSO): δ 12.09 (br s, 1H), 8.04 (s, 2H), 7.62 (d, 1H, J = 8.4 Hz), 7.58 (d, 1H, J = 1.2 Hz), 7.49 (dd, 1H, J = 8.4, 1.2 Hz), 2.41 (s, 3H). ^{13}C NMR (100.6 MHz, d_6-DMSO): δ 168.0, 139.2, 136.4, 135.8, 132.5, 130.3, 128.7, 124.8, 20.9. HRMS (ESI): m/z [M^+ + H] calcd for $C_{10}H_9N_3O_2$: 204.0773; found: 204.0781.

*[(R)-4-(5-Chlorobenzoxazol-2-yl)-7-methyl-[1,4]diazepan-1-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)methanone (**1**).* The amine DBT salt **16** (5.67 kg, 9.09 mol) was charged to a vessel and inerted. DCM (28 L) was added, followed by 4 N sodium hydroxide solution (prepared from 10 N NaOH [22.4 L] and water [36 L]). The slurry was then stirred at ambient temperature for 1 h until a solution was obtained. The layers were separated, and the aqueous phase was treated with sodium chloride solution (10.1 kg in 20 L water). DCM (5 L) was then added and the biphasic mixture stirred for 10 min before separating the layers. The combined organic layers were then concentrated under reduced pressure to a 10 L volume. The solution of the free amine was used directly in the next reaction

The triazole acid **5** (13.25 kg, 65.2 mol), DCM (88 L), and DMF (1.35 L, 17.4 mol) were charged to a vessel, and the resulting suspension was cooled to 0 °C. Oxalyl chloride (8.28 kg, 65.2 mol) was added portionwise, keeping the internal temperature between 5 and 10 °C (the anhydride formed above 10 °C), and then the reaction was aged for 30 min at this temperature. HPLC analysis showed acid **5** remained; an additional charge of oxalyl chloride (160 g, 1.26 mol) was made, and the solution stirred at 5 °C for 30 min. A solution of the amine (*R*)-**11** (16.5 kg, 62.1 mol) and triethylamine (13.19 kg, 130.0 mol) in DCM (∼8 L) was added to the acid chloride over 30 min, keeping the internal temperature less than 15 °C. The resulting slurry was aged for 30 min and then quenched by the addition of water (167 L) over 10 min, keeping the internal temperature <15 °C. The lower organic layer was removed and then concentrated under atmospheric pressure to a volume of 100 L. Assay at this stage showed 27.3 kg **1**, 98%. The solution was solvent switched to MeCN (∼560 L, 20 mL/g) by distillation under reduced pressure at <50 °C. The MeCN solution was treated with Ecosorb C-941 (2.8 kg) slurried in MeCN (10 L). The resulting slurry was aged for 30 min and then filtered through a Solka Flok pad and a 0.1 um cartridge filter, washing with MeCN (2 × 30 L). The MeCN filtrate was concentrated under reduced pressure at <50 °C to a final volume of ∼112 L. The slurry was cooled to 25 °C and water (280 L) added over 40 min. The resulting slurry was aged at 20 °C for 1 h and then filtered, washing the cake with 5:1 water/MeCN (60 L) followed by water (40 L). The solid was dried in the vacuum oven with nitrogen purge overnight at 50 °C. The final target **1** was isolated as a white solid, 26.72 kg, 95%, 98.5% ee, 99.6 LCAP, mp 153.1 °C.

The ^{1}H NMR data for this compound was extremely complicated due to its existence as four rotamers. These rotamers did not coalesce during high-temperature experiments.[4]

$[\alpha]^{25}_D$ −11.8 (c 1.0, MeOH) for a sample of 97.8% ee. HRMS (ESI): m/z [M^+ + H] calcd for $C_{23}H_{23}ClN_6O_2$: 451.1649; found: 451.1640.

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(9) We initiated our screening process by taking 10 acids and screening them with a particular solvent. This was continued for a range of solvents until a suitable hit was discovered (not all acids were screened with all the solvents). Acids used: dibenzoyl-L-tartaric acid, di-*p*-toluoyl-L-tartaric acid, L-tartaric acid, (1*S*)-(+)-10-camphorsulfonic acid, (1*R*,3*S*)-(+)-camphoric acid, L-malic acid, (*S*)-(+)-mandelic acid, (1*R*,3*R*,4*R*,5*R*)-(−)-quinic acid, deoxycholic acid, (*S*)-(−)-2-pyrrolidone-5-carboxylic acid. Solvents examined were: THF, acetone, EtOH, MeOH, IPA, iPAc, toluene, MeCN, DCE, water, DMF. The dibenzoyl-L-tartaric acid in THF gave the best result with a 1:1 acid/amine salt formed in 74% ee. Other solvents with the same acid gave a 2:1 acid/amine salt, which was found to be racemic.