JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

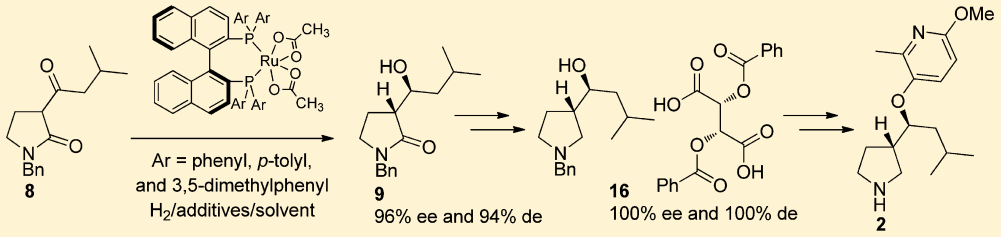
Additives Promote Noyori-type Reductions of a β-Keto-γ-lactam: Asymmetric Syntheses of Serotonin Norepinephrine Reuptake Inhibitors§

Nicholas A. Magnus,*,† Bret A. Astleford,† Dana L. T. Laird,‡ Todd D. Maloney,† Adam D. McFarland,† John R. Rizzo,† J. Craig Ruble,‡ Gregory A. Stephenson,† and James P. Wepsiec†

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

‡Eli Lilly and Company, Discovery Chemistry Research and Technology Division, Indianapolis, Indiana 46285, United States

Supporting Information



ABSTRACT: Serotonin norepinephrine reuptake inhibitor (SNRI) pyrrolidinyl ether **2** was synthesized by employing a dynamic kinetic resolution (DKR) with enantio- and diastereoselective hydrogenation on β-keto-γ-lactam **8** to afford β-hydroxy-γ-lactam **9** with 96% ee and 94% de. Reduction of **9** and purification via the dibenzoyl-(L)-tartaric acid diastereomeric salt **16** enriched the ee and de to 100%. While screening hydrogenation reaction systems with ruthenium-BINAP catalysts to prepare **9**, it was found that adding catalytic HCl and LiCl enabled higher yields. In addition, the rate and equilibrium of the DKR-hydrogenation of **8** to give **9** was studied by online NMR and chiral HPLC, which indicated that one of the enantiomers of **8** was reducing faster to **9** than the equilibration of the stereocenter of **8**.

Serotonin and norepinephrine have been implicated as modulators of endogenous analgesic mechanisms in descending pain pathways and serotonin norepinephrine reuptake inhibitors (SNRIs) have shown efficacy in the treatment of chronic painful conditions such as diabetic peripheral neuropathic pain and fibromyalgia.[1] Therefore, the pyrrolidine ether SNRIs **1**[2] and **2**,[3] illustrated in Figure 1, have been studied at Lilly for the potential treatment of pain.

The original routes used at Lilly to prepare compounds **1** and **2** started with (*S*)-*N*-*tert*-butoxycarbonylpyrrolidine-3-carboxylic acid **3**, which had been prepared in 5 steps featuring a 1,3-dipolar cyclo-addition, manipulation of protection groups, and an enzyme resolution.[4] The acid **3** was converted via a 3-step sequence to the diastereomers of secondary alcohol **4** which were separated by chromatography. Finally, the required ether linkages in **1** and **2** were made via SNAr chemistry and the resulting molecules deprotected (Scheme 1).[3] Although this route facilitated SAR studies and led to rapid synthesis of lead derivatives, it had several drawbacks for multigram-scale preparations of **1** and **2**. Further, since only one of the 4 possible stereoisomers of **1** and **2** was desirable for potential clinical evaluations, the development of stereoselective syntheses was attractive.

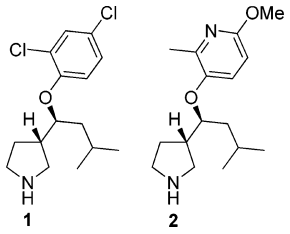
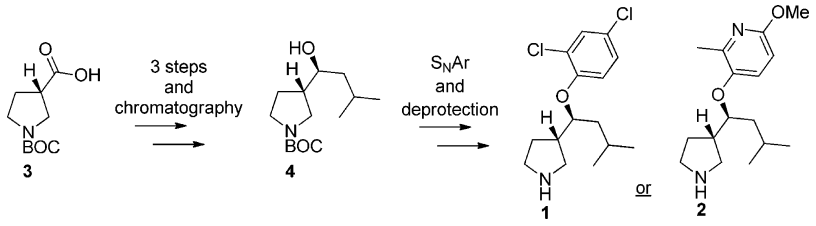


Figure 1. Structures of serotonin norepinephrine reuptake inhibitors **1** and **2**.

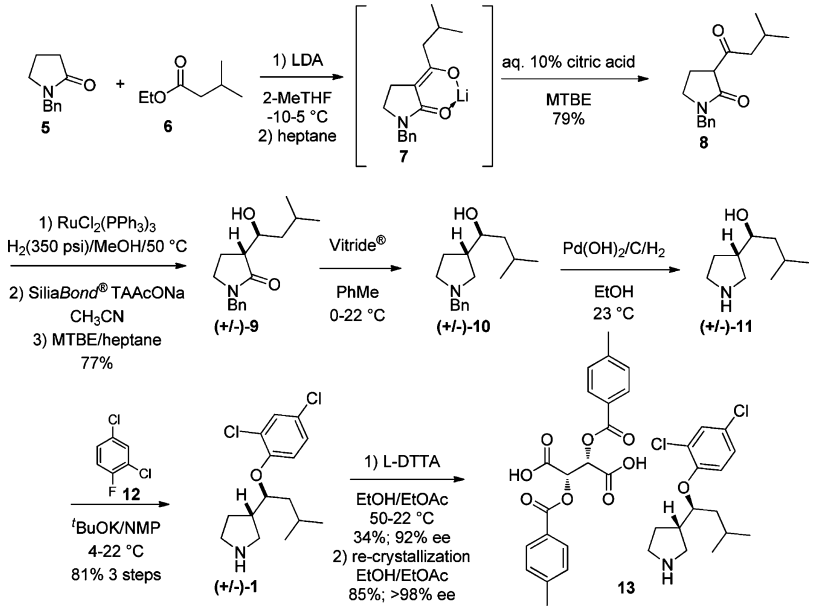
Our stereoselective routes to prepare **1** and **2**, illustrated in Schemes 2 and 4, are based on the precedent chemistry of Takasago International Corporation where the two stereocenters are derived from a dynamic kinetic resolution (DKR) accompanied by enantio- and diastereoselective hydrogenation of a β-keto-γ-lactam.[5] Preparations of β-keto-γ-lactams via Claisen condensation are typically run under cryogenic conditions (−78 °C) by adding the γ-lactam to the base to mitigate self-condensation.[6] To avoid cryogenic conditions and take advantage of the insolubility of intermediate enolate **7**, we chose to combine *N*-benzyl-γ-lactam **5** with ethyl isovalerate **6** in 2-MeTHF and add the mixture to LDA at −10 to 5 °C (Scheme 2). This caused enolate **7** to precipitate, and heptane was added to further induce the precipitation. The precipitate

Received: March 27, 2013
Published: May 7, 2013

Scheme 1. Original Route to 1 and 2



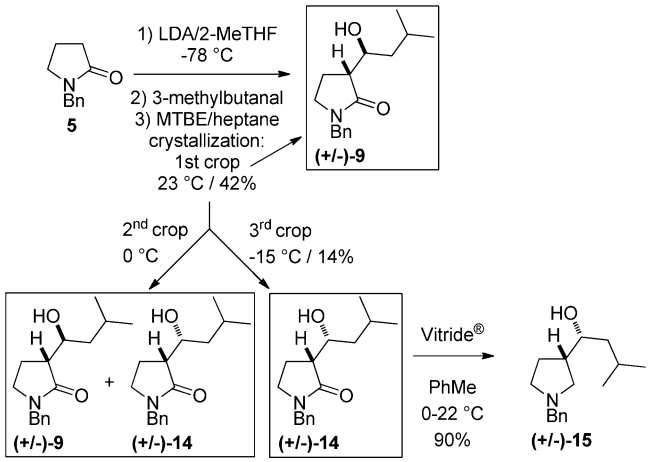
Scheme 2. Diastereoselective Synthesis of 1



was filtered off to afford a purification, but enolate **7** was not stable enough for long-term storage, so it was subjected to an acidic workup to give a 79% yield of β-keto-γ-lactam **8** as an oil. Diastereoselective hydrogenation of β-keto-γ-lactam **8** in the presence of $(PPh_3)_3RuCl_2$[7] required an absorbent (Siliabond triaminetetraacetate sodium salt (TAAcONa))[8] treatment to remove green color caused by residual rhodium affording a 77% yield of (±)-**9** as a solid. Vitride (sodium bis(2-methoxyethoxy) aluminum hydride) reduction of (±)-**9** in toluene afforded (±)-**10** as a crude oil, which was taken directly into a hydrogenation with $Pd(OH)_2$ on carbon in EtOH to remove the benzyl protection group giving (±)-**11** also as a crude oil.[5] The alcohol (±)-**11** was dissolved in NMP and reacted with 1,3-dichloro-4-fluorobenzene **12** and ^{t}BuOK to induce an SNAr reaction and provide (±)-**1** as an oil, that was purified by selective extraction into aqueous D,L-tartaric acid, in 81% overall yield from (±)-**9**.[2] The (±)-**1** was resolved by forming the diastereomer salt **13** with di-*p*-toluoyl-L-tartaric acid in a mixture of EtOAc/EtOH in an initial yield of 34% with 92% ee, and a recrystallization from the same solvent system gave an 85% recovery with >98% ee. The absolute *S,S*-stereochemical configuration of **1** was confirmed by single crystal X-ray analysis of **13** (see Supporting Information, SI).

In order to evaluate the enantio- and diastereoselectivity of the DKR-hydrogenation of β-keto-γ-lactam **8** and the stereochemical "upgrade" of pyrrolidine **10** via crystallization of a diastereomeric salt, we first needed to prepare these reference standards: the diastereomers of β-hydroxy-γ-lactams (±)-**9** which are (±)-**14**, and the diastereomers of pyrrolidines (±)-**10** which are (±)-**15** (Scheme 3). The aldol chemistry depicted in Scheme 3 between *N*-benzyl-γ-lactam **5** and 3-methylbutanal

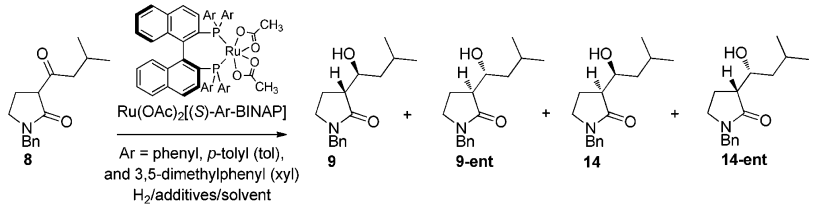
Scheme 3. Synthesis of Diastereomer Reference Standards



gave a stereochemical mixture of β-hydroxy-γ-lactams (±)-**9** and (±)-**14**. Fractional crystallization from MTBE/heptanes at 23 °C afforded isolation of (±)-**9**, cooling of the resulting liquors to 0 °C gave a crop of crystals containing a mixture of (±)-**9** and (±)-**14**, and finally cooling the liquors to −15 °C gave crystals of (±)-**14**. Vitride reduction of (±)-**14** afforded (±)-**15**.

dx.doi.org/10.1021/jo400589j | J. Org. Chem. 2013, 78, 5768−5774

Table 1. DKR-hydrogenation Screen of Silica Gel Purified 8 to Selectively Produce 9



entry[a]	catalyst[b]	S/C[c]	LiCl[d]	HCl[d]	solvent	8[e]	%ee[e]	%de[e]
1	$Ru(OAc)_2$[(*S*)-BINAP]	260	0	0	MeOH	67.3	9.8	50.5
2	$Ru(OAc)_2$[(*S*)-BINAP]	260	0	6	MeOH	0	89.4	81.4
3	$Ru(OAc)_2$[(*S*)-tol-BINAP]	280	0	0	MeOH	80.0	14.2	29.9
4	$Ru(OAc)_2$[(*S*)-tol-BINAP]	280	0	6	MeOH	0	93.4	88.1
5	$Ru(OAc)_2$[(*S*)-xyl-BINAP]	295	0	0	MeOH	73.8	4.5	69.5
6	$Ru(OAc)_2$[(*S*)-xyl-BINAP]	295	0	6	MeOH	0	87.0	90.7
7	$Ru(OAc)_2$[(*S*)-tol-BINAP]	280	0	0	EtOH	81.2	19.8	8.8
8	$Ru(OAc)_2$[(*S*)-tol-BINAP]	280	0	6	EtOH	0	94.8	93.1
9	$Ru(OAc)_2$[(*S*)-tol-BINAP]	280	0	0	IPA	86.5	31.1	17.0
10	$Ru(OAc)_2$[(*S*)-tol-BINAP]	280	0	6	IPA	42.2	98.2	93.6
11	$Ru(OAc)_2$[(*S*)-tol-BINAP]	280	0.01	6	IPA	35.1	96.7	94.7
12	$Ru(OAc)_2$[(*S*)-tol-BINAP]	280	0.1	6	IPA	33.3	96.3	93.9
13	$Ru(OAc)_2$[(*S*)-tol-BINAP]	280	1	6	IPA	0	96.3	95.3
14	$Ru(OAc)_2$[(*S*)-tol-BINAP]	280	10	6	IPA	24.3	96.3	93.6
15	$Ru(OAc)_2$[(*S*)-tol-BINAP]	280	1	0	IPA	88.0	23.8	74.4
16	$Ru(OAc)_2$[(*S*)-tol-BINAP]	280	1	2	IPA	73.1	98.4	98.4
17	$Ru(OAc)_2$[(*S*)-tol-BINAP]	280	1	10	IPA	2.5	96.1	96.3
18	$Ru(OAc)_2$[(*S*)-tol-BINAP]	470[f]	1	6	IPA	95.1	NA[g]	NA[g]
19	$Ru(OAc)_2$[(*S*)-tol-BINAP]	1400[f]	1	6	IPA	98.0	NA[g]	NA[g]

[a]Screening reactions run with **8** (400 mg), catalyst load (5 mg), and solvent (5 mL) at 65 °C under 70−85 psi of H_2 for 16.0 h. [b]Diacetato[(*S*)-(−)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]ruthenium(II) ($Ru(OAc)_2$[(*S*)-BINAP)]), diacetato[(*S*)-(−)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl]ruthenium(II) ($Ru(OAc)_2$[(*S*)-tol-BINAP)]), diacetato[(*S*)-(−)-2,2′-bis[di(3,5-xylyl)phosphino]-1,1′-binaphthyl]ruthenium(II) ($Ru(OAc)_2$[(*S*)-xyl-BINAP)]). [c]Substrate to catalyst mole ratio. [d]Mole percent relative to **8**. [e]Unreacted **8**, enantio- and diastereoselectivities determined by chiral HPLC (see SI). [f]Entry 18 catalyst load (3 mg) and entry 19 catalyst load (1 mg). [g]Not applicable (too small to accurately measure).

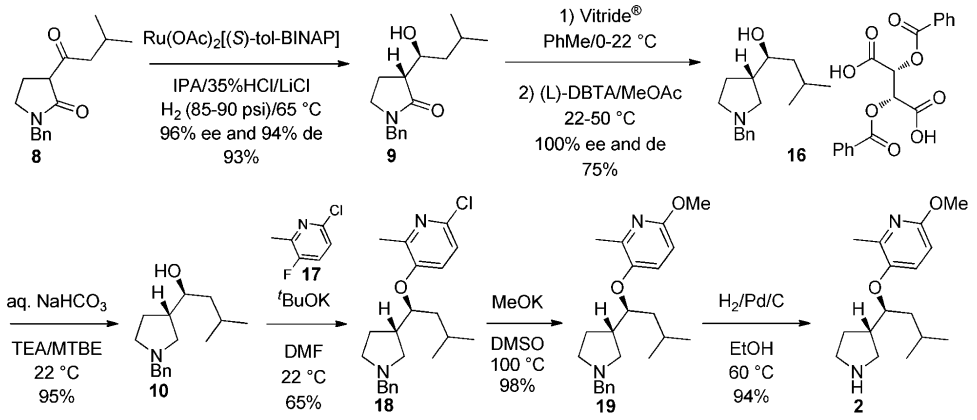
Our initial hydrogenation reactions to convert β-keto-γ-lactam **8** into β-hydroxy-γ-lactam **9** indicated that the catalyst diacetato[(*S*)-(−)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl]ruthenium(II) ($Ru(OAc)_2$[(*S*)-tol-BINAP)])[9] at a substrate to catalyst ratio (S/C) of 280 reliably gave high stereochemical selectivity (>95% ee and >94% de) and complete conversion of **8** to **9** at 65 °C under 70−85 psi of H_2 in IPA in the presence of about 6 mol % HCl.[10] In order to study the DKR-hydrogenation reaction in more detail via online NMR and chiral HPLC, we further purified the β-keto-γ-lactam **8** by silica gel column chromatography.[11] Unfortunately, after the silica gel purification β-keto-γ-lactam **8** would no longer completely convert to β-hydroxy-γ-lactam **9** (Table 1, entry 10). Perplexed by this development, we wondered if residual lithium from the preparation of **8** was playing a role in the catalysis since lithium has been shown to enhance the reactivity of ruthenium-BINAP catalytic systems.[12] Prior to chromatography **8** was found to be contaminated with very low levels of lithium ((0.11 μg/g) (lithium was below our ICP detection limit of 0.02 μg/g after chromatography)), so it seemed doubtful that lithium was the sole culprit in crude **8** for enhanced catalysis. However, in an attempt to more completely convert silica gel purified **8** into **9** LiCl[12a] was added to the DKR-hydrogenation reactions and improved conversions were observed (Table 1, entries 11−14).

Table 1 is a list of DKR-hydrogenation experiments that start with silica gel purified β-keto-γ-lactam **8** run at 65 °C under 70−85 psi of H_2. These experiments investigate the effects of (1) varying the methyl substitution on the aryl groups on the phosphorus atom of the BINAP catalysts, (2) MeOH, EtOH, and IPA solvent systems, and (3) the additives LiCl and HCl.

Hydrogenations to convert **8** to **9** with $Ru(OAc)_2$[(*S*)-BINAP)], $Ru(OAc)_2$[(*S*)-tol-BINAP)], and $Ru(OAc)_2$[(*S*)-xyl-BINAP)] in MeOH were examined with and without catalytic HCl (Table 1, entries 1−6). These experiments indicated that the $Ru(OAc)_2$[(*S*)-tol-BINAP)] catalyst gives the highest ee (80.7%) and de (90.7%) and that adding 6 mol % HCl promotes complete conversions of **8** to **9**. The $Ru(OAc)_2$[(*S*)-tol-BINAP)] catalyst was also screened in EtOH and IPA with and without catalytic HCl (entries 7−10), which indicated that IPA gives higher ee and de (96.4 and 94.9) than EtOH (94.8 and 93.1) and again that HCl is required for high conversions. However, while the conversion of **8** to **9** was 100% in EtOH with 6 mol % HCl (entry 8), it was only 57.8% in IPA with 6 mol % HCl (entry 10). Next, the $Ru(OAc)_2$[(*S*)-tol-BINAP)] catalyst was screened in IPA with 6 mol % HCl adding LiCl at 0.01, 0.1, 1, and 10 mol % levels (entries 11−14). Adding 0.01 and 0.1 mol % of LiCl gave small increases in conversion. While adding 1.0 mol % of LiCl gave complete conversion, and 10 mol % LiCl resulted in incomplete conversion of **8** to **9** (75.7%). Again with the $Ru(OAc)_2$[(*S*)-tol-BINAP)] catalyst in IPA, the LiCl amount was set at 1.0 mol %, and now the added HCl was varied at 0, 2, and 10 mol % (entries 15−17). At 0−2 mol % HCl the conversion of **8** to **9** was only 12−26.9%, and

dx.doi.org/10.1021/jo400589j | J. Org. Chem. 2013, 78, 5768−5774

Scheme 4. DKR-hydrogenation-based Synthesis of 2



with 10 mol % HCl the conversion was 97.5%. In the IPA system with 1 mol % LiCl and 6 mol % HCl, the $Ru(OAc)_2[(S)$-tol-BINAP)] substrate to catalyst ratio (S/C) was varied from the apparently optimal 280 (entry 13; 100% conversion; 96.3% ee and 95.3% de) to 470 and 1400 (entries 18−19) giving only 4.9 to 2% conversion of **8** to **9**, respectively.

When DKR-hydrogenation reactions to convert **8** to **9** were incomplete, the ratio of the enantiomers of **8** was 1:1, racemic by chiral HPLC, and we wondered if this was the case during the course of the reaction (i.e., were the enantiomers of **8** nonracemic during the DKR-hydrogenation). With access to a hydrogenation reactor with a flow loop to a NMR probe and a HPLC system, we became interested in observing the rate and equilibrium of the DKR-hydrogenation online by NMR and chiral HPLC. Due to the high viscosity of IPA relative to MeOH, and the need to pump the reaction effectively through these systems, the aforementioned studies were conducted with MeOH as the reaction solvent. The ^{1}HNMR experiment starting with **8**, catalytic $Ru(OAc)_2[(S)$-BINAP)] (S/C of 170), and HCl (3 mol %) at 65 °C under 70 psi of H_2 in MeOH gave complete conversion to **9** and **14** in about 30 min (see SI). It took about 30 min to cycle a sample from the reactor to the chiral HPLC for complete analysis. Therefore, a replicate reaction was run at 40 °C to slow the reaction down for HPLC analyses. It was observed that the racemic starting material (**8**) had enriched to a ratio of about 2:1 (36% ee) after 6 cycles (3.0 h), indicating that one of the enantiomers of **8** was reducing faster to **9** and **14** than the equilibration of the stereocenter of **8** (see SI).

To synthesize pyrrolidinyl ether **2**, β-keto-γ-lactam **8** was converted to β-hydroxy-γ-lactam **9** via hydrogenation in the presence of catalytic $Ru(OAc)_2[(S)$-tol-BINAP] in IPA containing catalytic HCl (6 mol %) and LiCl (1 mol %) with complete conversion (96% ee and 94% de; 93% yield) (Scheme 4).[13] Reduction of **9** with Vitride in toluene gave pyrrolidine **10** as an oil which was purified via a crystalline diastereomeric salt **16** formed with dibenzoyl-(L)-tartaric acid (L-DBTA) in MeOAc in 75% overall yield (100% ee and de). The salt **16** was freebased into MTBE with aqueous $NaHCO_3$ in the presence of TEA (necessary to improve solubility) to afford purified **10** in 95% yield. Pyrrolidine **10** was reacted with ^{t}BuOK and 6-chloro-3-fluoro-2-methylpyridine[14] **17** in DMF to give the SNAr adduct **18** in 65% yield. Chloride **18** was treated with KOMe in DMSO to install the methoxy moiety of **19** in 98% yield. Hydrogenation of **19** over Pd/C in EtOH gave a 94% yield of **2** (**2** was prepared in 8 steps and 31% overall yield starting from γ-lactam **5** (Scheme 2)).

CONCLUSION

Asymmetric syntheses of SNRIs **1** and **2** have been demonstrated utilizing diastereoselective hydrogenation, and enantio- and diastereoselective DKR-hydrogenation of β-keto-γ-lactam **8**. DKR-hydrogenation screening experiments starting with **8** to produce β-hydroxy-γ-lactam **9** revealed that $Ru(OAc)_2[(S)$-tol-BINAP] gave greater stereoselectivity than $Ru(OAc)_2[(S)$-BINAP)] and $Ru(OAc)_2[(S)$-xyl-BINAP)], and that selectivity was better in IPA than EtOH or MeOH. In addition, adding catalytic amounts of HCl and LiCl to the DKR-hydrogenation reactions in IPA gave more complete conversions of **8** to **9**. Diastereoselective salt resolutions via tartrates afforded separation of the diastereomers of pyrrolidinyl ether **1** and upgraded the ee and de of intermediate pyrrolidine **10** toward the synthesis of **2**. Finally, the required aromatic rings of **1** and **2** were installed utilizing SNAr reactions.

EXPERIMENTAL SECTION

HRMS measurements were made with an ion trap mass analyzer. All reactions were run under a nitrogen atmosphere unless otherwise stated.

1-Benzyl-3-(3-methylbutanoyl)pyrrolidin-2-one (8). Diisopropylamine (32.00 g; 316.2 mmol) was combined with 2-MeTHF (135 mL), cooled to −7 °C, and 2.5 M *n*-BuLi in hexanes (125.0 mL; 312.5 mmol) was added over 0.5 h. 1-Benzylpyrrolidin-2-one **5** (25.20 g; 143.8 mmol), ethyl 3-methylbutanoate **6** (22.50 g; 172.8 mmol), and 2-MeTHF (110 mL) were combined and added to the LDA/2-MeTHF mixture over 0.5 h, while maintaining the reaction temperature between −10 to 5 °C, to afford a yellow slurry. After 0.75 h, heptane (250 mL) was added to the mixture over 0.5 h at −5 to 5 °C. The slurry was filtered and the off-white solids (**7**) were rinsed with 1:1 2-Me-THF/heptane (50 mL). The solids were suspended in MTBE (250 mL), aqueous 10% citric acid (250 mL) added, and the mixture stirred for 0.5 h to give two homogeneous phases (aq. phase pH 4−5). MTBE (100 mL) was added and the organic phase was separated, washed with water (2 × 100 mL), dried ($MgSO_4$), and concentrated to afford **8** as a yellow oil (29.8 g, 79%). Note: due to the air instability of **7** only the ^{1}H NMR spectrum was collected: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33−7.28 (m, 1H), 7.25−7.17 (m, 2H), 4.25 (s, 2H), 3.03 (dd, *J* = 8.7, 7.1 Hz, 2H), 2.56 (dd, *J* = 8.7, 7.1 Hz, 2H), 2.08−1.95 (m, 1H), 1.81 (d, *J* = 7.0 Hz, 2H), 0.87 (d, *J* = 6.7 Hz, 6H). Spectra for **8**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 (m, 2H), 7.30−7.24 (m, 1H), 7.22−7.16 (m, 2H), 4.41 (d, *J* = 14.9 Hz, 1H), 4.34 (d, *J* = 14.9 Hz, 1H), 3.75 (dd, *J* = 9.3, 6.6 Hz, 1H), 3.21 (m, 2H), 2.72 (dd, *J* = 17.4, 7.4 Hz, 1H), 2.52 (dd, *J* = 17.4, 7.4 Hz, 1H), 2.26 (m,1H), 2.12−1.94 (m, 2H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H).

dx.doi.org/10.1021/jo400589j | J. Org. Chem. 2013, 78, 5768−5774

^{13}C NMR (100 MHz, DMSO-d_6) δ 206.3, 170.2, 137.0, 129.0, 128.0, 128.0, 55.0, 51.3, 46.2, 45.2, 23.8, 22.9, 22.6, 20.1. A small amount of the enol tautomer appears in the NMR spectra of **8** and the following assignments were made: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.88 (s, 1H), 4.40 (s, 2H), 3.28 (dd, J = 7.5, 7.3 Hz, 2H), 2.59 (dd, J = 7.5,7.3 Hz, 2H), 0.91 (d, J = 6.4 Hz, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.5, 23.0, 25.6, 40.6, 44.3, 45.5, 100.4, 163.2, 172.5. IR (film) 2957, 2871, 1714, 1682 cm^{-1}. HRMS (ESI+) calcd for $C_{16}H_{22}NO_2$ 260.1645, found 260.1647.

(*R*)-1-Benzyl-3-((*S*)-1-hydroxy-3-methylbutyl)pyrrolidin-2-one ((±)-9). Ketone **8** (24.65 g; 95.05 mmol), $(PPh_3)_3RuCl_2$ (0.91 g; 0.94 mmol), and MeOH (250 mL) were combined under 350 psi of H_2 and heated to 50 °C for 24.0 h. The reaction was concentrated to give green solids which were combined with CH_3CN (250 mL) and stirred at 22 °C to produce a thin green slurry. Siliabond triaminetetraacetate sodium salt (TAAcONa) (23.3 g) was added and the resulting mixture stirred at 22 °C for 16.0 h. The resulting slurry was filtered through a plug of TAAcONa (26.0 g) capped with a layer of Celite and the plug was rinsed with CH_3CN (750 mL). The resulting filtrate was concentrated to give a light yellow solid which was triturated in MTBE (150 mL) at 22 °C for 2.25 h. Heptane (150 mL) was added to the slurry over 0.5 h and the resulting mixture cooled to 0 °C and stirred for 1.0 h. The slurry was filtered, the solids rinsed with cold (0 °C) 1:1 MTBE/heptane (25 mL), and dried to afford (±)-**9** as an off-white solid (19.2 g; 77%). Mp 113.2−114.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32 (m, 2H), 7.28−7.19 (m, 3H), 4.60 (d, J = 6.1 Hz, 1H), 4.43 (d, J = 15.0 Hz, 1H), 4.33 (d, J = 15.0 Hz, 1H), 4.06−3.95 (m, 1H), 3.20−3.07 (m, 2H), 2.36 (ddd, J = 10.1, 7.8, 2.6 Hz, 1H), 2.08−1.93 (m, 1H), 1.88 (m, 1H), 1.71 (m, 1H), 1.34 (ddd, J = 13.6, 9.4, 5.3 Hz, 1H), 1.16 (ddd, J = 13.4, 8.6, 4.5 Hz, 1H), 0.89 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.7, 137.0, 128.4, 127.4, 127.0, 66.4, 47.3, 45.5, 44.8, 44.5, 24.0, 23.4, 22.0, 17.3. IR (solid) 3357, 2959, 2949, 2928, 2867, 1666 cm^{-1}. HRMS (ESI+) calcd for $C_{16}H_{24}NO_2$ 262.1802, found 262.1803.

(*S*)-1-((*S*)-1-Benzylpyrrolidin-3-yl)-3-methylbutan-1-ol (±)-10. Lactam (±)-**9** (15.20 g; 58.16 mmol) was dissolved in toluene (150 mL), cooled to 0 °C, and ≥65 wt % Vitride in toluene (37.22 g; 128.9 mmol) was combined with toluene (100 mL) and added over 0.5 h, giving a maximum temperature of 10 °C, and the resulting mixture warmed to 22 °C. After 22.0 h, the reaction mixture was added to a cold (0 °C) aqueous 10% Rochelle's salt solution (150 mL) and toluene (25 mL) added. The mixture was warmed to 22 °C and stirred for 3.0 h (slight emulsion). Water (150 mL) was added to the mixture and stirring continued for 0.75 h giving 2 phases. Aqueous 10% Rochelle's salt (50 mL) and toluene (50 mL) were added, the aqueous phase was removed, and the organic phase washed with water (2 × 150 mL). The organic phase was dried ($MgSO_4$) and concentrated to afford crude (±)-**10** as an orange oil (100% yield assumed and material taken directly into the next step). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33−7.19 (m, 5H), 4.38 (br, 1H), 3.54 (d, J = 13.0 Hz, 1H), 3.49 (d, J = 13.0 Hz, 1H), 3.29 (ddd, J = 9.5, 6.4, 2.7 Hz, 1H), 2.55 (m, 2H), 2.30 (m, 1H), 2.12−1.93 (m, 2H), 1.84−1.59 (m, 2H), 1.21 (ddd, J = 13.8, 9.8, 4.2 Hz, 1H), 0.98 (ddd, J = 13.8, 9.6, 2.8 Hz, 1H), 0.85 (d, J = 6.7 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 139.4, 128.3, 128.0, 126.6, 70.4, 59.8, 56.8, 53.5, 45.0, 44.2, 26.2, 23.9, 21.6. IR (film) 3386, 2953, 2921, 2868, 2799 cm^{-1}. HRMS (ESI+) calcd for $C_{16}H_{26}NO$ 248.2009, found 248.2009.

(*S*)-3-Methyl-1-((*S*)-pyrrolidin-3-yl)butan-1-ol (±)-11. Crude (±)-**10** (from previous experiment) (assumed 14.2 g; 57.4 mmol) was dissolved in EtOH (150 mL) and 20% $Pd(OH)_2$ on carbon 50% water wet (2.15 g; 15.3 mmol) added. The mixture was subjected to 50 psi of H_2 at 22 °C for 7 days to reach full conversion (H_2 leakage prolonged the reaction time). The reaction mixture was filtered through glass fiber filter paper, rinsed through with EtOH (50 mL), and concentrated to afford (±)-**11** as a colorless oil. The oil was dissolved in toluene (50 mL) and concentrated to remove residual EtOH in preparation for the next step (100% yield assumed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.30 (ddd, J = 9.6, 6.5, 3.0 Hz, 1H), 2.80−2.60 (m, 3H), 2.39 (dd, J = 10.5, 7.3 Hz, 1H), 1.86 (m, 1H), 1.77 (m, 1H), 1.70−1.58 (m, 1H), 1.51 (m, 1H), 1.25 (ddd, J = 13.9, 9.7, 4.3 Hz, 1H), 1.02 (ddd, J = 13.6, 9.4, 2.9 Hz, 1H), 0.86 (d, J = 6.7 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 70.6, 50.2, 47.1, 46.6, 46.1, 28.5, 24.3, 24.3, 22.1. IR (film) 3293, 3237, 3145, 2952, 2914, 2863 cm^{-1}. HRMS (ESI+) calcd for $C_9H_{20}NO$ 158.1539, found 158.1539.

(*S*)-3-((*S*)-1-(2,4-Dichlorophenoxy)-3-methylbutyl)-pyrrolidine (±)-1. Crude (±)-**11** (from previous experiment) (assumed 9.03 g; 57.4 mmol) was dissolved in NMP (45 mL) and cooled to 0 °C. 1,3-Dichloro-4-fluorobenzene **12** (9.50 g; 57.6 mol) and solid ^{t}BuOK (13.00 g; 115.9 mmol) were added to the reaction mixture causing the temperature to rise briefly to 19 °C and return to 0 °C. After stirring for 2.0 h at 0 °C, the mixture was warmed to 22 °C and held for 16.0 h. The mixture was combined with heptane (200 mL) and water (80 mL), and the organic phase separated and washed with water (2 × 80 mL). The organic phase was combined with aqueous 10% D,L-tartaric acid (150 mL) and the aqueous phase separated. The aqueous phase was combined with MTBE (200 mL) and 5 M NaOH (50 mL) and the organic phase separated, washed with water (2 × 50 mL), dried ($MgSO_4$), and concentrated to afford (±)-**1** (14.20 g, 81% yield over 3 steps) as a light yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51 (d, J = 2.5 Hz, 1H), 7.32 (dd, J = 8.9, 2.6 Hz, 1H), 7.23 (d, J = 9.0 Hz, 1H), 4.52 (ddd, J = 7.3, 5.8, 4.2 Hz, 1H), 2.84 (dd, J = 10.7, 7.9 Hz, 1H), 2.81−2.64 (m, 2H), 2.48 (dd, J = 10.7, 7.5, 1H), 2.29 (m, 1H), 1.79−1.46 (m, 4H), 1.45−1.33 (m, 1H), 0.87 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.2, 129.3, 128.0, 124.0, 123.2, 116.1, 79.5, 48.9, 46.5, 43.6, 41.8, 27.8, 24.2, 23.2, 22.3. IR (film) 2956, 2870, 1585, 1568 cm^{-1}. HRMS (ESI+) calcd for $C_{15}H_{22}NOCl_2$ 302.1073, found 302.1076.

(*S*)-3-((*S*)-1-(2,4-Dichlorophenoxy)-3-methylbutyl)-pyrrolidine Di-*p*-toluoyl-L-tartrate (13). Pyrrolidine (±)-**1** (14.20 g; 46.98 mmol) was dissolved in EtOAc (42 mL) and EtOH (42 mL) and di-*p*-toluoyl-L-tartaric acid (18.3 g; 47.4 mmol) was added to the mixture. The mixture was warmed to 50 °C and EtOAc (240 mL) containing seeds (5 mg of **13**) was slowly added to the mixture. This produced a hazy yellow mixture that was cooled to 30 °C and stirred for 16.0 h to give a thick slurry. The slurry was cooled to 22 °C, stirred for 4.0 h, and the solids filtered and washed with 20:3 EtOAc/EtOH (25 mL). After drying the white solids (11.23 g), chiral HPLC analysis indicated 92.8% ee. The solids were suspended in 20:3 EtOAc/EtOH (110 mL) and the thick slurry warmed to 50 °C to give a thin slurry. After 1.0 h, the slurry was cooled to 22 °C and stirred for 16.0 h. The solids were filtered, rinsed with 20:3 EtOAc/EtOH (22 mL), and dried to afford **13** (9.46 g; 29%) with 98.2% ee by chiral HPLC. $[\alpha]_D^{25}$ −80.0 (MeOH, c = 2.5). Mp 175.6−176.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.49 (bs, 3H), 7.83 (d, J = 8.2 Hz, 4H), 7.55 (d, J = 2.6 Hz, 1H), 7.32 (dd, J = 9.0, 2.6 Hz, 1H), 7.30 (d, J = 8.1 Hz, 4H), 7.25 (d, J = 9.0 Hz, 1H), 5.62 (s, 2H), 4.64 (dt, J = 7.0, 5.0 Hz, 1H), 3.26 (dd, J = 11.3, 8.1 Hz, 1H), 3.16 (ddd, J = 11.2, 8.4, 4.5 Hz, 1H), 3.05 (ddd, J = 11.2, 8.7, 7.5 Hz, 1H), 2.78 (dd, J = 11.4, 9.2 Hz, 1H), 2.49 (m, 1H), 2.36 (s, 6H), 1.89 (m, 1H), 1.75 (m, 1H), 1.64−1.43 (m, 2H), 1.32 (ddd, J = 13.9, 7.6, 4.8 Hz, 1H), 0.85 (d, J = 6.4 Hz, 3H), 0.80 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.5(2), 164.9(2), 152.7, 143.7(2), 129.5, 129.3(4), 129.2(4), 128.1, 127.0(2), 124.5, 123.3, 116.4, 77.2, 72.6(2), 45.6, 44.2, 41.7, 41.4, 25.3, 24.0, 22.9, 22.3, 21.2(2). IR (solid) 2956, 2870, 1717, 1669, 1611, 1586 cm^{-1}. HRMS (ESI+) calcd for $C_{15}H_{22}NOCl_2$ 302.1073, found 302.1076.

(*R*)-1-Benzyl-3-((*R*)-1-hydroxy-3-methylbutyl)pyrrolidin-2-one ((±)-14). 1-Benzylpyrrolidin-2-one **5** (25.00 g, 142.7 mmol) was combined with 2-MeTHF (200 mL) and the resulting solution cooled to −78 °C. A 2.0 M solution of LDA in THF/heptane/ethylbenzene (Aldrich) (80.00 mL; 160.0 mmol) was added to the reaction mixture keeping the temperature between −60 to −75 °C. After 1.0 h, 3-methylbutanal (12.50 g; 145.1 mmol) in 2-MeTHF (25 mL) was added to the reaction mixture keeping the temperature between −60 to −75 °C. The mixture was warmed to 0 °C and aqueous 10% citric acid (150 mL) was added. The organic phase was separated, washed with water (2 × 150 mL), and concentrated to give a yellow solid. The

dx.doi.org/10.1021/jo400589j | J. Org. Chem. 2013, 78, 5768−5774

solids were added to MTBE (50 mL) at 23 °C to form a thin slurry and heptane (200 mL) was slowly added. After 1.5 h, the solids were filtered and dried to afford 16.00 g (42% yield) of the diastereomer (±)-**9** as a white powder. The liquors were cooled to 0 °C and seeded with (±)-**9** to afford a further 4.80 g of (±)-**9** contaminated with the diastereomer (±)-**14**. The resulting liquor was cooled to −15 °C for 5.0 h to give white plate crystals which were filtered and dried to afford 5.46 g (14% yield) of the diastereomer (±)-**14**. Mp 57.3−58.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38−7.19 (m, 5H), 4.81 (d, J = 4.1 Hz, 1H), 4.43 (d, J = 14.9 Hz, 1H), 4.30 (d, J = 14.9 Hz, 1H), 3.78 (m, 1H), 3.15 (t, J = 7.1 Hz, 2H), 2.58−2.50 (m, 1H), 2.08−1.93 (m, 1H), 1.86−1.66 (m, 2H), 1.44 (ddd, J = 14.0, 10.0, 4.4 Hz, 1H), 1.00 (ddd, J = 12.9, 9.4, 2.9 Hz, 1H), 0.86 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.5, 136.8, 128.5(2), 127.7(2), 127.2, 69.4, 47.0, 45.5, 44.9, 42.1, 23.8, 23.8, 21.5, 20.3. IR (solid) 3407, 2951, 2925, 2867. 1652, 1643, and 1431 cm^{-1}. HRMS (ESI+) calcd for $C_{16}H_{24}NO_2$ 262.1802, found 262.1803.

(*R*)-1-((*S*)-1-Benzylpyrrolidin-3-yl)-3-methylbutan-1-ol ((±)-15). Lactam (±)-**14** (4.90 g; 18.8 mmol) and toluene (50 mL) were combined, cooled to 0 °C, and ≥65 wt % Vitride (sodium bis(2-methoxyethoxy)aluminum hydride or Red-Al) in toluene (12.41 g = 12.00 mL; 42.96 mmol) diluted with toluene (40 mL) was added over 0.25 h giving a maximum temperature of 10 °C. The mixture was warmed to 22 °C and stirred for 22.0 h. The reaction was cooled to 0 °C and 20% aqueous Rochelle's salt (50 mL) and toluene (15 mL) were added. After 1.0 h, the organic phase was separated, washed with water (2 × 50 mL), and concentrated to give (±)-**15** as a colorless oil (4.18 g; 90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.26 (m, 4H), 7.19 (m, 1H), 4.60−4.00 (br, 1H), 3.49 (d, J = 1.8 Hz, 2H), 3.24 (ddd, J = 10.0, 7.6, 2.7 Hz, 1H), 2.58−2.40 (m, 2H), 2.39−2.30 (m, 2H), 1.98 (m, 1H), 1.74 (m, 2H), 1.33 (m, 1H), 1.16 (ddd, J = 13.8, 9.7, 4.2 Hz, 1H), 1.06 (ddd, J = 13.3, 9.6, 2.7 Hz, 1H), 0.83 (d, J = 6.7 Hz, 3H), 0.80 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 139.4, 128.4(2), 128.0(2), 126.6, 71.1, 60.0, 56.5, 53.8, 45.0, 44.5, 27.4, 24.0, 23.9, 21.6. IR (film) 3387, 2954, 2923, 2868, 2796, 1469, and 1453 cm^{-1}. HRMS (ESI+) calcd for $C_{16}H_{26}NO$ 248.2009, found 248.2009.

(*R*)-1-Benzyl-3-((*S*)-1-hydroxy-3-methylbutyl)pyrrolidin-2-one (9). To a solution of ketone **8** (10.00 g, 38.56 mmol) in IPA (120 mL) was added 0.1 M LiCl in IPA (3.75 mL; 0.38 mmol), and 10% con. HCl (35%) in IPA (2.0 mL; 2.3 mmol). The mixture was purged with N_2 followed by the addition of Ru(OAc)$_2$[(*S*)-tol-BINAP) (0.125 g, 0.139 mmol). The reactor was purged with N_2 (5 × 85 psi), then purged with H_2 (3 × 85 psi), and heated to 65 °C for 16.0 h. The reactor was vented and held under N_2 for HPLC analysis which indicated less than 50% conversion to **9**. Another charge of Ru(OAc)$_2$[(*S*)-tol-BINAP) (0.125 g, 0.139 mmol) was made followed by purging with H_2 (3 × 85 psi) and placing the reaction mixture under 85 psi of H_2 with heating to 65 °C for 20.0 h to afford a complete conversion of **8** to **9** with 96.4% ee and 94.3% de. The reaction mixture was cooled to 22 °C and concentrated to give crude **9** as a greenish/yellow oil, which was purified via column chromatography using the following conditions: Crude **9** dissolved in 5% EtOH/25% MTBE in heptanes (130 mL) and loaded onto a silica column using Merck 9385, 60A., 230−400 mesh (700 g) eluting with 5% EtOH/25% MTBE in heptanes to afford 9.39 g (93% yield) of **9** as a yellow waxy oil (see (±)-**9** for NMR and HRMS data). IR (film) 2957, 2871, 1714, 1682 cm^{-1}.

(*S*)-1-((*S*)-1-Benzylpyrrolidin-3-yl)-3-methylbutan-1-ol Dibenzoyl-L-tartrate (16). Lactam **9** (8.10 g; 31.0 mmol; 96.4% ee and 94.3% de) and toluene (80 mL) were combined, cooled to 0 °C, and Vitride (13.51 mL; 68.18 mmol) diluted with toluene (80 mL) was added over 0.5 h giving a maximum temperature of 10 °C. The mixture was warmed to 22 °C and stirred for 18.0 h. The reaction was cooled to 0 °C and a mixture of saturated aqueous Rochelle's salt (100 mL) and water (50 mL) were added over 0.3 h. The mixture was warmed to 22 °C, stirred vigorously for 6.5 h, MTBE (100 mL) added, and stirring continued for 16.0 h. The organic phase was separated, washed with water (2 × 100 mL), brine (100 mL), dried (Na_2SO_4), and the solvent removed to give crude **10** as an orange oil (7.34 g). At 22 °C, the crude **10** was dissolved in MeOAc (85 mL) and dibenzoyl-L-tartaric acid (DBTA) (5.67 g; 15.50 mmol) added. The mixture was heated to 50 °C to give a thin slurry, and a mixture of DBTA (5.67 g; 15.5 mmol) dissolved in MeOAc (15 mL) was added to the slurry over 0.5 h. After 17.0 h, the slurry was cooled to 21 °C over 2.0 h, and the solids filtered, washed with MeOAc (2 × 50 mL), and dried. The DBTA salt **16** (14.08 g; 75% yield) was isolated as an off-white solid. A sample of the DBTA salt **16** was freebased to give **10** according to the procedure below and analyzed by chiral HPLC which indicated 100% ee and de. $[\alpha]_D^{25}$ −63.1 (MeOH, c = 2.5). Mp 148.2−150.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, J = 7.0 Hz, 4H), 7.65 (t, J = 7.4 Hz, 2H), 7.52 (t, J = 7.7 Hz, 4H), 7.45 (dd, J = 7.7, 1.8 Hz, 2H), 7.39−7.27 (m, 3H), 5.70 (s, 2H), 4.13 (s, 2H), 3.40 (dt, J = 9.0, 4.0 Hz, 1H), 3.22−2.88 (m, 3H), 2.74 (t, J = 10.0 Hz, 1H), 2.18 (dq, J = 15.8, 8.1, 7.2 Hz, 1H), 1.80 (q, J = 7.6 Hz, 2H), 1.75−1.60 (m, 1H), 1.21 (ddd, J = 14.0, 9.6, 4.7 Hz, 1H), 0.91 (ddd, J = 13.1, 9.2, 3.4 Hz, 1H), 0.83 (d, J = 6.7 Hz, 3H), 0.81 (d, J = 6.5 Hz, 3H) (exchangeable protons not observed). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.4(2), 164.9(2), 133.5(2), 132.1, 130.2(2), 129.6(2), 129.3(4), 128.8, 128.7(4), 128.5(2), 72.9(2), 67.3, 56.7, 54.2, 52.4, 44.6, 42.6, 23.9, 23.5(2), 21.7. IR (solid) 3239.5, 2954, 2870, 1749, 1734, 1706, 1612, and 1451 cm^{-1}. HRMS (ESI+) calcd for $C_{16}H_{26}NO$ 248.2009, found 248.2009.

(*S*)-1-((*S*)-1-Benzylpyrrolidin-3-yl)-3-methylbutan-1-ol (10). Salt **16** (20.00 g; 33.02 mmol; 100% de and ee) was suspended in MTBE (200 mL) at 22 °C. To the slurry was added TEA (64.0 mL; 330 mmol), followed by 50% saturated aqueous $NaHCO_3$ (200 mL). The mixture was stirred for 1.0 h to give two homogeneous phases. The organic layer was removed, washed with 50% saturated aqueous $NaHCO_3$ (200 mL), water (200 mL), saturated brine (200 mL), dried (Na_2SO_4), and concentrated to afford **10** (7.82 g, 95.7%) as an orange oil. $[\alpha]_D^{25}$ 1.8 (MeOH, c = 2.75). See (±)-**10** spectra.

3-((*S*)-1-((*S*)-1-benzylpyrrolidin-3-yl)-3-methylbutoxy)-6-chloro-2-methylpyridine (18). At 22 °C, solid ^{t}BuOK (1.51 g; 12.9 mmol) was added to DMF (25 mL) followed by alcohol **10** (2.00 g; 8.08 mmol) to afford a thin yellow slurry. After 16.0 h, 6-chloro-3-fluoro-2-methylpyridine **17** (1.30 g; 8.89 mmol) was added to the mixture giving a green color and a brief endotherm to 19 °C. After 24.0 h, water (50 mL) and MTBE (50 mL) were added to the reaction, the organic phase separated, and the aqueous phase extracted with MTBE (20 mL). The organic phases were combined, washed with water (2 × 20 mL) and saturated brine (20 mL), dried (Na_2SO_4), and concentrated to give an orange oil. The oil was purified by column chromatography over silica gel eluting with 20% EtOAc/hexanes to afford **18** as an orange oil (1.98 g) in 65% yield. $[\alpha]_D^{25}$ 12.3 (MeOH, c = 2.2). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47 (d, J = 8.7 Hz, 1H), 7.32−7.17 (m, 6H), 4.48 (dt, J = 7.8, 4.7 Hz, 1H), 3.56 (d, J = 13.0 Hz, 1H), 3.46 (d, J = 13.1 Hz, 1H), 2.61−2.38 (m, 4H), 2.30 (s, 3H), 2.20 (dd, J = 8.9, 6.9 Hz, 1H), 1.90−1.77 (m, 1H), 1.71−1.50 (m, 3H), 1.39 (ddd, J = 13.9, 7.8, 4.2 Hz, 1H), 0.87 (d, J = 6.4 Hz, 3H), 0.84 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.2, 148.7, 139.2, 138.9, 128.2(2), 128.0(2), 126.6, 122.6, 121.9, 78.2, 59.6, 55.6, 53.4, 41.2, 41.1, 25.5, 24.3, 23.1, 22.4, 18.9. IR (film) 2956, 2870, 2791, 1577, and 1438 cm^{-1}. HRMS (ESI+) calcd for $C_{22}H_{30}N_2OCl$ 373.2041, found 373.2043.

3-((*S*)-1-((*S*)-1-Benzylpyrrolidin-3-yl)-3-methylbutoxy)-6-methoxy-2-methylpyridine (19). At 22 °C, MeOK (0.94 g; 12.9 mmol) was added to chloride **18** (1.20 g; 3.22 mmol) in DMSO (10 mL) giving a dark pink color. The mixture was heated to 100 °C for 1.0 h and cooled back to 22 °C. Water (50 mL) was added to the reaction and the mixture extracted twice with MTBE (50 and 20 mL). The combined organic phases were washed with water (2 × 5 mL) and saturated brine (10 mL), dried (Na_2SO_4), and concentrated to afford **19** as a light yellow oil (1.17 g) in 98% yield. $[\alpha]_D^{25}$ 12.8 (MeOH, c = 3.4). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37 (d, J = 8.9 Hz, 1H), 7.32−7.17 (m, 5H), 6.56 (d, J = 8.8 Hz, 1H), 4.26 (dt, J = 7.9, 4.7 Hz, 1H), 3.76 (s, 3H), 3.56 (d, J = 13.0 Hz, 1H), 3.48 (d, J = 13.1 Hz, 1H), 2.61−2.52 (m, 2H), 2.41 (m, 2H), 2.26 (s+m, 4H), 1.88−1.74 (m, 1H), 1.71−1.56 (m, 2H), 1.51 (ddd, J = 13.6, 7.8, 5.6 Hz, 1H), 1.35 (ddd, J = 14.3, 8.1, 4.3 Hz, 1H), 0.86 (d, J = 6.6 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.5, 147.4, 144.3,

dx.doi.org/10.1021/jo400589j | J. Org. Chem. 2013, 78, 5768−5774

139.3, 128.2(2), 128.0(2), 126.6, 125.2, 107.4, 78.7, 59.6, 55.6, 53.5, 52.9, 41.4, 41.2, 25.7, 24.3, 23.2, 22.4, 19.0. IR (film) 2955, 2869, 2790, 1471, and 1427 cm^{-1}. HRMS (ESI+) calcd for $C_{23}H_{33}N_2O_2$ 369.2537, found 369.2540.

6-Methoxy-2-methyl-3-((*S*)-3-methyl-1-((*S*)-pyrrolidin-3-yl)-butoxy)pyridine (2). To a glass pressure vessel was charged 20 wt % Pd/C (10% wet, 0.50 mg) followed by a solution of **19** (2.57 g, 6.97 mmol) in EtOH (26 mL). The reaction vessel was purged with H_2 gas (3 × 50 psi), and the vessel placed under 50 psi of H_2 and warmed to 60 °C causing the pressure to increase to 55 psi. After 24.0 h, the reaction mixture was cooled to 22 °C and filtered through Celite (wet with MeOH to avoid ignition of the Pd/C), followed by washing of the Celite with MeOH (30 mL). The filtrate was concentrated to give **2** (1.83 g; 94.3%) as a light yellow oil. $[\alpha]_D^{25}$ −5.4 (MeOH, *c* = 3.0). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40 (d, *J* = 8.9 Hz, 1H), 6.57 (d, *J* = 8.8 Hz, 1H), 4.30 (dt, *J* = 7.6, 5.0 Hz, 1H), 3.76 (s, 3H), 3.33 (br, 1H), 2.86 (dd, *J* = 10.6, 8.0 Hz, 1H), 2.82−2.67 (m, 2H), 2.53 (dd, *J* = 10.7, 7.1 Hz, 1H), 2.34−2.20 (m, 1H), 2.27 (s, 3H), 1.78−1.43 (m, 4H), 1.35 (ddd, *J* = 13.3, 8.1, 4.4 Hz, 1H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.5, 147.4, 144.3, 125.3, 107.3, 78.6, 53.0, 48.8, 46.5, 43.4, 42.0, 27.7, 24.3, 23.2, 22.4, 19.0. IR (film) 2955, 2869, 1583, 1471, and 1426 cm^{-1}. HRMS (ESI+) calcd for $C_{16}H_{27}N_2O_2$ 279.2067, found 279.2070.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The chiral HPLC method and chromatograms for **9**, **10**, **13**, and Table 1. NMR spectra for Scheme 2, 3, and 4 compounds, and X-ray data for **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: magnus_nicholas_a@lilly.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge Daneen T. Angwin, Steven E. Bandy, John L. Bowers, Jonas Y. Buser, Lauren E. Click, and Thomas Z. Gunter for analyses, assistance with analytical method development, and chromatographic purifications.

■ DEDICATION

§Dedicated to Professor Philip D. Magnus, F.R.S., The University of Texas at Austin, on the occasion of his 70th birthday.

■ REFERENCES

(1) Kroenke, K.; Krebs, E. E.; Bair, M. J. *Gen. Hosp. Psychiatry* **2009**, *31*, 206.

(2) Stangeland, E.; Saito, D. R.; Hughes, A.; Schmidt, J.; Van Dyke, P.; Patterson, L. J. U.S. Pat. Appl. Publ. 2011, US 20110009465 A1 20110113; Theravance Inc., San Francisco, CA, 2011.

(3) (a) Dreyfus, N. J. F.; Filla, S. A.; Johansson, A. M.; Masquelin, T. J.; Shah, J. A.; Tromiczak, E. G.; Walter, M. W. PCT Int. Appl. 2010, WO 2010117979 A2 20101014; Eli Lilly and Company, Indianapolis, IN, 2010. (b) Dreyfus, N.; Myers, J. K.; Badescu, V. O.; de Frutos, O.; de la Puente, M. L.; Ding, C.; Filla, S. A.; Fynboe, K.; Gernert, D. L.; Heinz, B. A.; Hemrick-Luecke, S. K.; Johnson, K. W.; Johnson, M. P.; López, P.; Love, P. L.; Martin, L. J.; Masquelin, T.; McCoy, M. J.; Mendiola, J.; Morrow, D.; Muhlhauser, M.; Pascual, G.; Perun, T. J.; Pfeifer, L. A.; Phebus, L. A.; Richards, S. J.; Rincón, J. A.; Seest, E. P.; Shah, J.; Shaojuan, J.; Simmons, R. M. A.; Stephenson, G. A.; Tromiczak, E. G.; Thompson, L. K.; Walter, M. W.; Weber, W. W.; Zarrinmayeh, H.; Thomas, C. E.; Joshi, E.; Iyengar, S.; Johansson, A. M. *ACS Med. Chem. Lett.* **2013**, DOI: 10.1021/ml400049p.

(4) Mendiola, J.; García-Cerrada, S.; de Frutos, O.; de la Puente, M. L.; Gu, R. L.; Khau, V. V. *Org. Process Res. Dev.* **2009**, *13*, 292.

(5) (a) Yuwasa, Y.; Sotoguchi, T.; Seido, N. Eur. Pat. Appl., EP 855390 A1 19980729; Takasago International Corporation, Japan, 1998. (b) Hattori, K.; Yamada, A.; Kuroda, S.; Toshiyuki Chiba, T.; Murata, M.; Sakane, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 383. This related paper appeared during the preparation of this manuscript: (c) Lall, M. S.; Hoge, G.; Tran, T. P.; Kissel, W.; Murphy, S. T.; Taylor, C.; Hutchings, K.; Samas, B.; Ellsworth, E. L.; Curran, T.; Showalter, H. D. H. *J. Org. Chem.* **2012**, *77* (10), 4732.

(6) (a) Babudrif, F.; Ciminalel, F.; Di Nunno, L.; Florio, S. *Tetrahedron* **1982**, *38* (4), 557. (b) Christoffers, J.; Werner, T.; Unger, S.; Frey, W. *Eur. J. Org. Chem.* **2003**, 425. (c) Magnus, P.; Fielding, M. R.; Wells, C.; Lynch, V. *Tetrahedron Lett.* **2002**, *43*, 947.

(7) Wilkinson, G.; Osborn, J. A.; Jardine, F. H.; Young, J. F. *J. Chem. Soc., Sect. A: Inorg., Phys., Theor.* **1966**, *12*, 1711.

(8) Siliabond triaminetetraacetate sodium salt (TAAcONa) purchased from SiliCycle is a supported version of ethylenediaminetetraacetic acid (EDTA) in its sodium salt form (silica bound metal scavenger).

(9) Nara, H.; Sayo, N.; Fujiwara, T. Eur. Pat. Appl., EP 2166014 A2 20100324; Takasago International Corporation, Japan, 2010.

(10) King, S. A.; Thompson, A. S.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1992**, *57*, 6689.

(11) β-Keto-γ-lactam **8** was further purified via silica gel chromatography eluting with EtOAc (21−25%)/heptane.

(12) (a) Inoue, T.; Sato, D. PCT Int. Appl., WO 2006054644 A1 20060526; Nippon Soda Co LTD, Japan, 2006. (b) Ohkuma, T.; Kurono, N. *Synlett* **2012**, *23*, 1865. (c) Kurono, N.; Yoshikawa, T.; Yamasaki, M.; Ohkuma, T. *Org. Lett.* **2011**, *13* (5), 1254.

(13) 10 g scale reactions to convert **8** to **9** required more catalyst and time, than the 400 mg scale screening reactions, to reach completion due to the need to use larger pressure reactors with less efficient mass transfer.

(14) Sasse, K.; Fischer, R.; Santel, H. J.; Schmidt, R. R. Ger. Offen., DE 3614846 A1 19871105; Bayer AG, Germany, 1987.