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Synthesis of ((3*R*,6*R*)-6-Methylpiperidin-3-yl)methanol via Biocatalytic Transamination and Crystallization-Induced Dynamic Resolution

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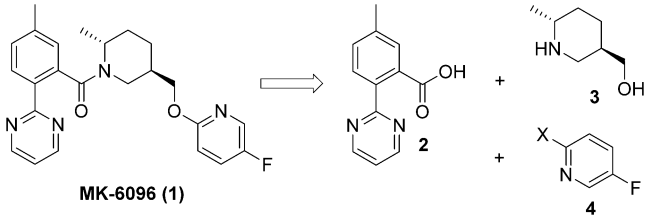
Supporting Information

ABSTRACT: An asymmetric synthesis of orexin receptor antagonist MK-6096 piperidine core, ((3*R*,6*R*)-6-methylpiperidin-3-yl)methanol (**3**), is described. The target is synthesized in four steps and 40% overall yield from methyl vinyl ketone and diethyl malonate. The key operation is a practical crystallization-induced dynamic resolution for the conversion of a trans/cis mixture of lactam acid **17** into the desired trans-lactam acid salt in >95% de and 91% yield. The substrate lactam acid mixture was prepared via a solvent-free Michael reaction and a practical biocatalytic transamination process.

MK-6096 (**1**) is a potent dual Orexin receptor antagonist in clinical trials for the treatment of sleep disorder (Scheme 1).[1] The first multikilogram synthesis of **1** was recently reported,[2] where key piperidine **3** fragment was accessed via a classical salt resolution, affording a low overall yield for the route. Specifically, the hydroxymethyl stereogenic center in piperidine **3** prepared from lactam ester **8a** was not well-controlled and a classical resolution via the (D)-camphorsulfonic acid (CSA) salt was used to upgrade the dr (Scheme 2). Subsequently, a second generation synthesis was developed which achieved complete stereochemical control and doubled the overall yield of **3** (Scheme 2),[3] but there was negligible cost reduction due to use of expensive reagents such as TMSOTf. It was projected that controlling the ester bearing center in lactam ester **8a** in an asymmetric fashion would greatly improve the overall process productivity. Herein we report development of an efficient synthesis of **3** via crystallization-induced dynamic resolution (CIDR)[4] of lactam acid **17** by salt formation with achiral amines.

Scheme 1. Retrosynthetic Analysis of MK-6096 (1)



In the first generation synthesis of **3**, lactam ester **8a** was prepared from methyl vinyl ketone (MVK) (**5**) and dimethyl malonate (**6a**) in two steps via a Michael addition reaction followed by a biocatalytic transamination (Scheme 2).[2] The transamination reaction set the methyl bearing center in >99.5% ee; however, the ester bearing center was an uncontrolled 1.2:1 mixture. The ester and the lactam functionalities in **8a** were then sequentially reduced to afford a 1.7:1 trans/cis mixture of piperidinols. This mixture was then resolved via the CSA salt to afford desired piperidinol diastereomer **3**·CSA in 43% yield for the step or 24% overall yield.

The first generation synthesis of **8a** used acetonitrile as a solvent for the Michael reaction and a three-enzyme system for the biocatalytic transamination. We wished to improve the efficiency of these processes and identified a solvent free-condition for Michael reaction,[5] and a single enzyme system[3,6] for the biocatalytic transamination−lactamization (Scheme 3). The modified conditions, started from diethyl malonate (DEM) **6b,** afforded lactam ethyl ester **8b** in similar overall yield and enantiomeric and diastereomeric purities as **8a** obtained from the first generation synthesis. The trans and the cis diastereomers of **8b** could be separated by chromatography, but they quickly and spontaneously epimerized to a ∼1:1 mixture even under neutral conditions. We decided to take advantage of this rapid epimerization, and envisioned dynamic asymmetric transformation processes via hydrogenation or hydrolysis of the ester group to improve the overall yield of piperidinol **3** synthesis.

For the catalytic hydrogenation of lactam ester **8a**, various ruthenium catalysts,[7] solvents, temperatures, and additives were evaluated. Although conditions that afforded nearly full conversion were found, the diastereoselectivity for the desired *trans*-lactam alcohol **9** was never higher than 30% de (trans/cis = 1.9/1.0). We then focused on evaluating enzymatic dynamic asymmetric ester hydrolysis. Using hydrolases at pH 9, the reaction afforded *trans*-lactam acid sodium salt **16** in ∼96% de. However, upon isolation by evaporation of aqueous mixture using isopropanol flushes, the diastereomeric purity of the solid product eroded to 25−80% de. Attempts to improve the stability and the solubility of *trans*-**16** in organic solvent by

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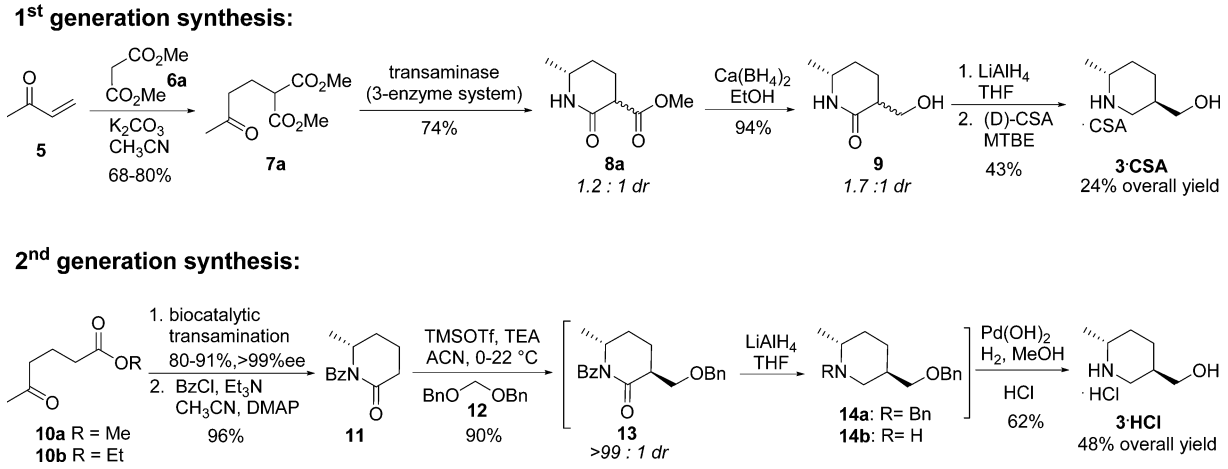
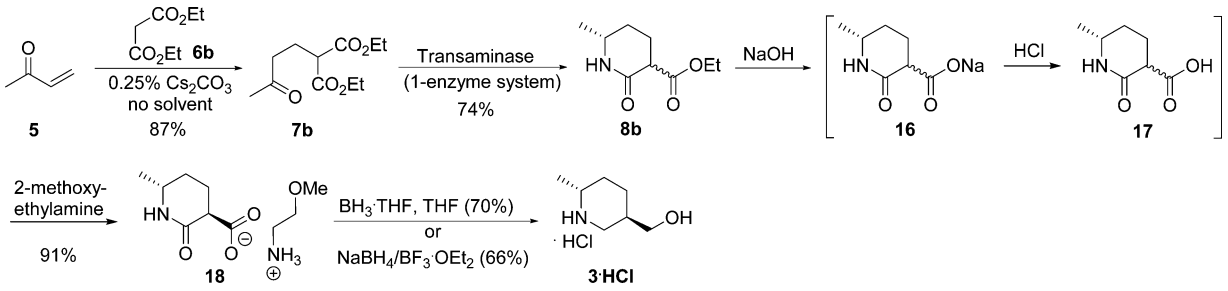
Scheme 2. First and Second Generation Routes to Piperidine 3



Scheme 3. Third Generation Synthesis of Piperidine 3 via CIDR

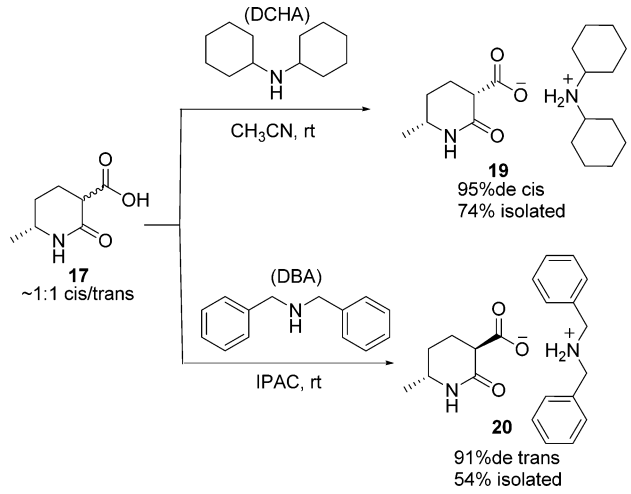


using tetraalkylammonium counterions and various solvents combinations did not suppress the de erosion.

In an effort to study lactam acid **17** without complication from the enzymes and buffers, we performed a simple saponification of **8b** to access clean **17** (Scheme 3). Care was taken to avoid excess HCl during acidification of the carboxylate salt in the basic solution in order to minimize decarboxylation. The acidified reaction mixture was azeotropically distilled with acetonitrile flushes, then filtered to remove NaCl to afford a filtrate containing near quantitative yield of lactam acid **17** as a 1.1−1.8:1 trans/cis mixture with <1% decarboxylation. With clean **17** in hand, we proceeded to examine the formation of the amine salts. Serendipitously, we discovered lactam acid **17** underwent a crystallization-induced dynamic resolution during salt formation to afford either the cis or trans diastereomers in high de depending on the amine used (Scheme 4). Treatment of **17** with dicyclohexylamine (DCHA) afforded the crystalline cis-isomer **19** in 95% de from acetonitrile (AcN), whereas treatment with dibenzylamine (DBA) afforded the crystalline trans-isomer **20** in 91% de from isopropyl acetate (IPAC). In both cases, the trans/cis ratios in the supernatant were nearly 1:1, consistent with a crystallization driven process. The trans-stereochemistry of DBA salt **20** was confirmed by a single crystal X-ray structure. Subsequent borane reduction of DBA carboxylate salt **20** proceeded stereospecifically to afford the desired hydroxymethylpiperidine **3**, albeit, with difficult DBA removal.

We therefore screened additional amines with the goal of finding amines that could be easily removed after reduction to the piperidinol. Twenty-four achiral amines (Table 1) and several chiral amines were investigated. Of all the achiral amines screened, only four amines afforded the trans-salt. The smallest

Scheme 4. Initial Hits of Dynamic Resolution of 17 via CIDR



amine which afforded the trans product in good diastereomeric selectivity (96% de) was 2-methoxyethylamine (MEA) (entry 11), which has the desired properties of low boiling point (95 °C) and excellent water solubility. The chemical composition of the resultant salt was confirmed to be a 1:1 molar ratio of acid and MEA by 1H NMR. Solubilities of this salt in IPAC (with 1% H_2O) and AcN/IPAC (5:1 with 1% H_2O) was <1 and <3 mg/mL, respectively, which led to excellent product recovery (91−96% yield). During the workup of **17**, it was critical to distill off most of the water until a free-flowing NaCl was obtained for efficient filtration and minimizing trapping of **17** in the wet NaCl slurry. The methoxyethylamine salt **18**, after

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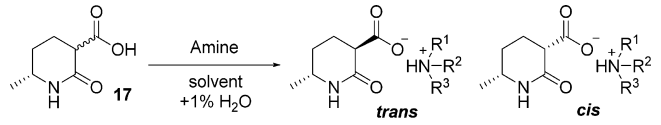
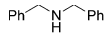
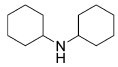
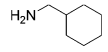
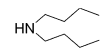
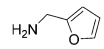
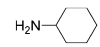
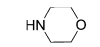
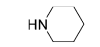
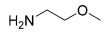
Table 1. Amine Salt Screen



	Amine	Bp (°C)	Solvent	Major	% de		Amine	Bp (°C)	Solvent	Major	% de
1		300	AcN IPAC	***trans***	**94%**	13		88	IPAC	*oil*	
2		295	IPAC	*gel*	0%	14		87	IPAC	*cis*	96%
3		256	AcN	*cis*	95%	15		78	IPAC	*oil*	
4		185	IPAC	***trans***	**94%**	16		71	AcN IPAC	*soln t/c = 1:1*	0%
5		160	IPAC	*cis*	26%	17		55	IPAC	*soln t/c = 1:1*	0%
6		159	AcN IPAC	*soln t/c =1:1*	0%	18		53	IPAC	*oil*	
7		146	IPAC	***trans***	**96%**	19		46	IPAC	*cis*	96%
8		134	IPAC	*cis*	94%	20		34	AcN IPAC	*cis*	94%
9		129	IPAC	*cis*	76%	21		7	IPAC	*oil*	
10		106	IPAC	*gum*		22		-6	IPAC	*oil*	
11		95	AcN IPAC	***trans***	**96%**	23		-33	IPAC	*oil*	
12		89	IPAC	*oil*		24		164	IPAC	*oil*	

filtration and vacuum drying, was isolated in 91% yield with a typical purity of 97−99 wt %, >96% de, and KF < 0.2%.

In order to establish the thermodynamic stability of MEA salt **18**, we subjected the salt to equilibration in the following three solvent mixtures and monitored the trans/cis ratio of the solid over time (Table 2): (1) 1 v % H_2O in acetonitrile, which was the solvent for the CIDR of MEA salt **18** (entries 1−4); (2) 1.7 v % H_2O in acetonitrile to test the sensitivity of excess water (entry 5); and (3) 87% THF/*n*-heptane, which was the solvent composition of choice for the subsequent borane reduction (entries 6−9).

Table 2. Equilibration Study of MEA Salt 18[a]

entry	solvent	equilibration time (h)	supernatant conc. (mg/mL)	trans/cis ratio of the solids
1	1% H_2O in MeCN	2	2.2	96.4:3.6
2	"	4	2.1	98.3:1.7
3	"	6	2.1	97.3:2.7
4	"	72	1.8	98.0:2.0
5	1.7% H_2O in MeCN	72	3.7	94.9:5.1
6	87% THF/ heptane	2	<0.4	97.0:3.0
7	"	4	<0.4	97.9:2.1
8	"	6	<0.4	97.2:2.8
9	"	72	<0.4	96.5:3.5

[a]Starting MEA salt **18** was ~95% de and 98.6 wt %. Each entries started with 50 mg of MEA salt **18** per mL solvent.

Entries 1−4 showed that a steady state with respect to solubility and epimerization in 1% water containing MeCN was reached in 2 h, and the high trans to cis ratios were maintained for at least 72 h. The experiment carried out in MeCN containing 1.7% water, where the solubility was 3.7 mg/mL (in 72 h) showed a slight lower de (entry 5). Entries 6−8 showed the lactam acid salt to be stable in the borane reduction solvent for at least 72 h. Several batches of MEA salt **18** before and after equilibration studies were examined by X-ray powder diffraction, thermal gravimetric analysis, differential scanning calorimetry, residual solvent contents (water, acetonitrile, and IPAc), and all were shown to be the same anhydrous polymorphic crystalline form.

With a robust preparation process defined for MEA salt **18**, we proceeded to examine the reduction step using BH_3·THF and $NaBH_4/BF_3$·OEt_2 (Table 3). While the use of BH_3·THF

Table 3. Borane Reduction of MEA Salt 18 to Piperidine 3

entry	condition	scale	BX_3 add'n time	piperidinol **3** trans:cis	isolated yield
1	BH_3·THF[a]	1 g	1 min	98.8:1.2	70%
2	$NaBH_4$, BF_3·OEt_2[b]	1 g	1 min	97.5:2.5	58%
3	$NaBH_4$, BF_3·OEt_2[b]	150 g	1.5 h	96.1:3.9	66%
4	$NaBH_4$, BF_3·OEt_2[b] reversed addn	1.5 g	2 min	96.9:3.1	66%
5	IPA trituration of entry 3 product	2 g		99.1:0.9	92%

[a]7 equiv. [b]5.5/7 equiv.

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maintained the diastereoselectivity of the product (entry 1), a slight erosion in dr was observed with $NaBH_4/BF_3{\cdot}Et_2O$ (entries 2−4). Gratifyingly, an increase in product diastereoselectivity was observed from 96:4 to 99:1 by a simple isopropanol trituration (entry 5). Isolation of piperidinol free base **3** from the reaction mixture was fairly straightforward involving a acid−base swing and extraction with MTBE/THF mixture. 2-Methoxyethylamine was easily removed by aqueous washes and evaporation during the work up. Subsequent treatment of the freebase with HCl in IPA afforded piperidinol **3** as hydrochloride salt in high purity.

In summary, we have discovered a crystallization-induced dynamic transformation of lactam acid by salt formation which provided the basis for an efficient, cost-effective manufacturing process of piperidine **3**.

EXPERIMENTAL SECTION

General. All reactions were carried out under a nitrogen atmosphere. All solvents and reagents were purchased from commercial sources and were used without further purification. ^1H and ^{13}C NMR chemical shifts were reported relative to residual proton solvent peaks. All yields are corrected for purity and determined by reverse phase HPLC assay using purified standards.

*Preparation of Diethyl 2-(3-Oxobutyl)malonate (**7b**).* To a dry vessel equipped with overhead stirrer, addition funnel, nitrogen inlet, and a thermostat was charged diethyl malonate (474 mL, 99 wt %, 3091 mmol) and powdered cesium carbonate (2.52 g, 7.73 mmol) and stirred at ∼300 rpm under N_2. The mixture was cooled to ∼15 °C. Methyl vinyl ketone (277 mL, 95 wt %, 3245 mmol) was slowly added over ∼2 h at such a rate to maintain internal temperatures of 20−25 °C. The reaction mixture was aged at 20−29 °C for 20 h until complete disappearance of MVK (monitored by HPLC at 210 nm). 85% H_3PO_4 (0.529 mL, 7.73 mmol) was added at 22−23 °C. After stirring for 30 min, HPLC assay showed 0% MVK, 9% DEM, and 621 g (87% yield) of keto-diester **7b**. The physical weight of the batch was 741 g, and the wt % purity of **7b** was 83.8 wt %. The mixture was used as is in the next step. All analytical results are consistent with the reported values.[8] HPLC Conditions: Zorbax Eclipse Plus C18, 50 × 4.6 mm, 1.8 μm, A = ACN, B = water w/0.1% H_3PO_4, 5% A to 95% A over 5 min, then hold for 7 min. Flow rate = 1.5 mL/min; temp. 25 °C; wavelength = 210 nm. Retention times: 1.33 min = MVK, 3.10 min = diethyl malonate, 3.40 min = MVK dimer, 3.44 min = keto-diethyl ester **7b**, 3.58 min = bis-Michael adduct.

*Preparation of Ethyl (6R)-6-Methyl-2-oxopiperidine-3-carboxylate (**8b**).* Transaminase CDX-010 (75.5 g) and pyridoxal-5-phosphate (7.55 g) were charged to a three-neck round-bottom flask. 0.2 M pH 8.5 borate buffer with 1 M *i*PrNH$_2$ (7.55 L) (preparation: a stock solution of 0.5 M borate buffer solution was prepared by dissolving sodium tetraborate decahydrate (286.02 g, 0.75 mol) in water (6 L). The solution was adjusted to pH 9 with 6 N HCl. 0.5 M borate buffer stock solution (2.81 L) was diluted to 0.2 M by addition of 4.13 L water. 636 mL of neat *i*PrNH$_2$ was added to the buffer solution and was then pH adjusted to 8.5 with 6 N HCl) was charged to the flask and began stirring. The bright yellow mixture slowly thinned to a hazy solution. The solution was heated to 45 °C. The pH was adjusted to 8.5 with 4 M *i*PrNH$_2$. Neat ketone diester **7b** (675.31g, 83.8 wt %, 2.458 mol) was added to the hot solution over 3 h via an addition funnel. The solution was maintained at 45 °C and pH 8.5 for 16 h. The reaction mixture thickened over time and slowly became light brown in color. It was sampled and analyzed by LC. Upon complete conversion, the heating source was removed, and the reaction mixture was allowed to cool. Solka-floc (150 g, 200 wt % relative to enzyme) was added to the warm reaction, and the pH was adjusted to 3.6−4 with 6 N HCl. The slurry further thickened. The thick slurry was aged for 2 h at rt. The slurry was filtered through a 24-in. filter pot lined with filter paper and two layers of cheesecloth. No rinse was performed. The filtrant was assayed and extracted with 2 × 3 L dichloromethane (left rag layer in with aqueous). The organic layers were combined, dried over $MgSO_4$, and filtered. The filter cake was washed with additional dichloromethane and combined with organics. Product loss to aqueous layer was about 4%. The organic was concentrated to afford **8b** an oil (564 g, 60 wt % as a 1.1:1 trans:cis mixture, 74% yield, > 99.5% ee at C6) and used directly in the next step. This crude oil was stable for at least 30 days at rt. Crude NMR spectra are consistent with previous literature reports.[9] HPLC method: Zorbax Eclipse Plus C18, 50 × 4.6 mm, 1.8 μm; A = acetonitrile, B = water w/0.1% H_3PO_4; 5% A to 95% A over 5 min then hold for 2 min; flow rate = 1.5 mL/min; temp. 25 °C; detection = 210 nm; retention time: 2.45 min = *cis*-ester-lactam **8b**, 2.49 min = *trans*-ester-lactam **8b**, 3.44 min = keto-diethyl ester **7b**. Chiral HPLC method: AD-RH 150 × 4.6 mm, 5 μm; A = 0.1% H_3PO_4/H_2O, B = 2-propanol; 20% to 60% B over 30 min, hold at 60% B for 15 min; flow rate = 0.75 mL/min; column temperature = r.t.; Retention time: 4.83 min = ethyl (3*S*,6*S*)-6-methyl-2-oxopiperidine-3-carboxylate, 5.79 min = ethyl (3*S*,6*R*)-6-methyl-2-oxopiperidine-3-carboxylate, 6.60 min = ethyl (3*R*,6*S*)-6-methyl-2-oxopiperidine-3-carboxylate, 7.57 min = ethyl (3*R*,6*R*)-6-methyl-2-oxopiperidine-3-carboxylate.

*Preparation of 2-Methoxyethan-1-aminium (3R,6R)-6-methyl-2-oxopiperidine-3-carboxylate (**18**).* Ester-lactam **8b** (220 g, 60 wt %, 712.7 mmol) and water (110 mL) was charged to a vessel, cooled to 5 °C, and rinsed with 10 mL of THF. 5 N NaOH (242 mL, 1212 mmol) was added over 0.2 h at <15 °C and then stirred at rt. After stirring for 1−1.5 h at 23 °C, an HPLC assay showed 99.8% conversion to acid-lactam **17** (vs 2.43 min peak for **8b**). The mixture was cooled to 2 °C, diluted with acetonitrile (1320 mL), and followed by slow addition of 36.6% HCl (101 mL, 1212 mmol) at <5 °C over 0.5 h (final pH 1.5−2.5), then rinsed with acetonitrile (100 mL). The mixture was allowed to warm to rt, with a total volume ∼2067 mL (two layers), and was concentrated on rotovap at <20 °C to ∼900 mL (two layers), then acetonitrile (1200 mL) was added. This was repeated several times until KF ∼ 1.38 wt/v%. The mixture was filtered through a M-porosity sintered glass funnel (to remove ∼72 g NaCl) and washed with acetonitrile (400 mL). The combined filtrate (1276 mL, KF = 0.98%) was determined with a HPLC assay to contain 106 g of acid-lactam **17** (trans:cis = 1.8:1, 0.6 A% decarboxylation product). To this organic solution (∼1276 mL, 5.8 vol rel. to SM) at 19 °C was seeded with a small amount of **18**, then added 2-methoxyethylamine (104 mL, 1183 mmol) over 1 h, as it exothermed from 19 to 29 °C. Crystallization initiated after ∼35 mL of 2-methoxyethylamine was added. After the addition, the resultant thick slurry was stirred at 23 °C for 2−16 h (supernatant concentration ∼3.7 mg/mL), then added isopropyl acetate (255 mL) over 30 min. After stirring for 1 h, the supernatant acid-lactam concentration was 2.7 mg/mL (∼4% loss). The product was isolated by filtration and washing with 1:1 acetonitrile−isopropyl acetate (440 mL). The wet cake was

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vacuum-dried under N_2 at rt to afford *trans*-acid-lactam MEA salt **18** as a white solid (154.5 g, KF ~ 0.17%; 98 wt %; 91.2% yield, > 97% de trans). Mother liquor/washes (1600 mL) contained about 3.5% product. The product could be dissolve in D_2O without epimerization for NMR analysis. Dissolving the product in CD_3OD led to complete epimerization to 1:1 mixture within minutes. MEA salt **18**: ^{1}H NMR (500 MHz, D_2O) 3.74 (m, 2H), 3.64 (m, 1H), 3.56 (s, 3H), 3.25 (m, 2H), 3.21 (dd, J = 8.5, 6.7 Hz, 1H), 2.21 (m, 1H), 2.03−1.89 (m, 2H), 1.45 (m, 1H), 1.22 (d, J = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, D_2O) 178.8, 173.0, 67.8, 58.2, 51.1, 48.4, 38.9, 27.8, 23.9, 21.2. HRMS (ESI) m/z calcd for $C_{10}H_{20}N_2O_4H$ $[M + H]^+$ 233.1501, found 233.1592. HPLC method: Zorbax Eclipse Plus C18, 50 × 4.6 mm, 1.8 μm; A = 0.1% H_3PO_4 in water, B = acetonitrile; 5% B to 95% B over 5 min then hold for 2 min; flow rate = 1.5 mL/min; temp. 25 °C; detection = 210 nm; retention times: 1.60 min = *cis*-acid-lactam **17**, 1.72 min = *trans*-acid-lactam **17**, 2.45 min = *cis*-ester-lactam **8b**, 2.49 min = *trans*-ester-lactam **8b**.

*Thermodynamic Stability of MEA Salt **18**.* The stability and solubility of **18** were examined in the following three solvent solutions: (1) 1 vol % water in MeCN; (2) 1.7 vol % water was prepared by adding 0.43 mL water to 25 mL MeCN; and (3) 1.5 mL of heptane was added to 10 mL of THF. 80 mg of acid lactam MEA salt **18** (~95% de, 98.6 wt %) each was slurried in 1.5 mL of solvents 1 and 2 above. 50 mg of the acid lactam was slurried in 1 mL of solution 3. The samples were stirred and sampled at certain period of time (2, 4, 6, and 72 h). The slurries were centrifuged first to compact the solids. The supernatant solutions were then filtered through 0.2 μm Nylon filter, and the solids were dried for 15 min under vacuum at room temperature. The solutions were analyzed for total diastereomer concentration, and the solids were analyzed for de (see Table 2).

*Preparation of ((3R,6R)-6-Methylpiperidin-3-yl)methanol Hydrochloride (**3**). Method **1**.* To a vessel was charged acid-lactam MEA salt **18** (94.5% de; 98.6 wt %) (1 g, 4.24 mmol) and heptane (5.00 mL). The suspension was cooled to −10 °C under N_2. 7 equiv of 1 M BH_3·THF (29.7 mL, 29.7 mmol) was slowly added over 20 min at < −5 °C. The resultant clear solution was stirred at −10 °C for 10 min, rt for 1 h, then at 60 °C under a condenser and N_2. After heating for 17−20 h, HPLC assay showed the complete consumption of SM and about 4% alcohol-lactam intermediate (i.e., 96% conversion). After aging at rt for additional 6 h, the reaction solution was cooled to 2 °C, then slowly added 6 N HCl (7.07 mL, 42.4 mmol) over 10 min at <15 °C. The slurry was stirred at rt overnight (or at least for 2 h). The mixture, pH ~ 0−1, was made alkaline (pH 13−14) with addition of 10 N NaOH (30%) (7.22 mL, 72.2 mmol) in one portion, which exothermed to 39 °C. The resulting slurry was filtered and washed with a mixture of EtOH (1.4 mL) and MTBE (3.3 mL). The layers were separated and aqueous back-extracted with 3:1 MTBE−THF (2 × 10 mL). HPLC assay of the combined organic showed 78% yield piperidinol with trans/cis = 98.2:1.8. The aqueous layer showed absence of piperidinol. Organic was dried over Na_2SO_4, filtered, and washed with 20 mL MTBE. It was concentrated to dryness, and the oil was flushed with 2 × 10 mL of 2-propanol. The resulting 0.78 g solid−oil was dissolved in 2 mL of THF, then seeded with piperidinol HCl salt **3** (2 mg). 4.5 N HCl in 2-propanol (0.849 mL, 3.82 mmol) was slowly added. Crystallization was initiated immediately, and it was stirred at rt overnight. The product was isolated by filtration, washing with THF (2 mL), and vacuum drying at rt under N_2 for >6 h to afford 492 mg of piperidinol **3**·HCl (70% yield) with trans:cis ratio >99.9:0.1. Losses to ML/washes were 2.5% (trans:cis = 68:32). All analytical results are consistent with the reported values.[3] HPLC method 1: Zorbax Eclipse Plus C18 50 × 4.6 nm 1.8 um; A = acetonitrile, B = 0.1% aq. H_3PO_4; 5% A to 95% A over 5 min hold for 2 min; flow rate = 1.5 mL/min; temp 25 °C; wavelength = 210 nm; retention times, 1.46 min = *cis*-hydroxy-lactam **9**, 1.59 min = *trans*-hydroxy-lactam **9**, 1.60 min = *cis*-acid-lactam **17**, 1.72 min = *trans*-acid-lactam **17**. HPLC method 2: Atlantis dC18, 250 × 4.6 mm, 5 μm; A: 0.1% TFA in water, B: 0.1% TFA in acetonitrile; 0 min, 2% B; 5 min, 2%B; 12 min, 50% B; 20 min, 70% B; flow rate = 1 mL/min; 15 °C; Corona detecor; retention times, 8.57 min = *trans*-**3**, 8.89 min = *cis*-**3**.

*Preparation of ((3R,6R)-6-Methylpiperidin-3-yl)methanol Hydrochloride (**3**). Method **2**.* To a 12 L three-neck round bottomed flask equipped with a mechanical stirrer, condenser, thermostat, and N_2 inlet was charged solid acid-lactam MEA salt **18** (150 g, 630 mmol) and solid $NaBH_4$ (131 g, 3469 mmol). The mixture was cooled in a −14 °C bath and added heptane (750 mL) to give a thick slurry. Anhydrous THF (3000 mL, KF = 61) was slowly added over 1 h keeping at < −10 °C. To the −14 °C suspension was slowly added BF_3·OEt_2 (554 mL, 4407 mmol) over 1.5 h at < −9 °C. The resultant suspension was stirred at −14 to −10 °C for 40 min, then warm to 22 °C over 1.5 h, and then heated at 55−60 °C under a condenser and N_2 for 20 h. At of 20 h, HPLC assay showed 97% conversion based on 3% remaining starting material (LC sample preparation involved diluting a 10 μL reaction mixture to 1 mL with 1:1 0.1% aq. TFA: 50% AcN/H_2O). The reaction mixture was cooled to 0−5 °C and slowly added H_2O (524 mL) over 25 min at <20 °C. After aging at 0−5 °C for 1 h, 12 N HCl (525 mL, 6296 mmol) was slowly added at <20 °C. The resulting slurry (pH ~ 0) was stirred at rt overnight. The mixture was cooled in 17 °C bath, and 10 N NaOH (1007 mL, 10070 mmol) was slowly added over 20 min as it exothermed to 30 °C (pH ~ 8.5). Solid NaOH (302 g, 7.556 mol) was added, and the mixture exothermed from 28 to 46 °C. After stirring for 1 h as it cooled to 21 °C (pH 13−14), the mixture was filtered, and the wet cake was washed with a mixture of EtOH (210 mL) and MTBE (495 mL). The filtered borate salt (~630 g white solid) was discarded. The filtrate was transferred to a separatory funnel, rinsed with MTBE (2 × 150 mL), and the layers separated. The aqueous layer (pH ~ 14) was back-extracted with 3:1 MTBE:THF (2 × 1.5 L). The combined organic was dried over Na_2SO_4, filtered, and washed with MTBE (1 L). The combined filtrate (KF = 2.1%) was concentrated at <25 °C to ~200 g of brown oil. The residue was diluted with 750 mL of 2-propanol. The resulting slurry was concentrated to ~200 g of oil-solid, then diluted with 750 mL of 2-propanol (supernatant KF = 0.68%), concentrated to ~165 g oil-solid, and added 300 mL of dry THF to give total volume ~500 mL with KF ~ 0.16%. The precipitated NaCl was filtered off and washed with 100 mL THF. The combined filtrate was concentrated to ~135 g brown oil and diluted with 300 mL THF to give total volume ~470 mL with KF ~ 0.13%. Then it was seeded with ~50 mg of product **3**, and 4.8 N HCl/IPA (111 mL, 535 mmol) was slowly added over 40 min as it exothermed from 20 to 37 °C. Crystallization was initiated immediately. After stirring at rt overnight, supernatant showed product concentration (as free base) at 18.2 mg/mL as a 25:75 trans:cis mixture. The slurry was filtered and washed with 5:1

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THF:IPA (60 mL) and THF (2 × 60 mL). The wet cake was vacuum-dried at rt under N_2 overnight to afford 69.22 g of piperidinol **3** hydrochloride salt as a white solid (99 LCAP, 100.5 LCWP, 66% yield). Analyses showed 21 wt % Cl (vs theory 21.4%), B ∼ 1400 ppm, any other metal <10 ppm, IPA ∼ 0.18 wt %, THF ∼ 0.55%, KF ∼ 0.15 wt %. Trans:cis ratio was 96.05:3.95 based on benzoylation derivatization (n = 4, org layer) HPLC assay. Product loss to ML/washes was ∼2% as a 25:75 trans:cis mixture.

The trans:cis ratio of this 96:4 trans:cis **3**·HCl salt could be upgraded to 99:1 by the following procedure. A slurry of **3**·HCl salt (1 g, 5.98 mmol) in anhydrous 2-propanol (2 mL) was heated at 85 °C for 1 h. After stirring at rt overnight, the slurry was filtered and washed with THF (2 mL). The wet cake was vacuum-dried under N_2 at rt to afford 0.903 g (91%) **3**·HCl salt.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.5b00259.

^{1}H and ^{13}C NMR spectra for compound **18**. Compound **3** trans−cis ratio determination via benzoyl derivatization and chiral LC method. Single crystal X-ray of compound **20**. X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA) of compound **18** (PDF)

Crystal data (CIF)

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Notes

The authors declare no competing financial interest.

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