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Process Development toward the Pilot Scale Synthesis of the Piperidine-Based Cocaine Analogue and Potent Dopamine and Norepinephrine Reuptake Inhibitor CTDP 31,446

Bingidimi I. Mobele,* Taryn Kinahan, Luckner G. Ulysse, Steven V. Gagnier, Michael D. Ironside, Graham S. Knox, and Farahnaz Mohammadi

Chemical Development Department, Albany Molecular Research Inc., 21 Corporate Circle, P.O. Box 15098, Albany, New York 12212, U.S.A.

Abstract:

(±)-Methyl 4*β*-(4-chlorophenyl)-1-methylpiperidine-3α-carboxylate hydrochloride (CTDP 31,446) is known as a dopamine reuptake inhibitor. This cocaine analogue lacking the tropane skeleton is being considered for potential treatment of cocaine addiction. Herein we report the development of a scalable process for the preparation of this compound. This study was mainly aimed at improving the process throughput, eliminating chromatographic purifications for the separation of (±)-6-cis isomer from (±)-6-trans isomer, and developing a robust crystallization for isolation of pure (±)-6-cis in a single crop with a good mass recovery. The process development work also highlights an efficient recycle of (±)-6-trans *via* a kinetic epimerization followed by crystallization of the resulting (±)-6-cis isomer. The resolution of (±)-6-cis and the crystallization of the final HCl salt were optimized and implemented to afford CTDP-31,446 with high purity and good mass recovery.

Introduction

Cocaine (**1**) is a powerful, abused drug with strong reinforcing properties. Several investigations have established that cocaine binds to neuronal proteins including the dopamine transporter (DAT), the serotonin transporter (SERT), and the norepinephrine transporter (NET), resulting in its reinforcing effect.[1] It is now well-established that the binding of cocaine to the DAT results in the inhibition of the reuptake of DA after synaptic transmission in the brain.[2] The development of drugs for the treatment of cocaine addiction has been a main focus of several research laboratories worldwide. These extensive investigations have resulted in the development of different classes of molecules targeting the DAT with the aim of modulating the action of cocaine. These DAT inhibitors are categorized mainly into tropane analogues (mostly compounds of the WIN series, **2**), benztropine analogues, methylphenidate analogues, mazindol analogues, piperazine analogues (also called GBR series, **4**), and most recently piperidine analogues (**3**). Most notably in the latter category, piperidine 3-carboxylic acid esters bearing chlorophenyl substituents in position 4 have been extensively studied as possible dopamine reuptake inhibitors. This series of compounds, which may be viewed as truncated versions of the WIN series, was first reported by Clarke and co-workers[3] in 1973 and has received revived interest more recently, most notably by Kozikowski and co-workers.[2a,4]

To prepare kilogram quantities of CTDP-31,446 needed for clinical trials, a scalable process was required. The existing synthetic route provided by the National Institute on Drug Abuse (NIDA) is based on work by Kozikowski et al.,[4] who prepared a large number of potent piperidine-based analogues. This route involved initial Grignard addition of 4-chlorophenylmagnesium bromide to arecoline to generate a mixture of racemic (±)-**6**-cis and (±)-**6**-trans (Scheme 1).

The (±)-**6**-cis was crystallized from ethyl acetate/hexanes and recovered in 22% yield in a first crop. Further recovery from the mother liquors (34%) was accomplished *via* chromatography, which also yielded 18% of the (±)-**6**-trans isomer. To prepare CTDP-31,446, the authors took advantage of the relative ease of resolution of (±)-**6**-cis to generate enantiomerically homogeneous (−)-**6**-cis, which was then epimerized to the desired (+)-**6**-trans isomer with sodium methoxide in refluxing methanol. Subsequent treatment of the enantiomerically pure (+)-**6**-trans with HCl (g) in methanol then afforded CTDP-31,446. Noteworthy and critical to the choice of this approach was the difficulty in achieving a direct resolution of (±)-**6**-trans.

For this route to be efficiently and safely scaled up, a number of significant process issues needed to be addressed. (1) The original procedure[4] employed large amounts (∼90 volumes) of diethyl ether as the reaction solvent, which would significantly impact the process throughput on scale. In addition, the inherent hazards posed by the use of the highly flammable diethyl ether on scale were a concern. (2) Serious stirring issues stemmed from the generation of a thick gel during the Grignard reaction, particularly when carried out under less dilute conditions, making an inverse quench

* Author for correspondence. E-mail: Bingidimi.Mobele@albmolecular.com. Telephone: +1 518 464 0279. Fax: +1 518 464 0289.

(1) For general reviews, see: (a) Smith, M. P.; Hoepping, A.; Johnson, K. M.; Trzcinska, M.; Kozikowski, A. P. *Drug Discovery Today* **1990**, *4*, 322. (b) Howell, L. L.; Wilcox, K. M. *J. Pharmacol. Exp. Ther.* **2001**, *298* (1), 1. (c) Carroll, F. I.; Lewin, A. H.; Kuhar, M. J. *Neurotransm. Transp.* **1997**, 263. (d) Kuhar, M. J.; Ritz, M. C.; Boja, J. W. *Trends Neurosci.* **1991**, *14* (7), 299. (e) Singh, S. *Chem. Rev.* **2000**, *100*, 925.

(2) (a) Tamiz, A. P.; Zhang, J.; Flippen-Anderson, J.; Zhang, M.; Johnson, K. M.; Deschaux, O.; Tella, S.; Kozikowski, A. P. *J. Med. Chem.* **2000**, *43*, 1215. (b) Carroll, F. I.; Pawlush, N.; Kuhar, M. J.; Pollard, G. T.; Howard, J. L. *J. Med. Chem.* **2004**, *47*, 296.

(3) Clarke, R. L.; Daum, S. L.; Gambino, A. J.; Aceto, M. D.; Pearl, J.; Levitt, M.; Cumiskey, W. R.; Bogado, E. F. *J. Med. Chem.* **1973**, *16* (1), 1260.

(4) Kozikowski, A. P.; Araldi, G. L.; Boja, J.; Meil, W. M.; Johnson, K. M.; Flippen-Anderson, J. L.; George, C.; Saiah, E. *J. Med. Chem.* **1998**, *41*, 1962.

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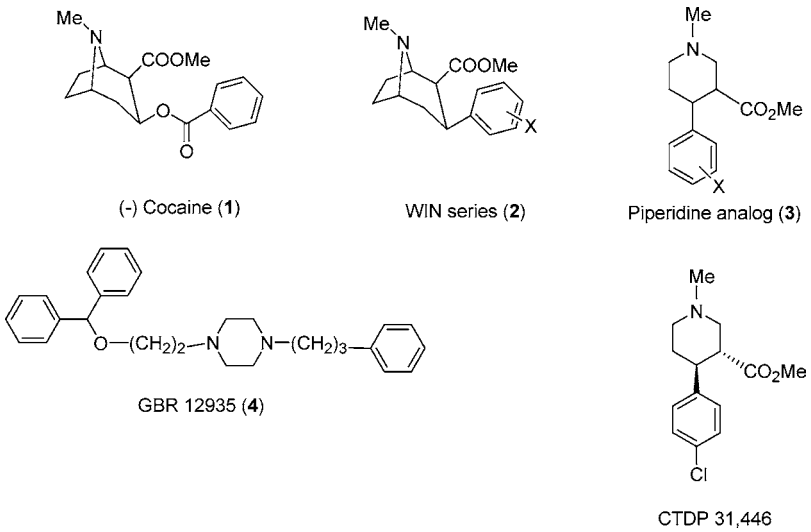
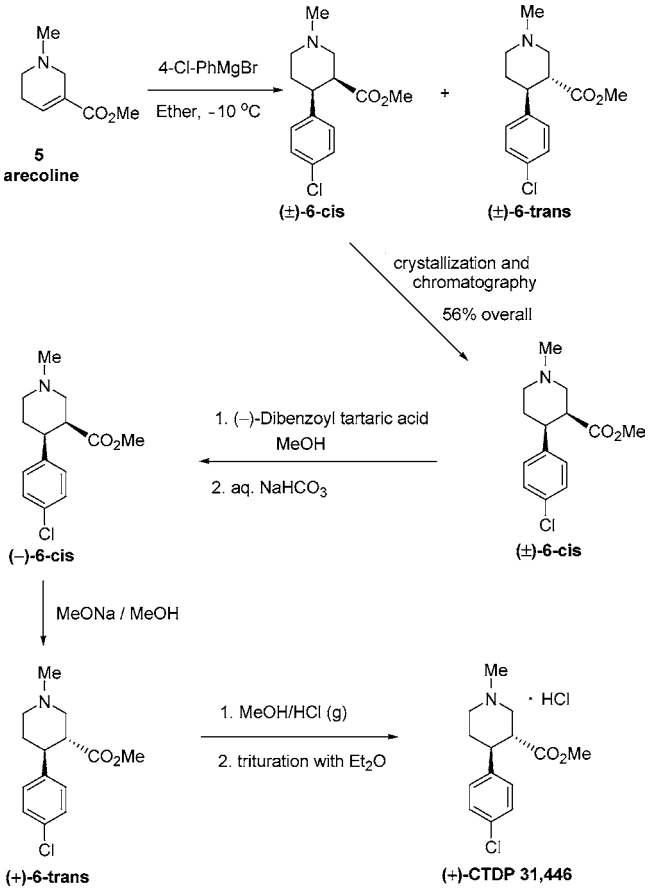


Figure 1.

Scheme 1



such as that employed in the original procedure difficult to implement on scale. It should be noted that this stirring issue has been previously observed and documented by others in related Grignard addition reactions to arecoline.[5] (3) Isolation of the desired (±)-**6**-cis isomer was not straightforward and necessitated chromatography of the mother liquors from the initial low-yielding crystallization. (4) Additionally (±)-**6**-trans was isolated as an oil which required chromatographic purification prior to conversion to the corresponding HCl salt.

Optimization of the Grignard Addition. It is interesting to note that the addition of various Grignard reagents to arecoline as originally described by Plati et al.[6] remarkably generates predominantly the adducts derived from a Michael addition rather than products from reaction at the ester moiety when carried out in diethyl ether. Attempts to use other ethereal solvents such as THF, typically employed in Grignard addition reactions, provide little or none of the desired 1,4-conjugate addition products. Instead, adducts derived from the competing 1,2-addition to the ester predominate.[5b]

Initial attempts to avoid the use of diethyl ether altogether by using THF in the presence of catalytic amounts of copper additives (up to 10 mol %), such as CuI or $Li_2Cu_2Cl_4$, were unsuccessful. In all cases, a faster addition to the ester was prevalent, leading to a presumed intermediate α,β-unsaturated ketone which then underwent a further 1,4-addition resulting in an overall incorporation of two 4-chlorophenyl units. It is worth noting that successful Grignard addition reactions to related α,β-unsaturated esters have been accomplished in the presence of up to 50 mol % of a CuBr·Me_2S complex in tetrahydrofuran as the reaction solvent. For example, Casamitjana and co-workers[7a] showed that the conjugate addition of ethylmagnesium bromide or phenylmagnesium bromide to 3-benzyloxycarbonyl-5,6-dihydropyridin-2-one afforded 1,4-adducts in good yields in tetrahydrofuran using 50 mol % of the CuBr·Me_2S complex. Similarly, Davies and co-workers[7b] have also successfully employed 50 mol % of the CuBr·Me_2S complex in tetrahydrofuran at 0 °C to ambient temperatures to achieve the conjugate addition of Grignard reagents to anhydroecgonine derivatives and related α,β-unsaturated esters incorporating a bridging heteroatom in the bicyclic framework, such as 6-azabicyclo[3.2.2]non-3-ene and 6-azabicyclo[3.2.2]non-2-ene derivatives. In our case,

(5) (a) Crowe, D.; Ward, N.; Wells, A. S. World Patent WO 01/29032. (b) Ward, N.; West, V. World Patent WO 02/32870.

(6) Plati, J. T.; Ingerman, A. K.; Wenner, W. *J. Org. Chem.* **1957**, *22*, 261.

(7) (a) Ecija, M.; Diez, A.; Rubiralta, M.; Casamitjana, N.; Kogan, M. J.; Giralt, E. *J. Org. Chem.* **2003**, 68, 9541. (b) Davies, H. M. L; Hodges, L. M.; Gregg, T. M. *J. Org. Chem.* **2001**, 66, 7898.

Table 1. **Dependence of Isomer Ratio on Quench Method**

entry	reaction temp (°C)	inverse quench of in-process aliquots into aq. NH_4Cl[a] cis:trans ratio	normal quench at various temperatures by adding TFA to bulk reaction mixtures[b]		
			quench temp (°C)	quench time	cis:trans ratio
1	−40 to −30	not measured	−75 to −70	2 h	1:3.8
2	−30 to −25	2.8:1	−72 to −60	25 min	1.6:1
3	−20 to −10	3:1	−15 to 12	6 min	1:1
4	−10 to −5	3:1	−42 to −30	2 min	1:1

[a] In-process check by inverse quench of small aliquots into excess saturated aqueous NH_4Cl prior to GC analysis. [b] Quench upon completion of reaction.

the use of the $CuBr{\cdot}Me_2S$ complex was deemed environmentally unacceptable on scale.

Therefore, given the tight timelines, no further evaluation of the conjugate addition reaction in alternative solvents in the presence of other copper additives was pursued, and efforts were focused instead on optimizing the Grignard addition reaction in diethyl ether with the following objectives: (1) to reduce the amount of diethyl ether by using an appropriate cosolvent; (2) to improve the process throughput by reducing the amount of solvent without compromising the stirring efficiency; (3) to maximize the cis-selectivity in the Grignard addition reaction and optimize product recovery by crystallization; and (4) to further improve the mass recovery of the desired (±)-**6**-cis product by recycling (±)-**6**-trans.

The decision to focus on the isolation and resolution of (−)-**6**-cis was based on two considerations: (a) unlike the trans isomer, which was an oil at ambient temperature and difficult to purify in a single step *via* nonchromatographic methods,[8] the cis isomer was easily crystallized from heptanes or heptanes/dichloromethane, heptanes/ethyl acetate and could be isolated with high purity; (b) the cis isomer was readily resolved with good mass recovery, whereas the resolution of the trans isomer was problematic and would have required a substantial development and optimization time.[9]

Initial trial reactions were conducted by slowly adding a solution of arecoline in 5 volumes of ether to a cold Grignard solution (1 M solution in ether, 2 equiv, and ∼9 volumes) at −30 °C. In-process GC analysis revealed that the reaction was essentially complete within an hour after completing the Grignard addition. Furthermore, careful examination of the reaction profile indicated that only 1.4 equiv of Grignard reagent were typically required to achieve complete consumption of arecoline. Subsequent treatment of the reaction mixture at low temperature (−70 °C) with TFA in the hopes of quenching the kinetic enolate to maximize the recovery of (±)-**6**-cis afforded variable ratios of the stereoisomers, generally favoring the thermodynamic (±)-**6**-trans adduct.

A careful examination of the isomeric distribution dependence on the quench method revealed that the amount of kinetic (±)-**6**-cis product was significantly increased when the quench was carried out fast, regardless of the reaction temperature at which the Grignard addition had been conducted (Table 1). Particularly noteworthy, and perhaps more significant, was the observation that when small aliquots were withdrawn from the reaction mixtures and inversely quenched into saturated aqueous ammonium chloride, the (±)-**6**-cis isomer was consistently and reproducibly generated as the major component (cis/trans ratio = 2.8:1 to 3:1; see entries 2−4 in Table 1). These experiments clearly established that the inverse quench method provided essentially an instantaneous protonation of the enolate and could, therefore, be used advantageously for improving the isomeric ratio of the Grignard addition product.

The predominant formation of (±)-**6**-cis upon rapid quench has not been fully investigated and is not completely understood. Nonetheless, the experimental results can be rationalized by considering that a potentially favored chelated kinetic enolate depicted by structure **7** (Figure 2) is predominantly generated upon conjugate addition of the Grignard reagent. A fast protonation of **7** in the equatorial direction, which corresponds to the most accessible face of the π-system, would provide (±)-**6**-cis as the major isomer.[10]

Conversely, when a comparatively slower quench is conducted, the initially generated (±)-**6**-cis may undergo in situ epimerization to afford the thermodynamic adduct (±)-**6**-trans. The limited experimental data gathered in the course of this study do not provide enough evidence to suggest to

(8) The isolation and purification of (±)-**6**-trans *via* crystallization entailed the following chemical and process steps: (a) treatment of the crude extracts from the Grignard reaction with sodium methoxide after solvent exchange into methanol to maximize the amount of (±)-**6**-trans upon thermodynamic epimerization of the cis isomer, (b) conversion of crude (±)-**6**-trans into the corresponding HCl salt in methanol and crystallization, and (c) regeneration of the free base by treatment of the salt with aqueous base and extraction. Only a modest 33% yield was achieved under these conditions. Overall, the number of steps required for generating material of suitable purity for a direct resolution of (+)-**6**-trans presented no obvious throughput advantage compared to the isolation and elaboration of the (±)-**6**-cis isomer.

(9) At the inception of the process development work and concurrently with the optimization of the Grignard reaction, several resolving agents were evaluated for their ability to provide a direct resolution of (±)-**6**-trans. These included (−)-dibenzoyl-L-tartaric acid, (*S*)-(+)-mandelic acid, L-(+)-tartaric acid, di-*p*-toluoyl-L-tartaric acid, D-(+)-malic acid, dipivaloyl-L-tartaric acid, (*S*)-(−)-2-pyrrolidone-5-carboxylic acid, (1*S*)-(+)-10-camphorsulfonic acid, and *D*-(−)-quinic acid. Most of these resolving agents provided low to no enantiomeric enhancement in pilot screening experiments in a variety of solvents, to the exception of di-*p*-toluoyl-L-tartaric acid, which afforded 31% ee and 29% ee in methyl isobutyl ketone (MIBK) and ethyl acetate, respectively, using 1 molar equiv of the resolving agent. The chiral purity could be increased up to 71% ee using substoichiometric amounts of di-*p*-toluoyl-L-tartaric acid, albeit with a lower mass recovery. Due to time constraints, however, further optimization of the direct resolution of (±)-**6**-trans was not pursued, and efforts focused instead on streamlining the resolution of (±)-**6**-cis.

(10) For a review on the stereochemistry of kinetic protonation of enolates in cyclic systems, see: Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263.

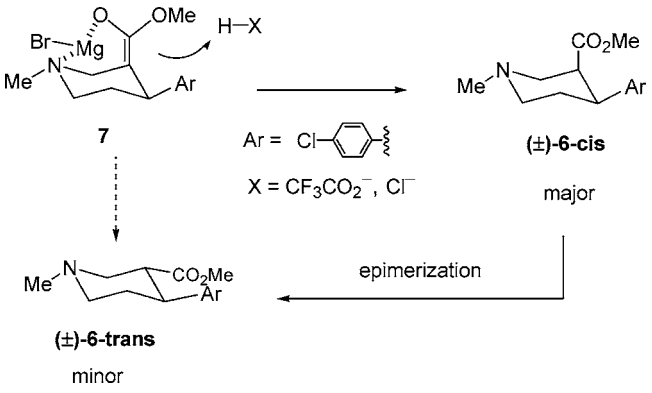


Figure 2.

Table 2. **Grignard Reaction Scale-Up Runs Using Inverse Quench into 2 M aq HCl**

entry	arecoline (g)	cis/trans ratio crude product	% yield crystallization	remarks
1	50	2.7:1	50	single crop[a]
2	200	2.6:1	54	two crops[b]
3	350	2.5:1	53	single crop[c]

[a] Cis/trans ratio of isolated product, 12:1. [b] Cis/trans ratio of first crop, 39:1. [c] Cis/trans ratio of isolated product, 12:1

what extent protonation of the enolate from the axial direction is competitive with epimerization of (±)-**6**-cis to account for the formation of (±)-**6**-trans. Additional future investigations using for instance in situ IR spectroscopy may shed some light on the mechanistic details of this reaction.

Upon incremental scale-up, minor variations in the isomeric distribution were observed that may somewhat reflect mass transfer efficiency differences at the quench (Table 2, inverse quench into 2.0 M aqueous HCl). However, a systematic evaluation of processing parameters likely to impact the mass transfer, such as mixing efficiency at the quench and its impact on the isomeric distribution, was not pursued during this study.

It is worth pointing out that methyl *tert*-butyl ether (MTBE) was found to be a convenient and safe cosolvent compatible with the Michael addition reaction, and it was therefore used in all runs reported in Table 2. This allowed us to further reduce the amount of diethyl ether in the process from 17 to 7 volumes, by restricting its use to the amount present in the commercial Grignard solution. Under the optimized conditions, 5.0−5.5 volumes of MTBE cosolvent were used in the process, providing a solvent ratio of ∼1:1.5 (MTBE/ether, v/v). The stirring issue typically observed mid-way through this Grignard reaction was significantly alleviated by carrying out the reaction at higher temperature (−15 to −5 °C) to generate a stirrable slurry that was readily amenable to the inverse quench with aqueous HCl to maximize the amount of (±)-**6**-cis. This quench was conveniently carried out by adding the reaction mixture slurry to a cold (0−5 °C) 2.0 M aqueous HCl solution.

To isolate (±)-**6**-cis, the quenched reaction mixture layers were first separated, the pH of the aqueous layer was adjusted to pH 10 with ammonium hydroxide, and the crude free base was extracted into dichloromethane. Subsequently, a solvent exchange into heptanes and a cooling crystallization were implemented, which allowed the isolation of (±)-**6**-cis consistently with 92−97% isomeric purity, as determined by GC analysis, and with good mass recovery.[11] The crystallization was initially carried out on a rotary evaporator (entries 1 and 2, Table 2) but was subsequently optimized and demonstrated in the third batch by carrying out a formal distillation to generate a supersaturated solution. The batch was then naturally cooled to ambient temperature, and the crystallization was allowed to proceed for 16 h to maximize the mass recovery in a single crop (entry, Table 2).

An additional amount of (±)-**6**-cis was readily obtained by carrying out a kinetic epimerization of (±)-**6**-trans from the mother liquors (cis/trans ratio in mother liquors for the 350 g scale batch, 1:6) using LDA as the base and THF as the solvent, then implementing an inverse quench into aqueous HCl and a selective crystallization of (±)-**6**-cis (*vide supra*; cis/trans ratio of isolated product, 8:1 for the 350 g scale batch). By applying this recovery protocol, a combined mass recovery of 75−80% was achieved on a 200−350 g scale, with a single recycle of (±)-**6**-trans.

Resolution of (±)-6-cis with (−)-Dibenzoyl-L-tartaric Acid. With an efficient protocol to generate large amounts of (±)-**6**-cis in place, efforts were focused on optimizing the resolution procedure and streamlining the generation and isolation of the final HCl salt. Previous investigations into the resolution procedure showed that when (±)-**6**-cis was treated with 1 mol equiv of the resolving agent in 12 volumes of methanol at ambient temperature overnight, the desired (−)-**6**-cis was obtained with 90% enantiomeric excess and 35−40% mass recovery. The chiral purity could be improved to 94−98% ee by either working under more dilute conditions (20−30 volumes of methanol) or using substoichiometric amounts of the resolving agent.

In an effort to further improve the resolution procedure with a view to generating (−)-**6** with ≥98% ee without a need for a recrystallization, the resolution was further studied at a slightly higher temperature (30 °C). It was expected that, by implementing the isolation at this temperature, most of the more soluble, unwanted diastereomeric salt would remain in solution, thus making possible the recovery of the desired diastereoisomer with higher chiral purity. The resolution was thus carried out using 1 mol equiv of the resolving agent and 15 volumes of methanol, by adding a slurry of (±)-**6**-cis in methanol to a warm solution (50−60 °C) of (−)-dibenzoyl-L-tartaric acid in methanol. The mixture was briefly heated at reflux and then slowly cooled to 30 °C over 5 h and further allowed to crystallize at 30 °C for 17 h. Gratifyingly, when filtration was carried out at 30 °C, the unwanted enantiomer was completely purged out and the desired (−)-**6**-cis enantiomer was isolated with >99% ee and 34% overall mass recovery after conversion of the salt to the free base.

These conditions were readily scaled up and reproducibly implemented on a 214 g scale with a minor modification. Since (±)-**6**-cis was less soluble in methanol at ambient

(11) Based on the amount of (±)-**6**-cis isomer present in the quenched reaction mixture, approximately 70−75% of the theoretical amount was isolated in a single crop.

temperature than (−)-dibenzoyl-L-tartaric acid, it was deemed operationally more convenient to prepare a slurry of (±)-**6**-cis and heat it to 65 °C to obtain a clear solution and then dropwise add a solution of the resolving agent in methanol. Subsequent slow cooling to 30 °C and further crystallization at this temperature over 17 h afforded 36% mass recovery with 99% ee.

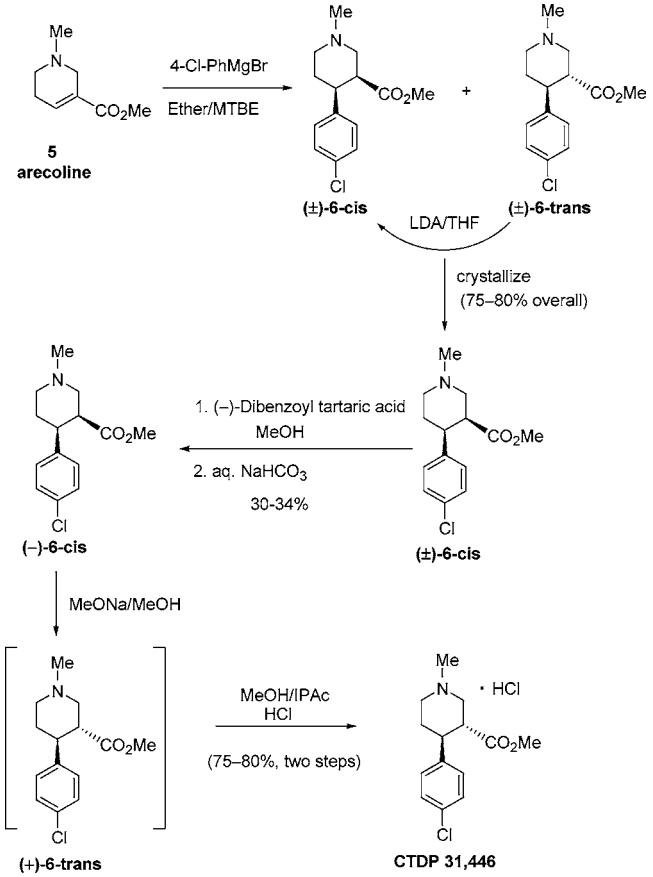
The dibenzoyl-L-tartrate salt was converted to the corresponding free base by treatment with saturated aqueous sodium bicarbonate. Extraction of the free base with dichloromethane followed by solvent exchange into heptanes and crystallization afforded a slurry of elongated needles that could be readily isolated by filtration, with >99% ee and 31% overall mass recovery from (±)-**6**-cis.

Thermodynamic Epimerization of (−)-6-cis and Isolation of (+)-CTDP 31,446 as the Hydrochloride Salt. The thermodynamic epimerization of the resolved (−)-**6**-cis with sodium methoxide in refluxing methanol worked well and did not require any significant optimization. This reaction was typically conducted in 7 volumes of methanol using 1 molar equiv. of sodium methoxide and proceeded to >98% conversion within 6 h, as determined by GC analysis. In the original procedure, the free base derived from the thermodynamic epimerization reaction was isolated as a viscous oil by stripping the batch to dryness and redissolving the residue into dichloromethane, followed by washing the resulting solution with water and further stripping the extracts to dryness. The final HCl salt formation and crystallization was then carried out by precipitating the salt from methanol upon treatment of the crude free base solution with anhydrous HCl, typically affording moderate yields of CTDP-31,446. To improve the mass recovery, diethyl ether was added as an antisolvent on small scale runs, and the product was isolated in multiple crops.

Due to efficiency and safety concerns, an alternative procedure for the final hydrochloride salt formation and crystallization more amenable to pilot scale production that avoided or minimized the use of diethyl ether was desirable. Advantage was taken of the observation that isopropyl acetate was an excellent solvent for extraction of the free base (±)-**6**-trans but a rather poor solvent for the HCl salt. These characteristics could therefore be used advantageously to further streamline the process by telescoping the final salt formation in the solvent used for the free base extraction.

Indeed, initial pilot experiments to crystallize the hydrochloride salt directly from crude isopropyl acetate extracts afforded the salt in high yields in a single crop and with excellent purity. Minimal optimization was required, other than a controlled addition of the HCl solution to the free base at 0 °C to minimize the exotherm due to the salt formation and crystallization. In the optimized process, the free base (±)-**6**-trans derived from the thermodynamic epimerization was first extracted into isopropyl acetate after distillation of methanol, washed with water, clarified by polish filtration, and cooled to 0−5 °C. A solution of anhydrous HCl in methanol (1.5 equiv of HCl) was then slowly added to the free base while maintaining the batch temperature below 5 °C to afford CTDP-31,446 as a colorless and easily filtered solid (75−80% yield in a single crop, Scheme 2).

Scheme 2



Conclusions

The original synthetic approach to enantiomerically pure CTDP-31,446 was optimized and streamlined to define processing parameters that are more amenable to pilot scale production. First, the use of diethyl ether was minimized and restricted to only the amount present in the commercial Grignard solution. At the same time, MTBE was successfully incorporated as a cosolvent, and a temperature threshold that allowed the generation of a mobile slurry was defined. This made possible the implementation of a more concentrated process and an inverse quench strategy to maximize the recovery of the crystalline and easily resolved (±)-**6**-cis isomer. The resolution procedure was optimized to completely remove the unwanted enantiomer in a single pass. Finally, isopropyl acetate was identified as a suitable solvent not only for the extraction of the resolved (+)-**6**-trans but also as an effective antisolvent in a binary crystallization solvent system to isolate CTDP-31,446 with good mass recovery and high purity.

Experimental Section

General. Reagents purchased from commercial sources were used as received. Solvents for reactions and isolations were reagent-grade and used without purification. Proton and carbon nuclear magnetic resonance spectra were obtained on a Bruker AVANCE 300 spectrometer at 300 MHz for

proton and at 75 MHz for carbon. Tetramethylsilane was used as an internal reference for the proton spectra, and the solvent peak was used as the reference peak for the carbon spectra. Mass spectra were obtained on a Finnigan LCQ Duo LC-MS (APCI) mass spectrometer. IR spectra (ATR) were obtained on an Avatar 370 FT-IR Thermo Nicolet. DSC analysis was obtained on a Mettler Toledo DSC822. HPLC analysis for chemical purity was performed using a YMC ODS-AQ (4.6 mm × 250 mm, 5 μm, 120 Å) C18 column, using a gradient elution with a mobile phase A (0.05% methanesulfonic acid in water) and mobile phase B (0.04% methanesulfonic acid in methanol) from 98:2 to 10:90 (A:B, v/v) and detection at 221 nm. HPLC analysis for chiral purity was carried out using a Chiralpak AD-H (4.6 mm × 250 mm, 5 μm) column, using an isocratic elution with *n*-heptane/ethanol (98.5:1.5, v/v) modified with 0.05% diethylamine, and detection at 221 nm. GC analysis was conducted using a Restek RTX-5 (30 m × 0.32 mm × 0.25 μm) capillary column fitted to a Hewlett-Packard 5890 gas chromatograph interfaced with a Hewlett-Packard 3396A integrator. The analysis conditions were injector 250 °C, carrier gas helium, splitless injection (1 μL), oven temperatures 80 °C, isothermal for 4 min, ramp at 15 °C/min to 250 °C, hold at 250 °C for 10 min, and detector FID at 250 °C. Retention times: (±)-**6**-trans 20.6 min and (±)-**6**-cis 21.7 min. Elemental analysis was performed by Quantitative Technologies, Inc.

Preparation of (±)-Methyl 4β-(4-Chlorophenyl)-1-methylpiperidine-3β-carboxylate, (±)-6-cis. A 12-L reactor equipped with an overhead mechanical stirrer and a thermocouple was charged with a 1.0 M solution of *p*-chlorophenylmagnesium bromide in diethyl ether (3.1 L, 3.1 mol, 1.4 equiv) under a nitrogen atmosphere. The Grignard solution was cooled to −20 °C, and then a solution of arecoline (350 g, 2.26 mol) in anhydrous methyl *tert*-butyl ether (1.8 L, 5.1 volumes) was charged dropwise over 1 h while maintaining the batch temperature below −5 °C. The batch was vigorously stirred throughout the addition of the arecoline solution, and the reaction progress was monitored by GC analysis. After further reaction for 2 h, GC analysis indicated <5% residual arecoline. The reaction was quenched by carefully transferring the slurry into a quench vessel containing ice-cold 2 M aqueous HCl (3.5 L), with vigorous stirring. A small amount of residual reaction mixture in the reactor was quenched with an additional 1 L of ice-cold 2 M aqueous HCl, and the wash was combined with the bulk of the quenched reaction mixture. The resulting biphasic mixture was allowed to stir for 15 min, the layers were separated, and the organic layer was washed with ice-cold 2 M aqueous HCl (1 × 1 L). The combined aqueous layers were chilled to 0 °C, carefully made alkaline (approximately pH 10) with concentrated aqueous ammonium hydroxide (ca. 650 mL) and extracted with dichloromethane (1 × 2 L, then 2 × 1 L). The combined dichloromethane extracts were concentrated by distillation under reduced pressure to approximately 1 L of residual solution. Heptanes (1 L) were added to the residual methylene chloride solution, and distillation was continued, with a final batch temperature of 70 °C. The batch was then allowed to naturally cool to ambient temperature and further aged for 16 h. The resulting solids were collected by filtration and dried in a vacuum oven (40 °C) to afford 322 g of product (53% isolated yield; cis/trans ratio, 12:1) as a tan solid. ^{1}H NMR (±)-**6**-cis ($CDCl_3$, 300 MHz) δ 1.80 (dq, J = 12.5, 3.1 Hz, 1H), 2.07 (dt, J = 11.2, 2.9 Hz, 1H), 2.28 (s, 3H), 2.36 (dd, J = 11.6, 3.7 Hz, 1H), 2.66 (dq, J = 11.8, 3.7 Hz, 1H), 2.79 (dt, J = 11.8, 3.9 Hz, 1H), 2.93−3.03 (m, 2H), 3.19 (dd, J = 11.5, 1.5 Hz, 1H), 7.16−7.31 (m, 4H). The filtrate was concentrated to give 231 g of a brown oil which contained a 1:6 mixture of (±)-**6**-cis/(±)-**6**-trans.

Kinetic Epimerization of (±)-Methyl 4β-(4-Chlorophenyl)-1-methylpiperidine-3β-carboxylate, (±)-6-trans. A 5-L reactor equipped with an overhead mechanical stirrer and a thermocouple was charged under a nitrogen atmosphere with the filtrate residue containing a mixture of (±)-**6**-cis and (±)-**6**-trans (1:6 ratio by GC analysis, 231 g, 817 mmol) and anhydrous THF (2 L). The resulting solution was cooled to −70 °C, and LDA (477 mL, 2.0 M in THF, 954 mmol, 1.2 equiv) was charged dropwise over 1 h. The reaction mixture was stirred for an additional hour, and then the reaction was quenched by transferring the mixture into a quench vessel containing ice-cold 2 M aqueous HCl (1 L) with vigorous stirring. The resulting mixture was transferred back into the reactor, and THF was removed by distillation under reduced pressure. The aqueous residue was washed with methyl *tert*-butyl ether (1 × 1 L), chilled to 0 °C, made alkaline (approximately pH 10) with concentrated ammonium hydroxide (200 mL), and extracted with dichloromethane (3 × 1 L). The combined dichloromethane extracts were distilled under reduced pressure to ca. 500 mL, diluted with heptanes (500 mL), and further distilled to remove the bulk of the residual dichloromethane. The final solution in heptanes was allowed to naturally cool to ambient temperature and age for 18 h. The crystallized solids that formed were collected by filtration and dried under a vacuum (40 °C) for 24 h to afford 128.6 g of product (56% recovery; cis/trans ratio, 8:1) as a tan solid.

Resolution of (±)-Methyl 4β-(4-Chlorophenyl)-1-methylpiperidine-3β-carboxylate, (±)-6-cis. A 5-L reactor equipped with an overhead mechanical stirrer, a reflux condenser, and a thermocouple was charged with (±)-methyl 4β-(4-chlorophenyl)-1-methylpiperidine-3β-carboxylate, (±)-**6**-cis (214 g, 0.80 mol), and methanol (1.8 L, 8.4 volumes). The resulting slurry was heated to ca. 65 °C, and a solution of (−)-dibenzoyl-L-tartaric acid monohydrate (301 g, 0.8 mol, 1.0 equiv) in methanol (1.5 L, 7.0 volumes) was added at such a rate as to maintain the batch temperature above 60 °C (required 30 min). The resulting slightly turbid solution was then cooled to 30 °C over 5 h at a rate of 7 °C/h and aged at this temperature for 17 h. The crystallized salt was harvested by filtration at 30 °C, and the wet cake was washed with methanol (214 mL, 1 volume), conditioned at ambient temperature for 30 min, and further dried under a vacuum (25 in. Hg) at 40 °C for 14 h to afford the dibenzoyl tartrate salt as a white solid (181.5 g, 36.3% yield). The salt (181 g) was taken up in 5% aqueous bicarbonate (1.2 L, pH adjusted

to pH 10 with NaOH) and dichloromethane (0.9 L), and the layers were separated. The aqueous layer was further extracted with dichloromethane (1 × 0.9 L), and the combined organic layers were washed with water (1 × 0.9 L) and then distilled to a residual volume of approximately 0.5 L. To the residue were added heptanes (750 mL), and the resulting mixture was further distilled under reduced pressure to a residual volume of approximately 300 mL. The resulting slurry was aged at ambient temperature for 1 h, filtered, and dried under a vacuum (25 in. Hg) at 40 °C for 12 h to afford (−)-methyl 4β-(4-chlorophenyl)-1-methylpiperidine-3β-carboxylate, (−)-**6**-cis [67 g, 31.3% yield from (±)-**6**] as colorless needles.

Thermodynamic Epimerization of (−)-Methyl 4β-(4-Chlorophenyl)-1-methylpiperidine-3β-carboxylate, (−)-6-cis, and Preparation of CTDP 31,446. A 1-L reactor equipped with an overhead mechanical stirrer, a reflux condenser, and a thermocouple was charged with a slurry of (−)-methyl 4β-(4-chlorophenyl)-1-methylpiperidine-3β-carboxylate (60 g, 0.224 mol) in methanol (420 mL, 7.0 volumes), followed by sodium methoxide (12.1 g, 0.224 mol, 1.0 equiv). The resulting mixture was then heated to 60 °C, and the reaction was allowed to proceed for 6 h, whereupon GC analysis of an aliquot indicated <2% residual (−)-**6**-cis isomer. The bulk of methanol was removed by distillation (ca. 410 mL removed), and the residue was treated with a mixture of isopropyl acetate (450 mL, 7.5 volumes) and saturated aqueous ammonium chloride (450 mL, 7.5 volumes). The layers were separated, and the aqueous layer was further extracted with isopropyl acetate (1 × 450 mL). The combined organic extracts were washed with water (1 × 450 mL, then 1 × 300 mL) and concentrated under reduced pressure to approximately 360 mL of residual solution. This solution was polish-filtered through a 1.0 μm filter and charged into a 1-L reactor equipped with an overhead mechanical stirrer, a pressure-equalizing addition funnel, and a thermocouple. The crude free base solution was cooled to 0 °C, and then a solution of anhydrous HCl in methanol (ca. 9 wt %, 7 mg/mL, 175 mL) was added dropwise over 30 min while maintaining the batch temperature below 5 °C. The resulting slurry was allowed to age at 0 °C for 1 h and then filtered. The wet cake was washed with 20% (v/v) methanol in isopropyl acetate (1 × 60 mL), conditioned under a vacuum at ambient temperature for 2 h, and further dried under a vacuum (25 in. Hg) at 40 °C for 45 h to afford CTDP 31,446 as a white crystalline solid [55.4 g, 81.4% yield from (−)-**6**-cis]. Mp: 246.5 °C. $[\alpha]^{25}_{D}$ +56.2 ° (*c*1.03, EtOH). HPLC assay for chemical purity: 99.8% (AUC). HPLC assay for chiral purity: 99.9% ee. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.92 (d, J = 12.6, 1H), 2.22 (dq, J = 12.9, 2.9 Hz, 1H), 2.78 (s, 3H), 2.99 (dt, J = 12.0, 3.7 Hz, 1H), 3.06−3.26 (m, 2H), 3.31−3.52 (m, 2H), 3.36 (s, 3H), 3.64 (d, J = 11.1 Hz, 1H), 7.22 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 11.56 (br s, 1H). ^{13}C NMR (DMSO-d_6) 29.7, 41.7, 42.6, 45.7, 52.2, 53.1, 53.8, 129.0, 129.3, 132.0, 141.1, 171. Anal. Calcd for $C_{14}H_{18}ClNO_2$·HCl: C, 55.27; H, 6.29; N, 4.60; Cl, 23.30. Found: C, 55.29; H, 6.34; N, 4.50; Cl, 23.10. MS *m*/*z* (APCI): 268 $[M + H]^+$.

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