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Efficient Asymmetric Synthesis of *N*-[(1*R*)-6-Chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-yl]-2-pyridinecarboxamide for Treatment of Human Papillomavirus Infections

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Abstract:

An efficient asymmetric synthesis of *N*-[(1*R*)-6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-yl]-2-pyridinecarboxamide 1, a potential treatment for human papillomavirus infections, is described. The key step in the synthesis of this molecule is an asymmetric reductive amination directed by chiral (phenyl)-ethylamines resulting in up to 96% disastereo facial selectivity. The synthesis is also highlighted by isolation of a unique 2-picolinic acid salt of (1*R*)-6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine (13). Subsequent application of 1-propylphosphonic acid cyclic anhydride (T3P) for convenient amide formation from the two components of the salt provides the product 1 in high yield. The process research work leading to the final synthesis includes a racemic synthesis followed by resolution with chiral supercritical fluid chromatography, and an enantioselective reductive amination via chiral transfer hydrogenation catalyzed by Ru(II) complexes of *N*-[(1*S*,2*S*)-2-amino-1,2-diphenylethyl]-1-naphthalenesulfonamide or (*R*)-BINAP. Highlighting the practicality of the synthesis, the process has been scaled up in 200-gallon reactors for delivery of multikilograms of the target compound 1 in over 99.5% enantiomeric purity.

Introduction

Human papillomaviruses (HPVs) are small, non-enveloped DNA viruses that cause a wide variety of benign and premalignant epithelial tumors. Several HPVs infect the genital mucosa. These are sexually transmitted with an incidence roughly twice that of *Herpes simplex* infection. HPV infection is considered the most common sexually transmitted disease throughout the world.[1] There are over 5.5 million new cases of sexually transmitted HPV in the United States each year, with at least 20 million people currently infected.[2]

Papillomaviruses that cause genital infections are classified as low-risk or high-risk HPVs.[3] The low-risk HPVs (such as HPVs 6 and 11) cause genital warts, while the high-risk HPVs (such as HPVs 16 and 18) are highly associated with the development of genital cancers including cervical carcinoma. The role of HPV as the principle agent in the etiology of cervical cancer has been clearly established[4] with a lifetime risk of invasive cancer in the range of 5−10% for untreated infections. While most HPV infections are transient, lasting less than 1 year, a high proportion of persistent infections with high-risk types may progress to cervical dysplasia, the precursor to cervical cancer.

Currently available treatment for genital warts and cervical dysplasia involve surgical removal or chemical destruction of the infected tissue. The immunomodulator imiquimod (Aldara) has been approved for the treatment of external genital warts, but present treatments do not target the viral infection. Recently, vaccines (Cervarix and Gardasil) have been developed to prevent HPV infection. How effective these will be in reducing new HPV infections remains to be seen.[5]

A novel series of tetrahydrocarbazoles[6] was identified via a cell-based screen.[7] Optimization of these tetrahydrocarbazoles resulted in identification of **1** as a suitable development candidate. A large supply of **1** was required to support the preclinical and clinical development work. Herein we report our process research work on three generations of synthetic routes to **1**: a racemic synthesis followed by a resolution through chiral chromatography, an enantioselective synthesis through chiral catalysis, and a chiral auxiliary directed

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(1) (a) Howley, P. M. In Fundamental Virology; Howley, P. M., Ed.; Lippincott-Raven Publishers: Philadelphia, PA, 1996; pp 947−978. (b) Kroutsky, L. *Am. J. Med.* **1997**, *102*, 3.

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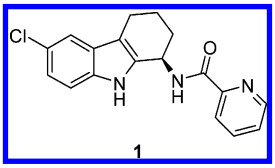
diastereoselective synthesis. The process research led to a robust and efficient synthesis of **1** on multikilogram scale.



Results and Discussion

The target molecule (**1**) is a 2-picolinamide of (*R*)-6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine. While a number of syntheses of substituted 2,3,4,9-tetrahydro-1*H*-carbazole exist,[6] our efforts focused on obtaining the chiral amine **2** via a reductive amination of the ketone **3** (Figure 1). Picolinic acid or any other carboxylic acid could then be incorporated in the last synthetic step. This strategy was aligned with the structure−activity studies in the drug discovery program which explored various different tetrahydrocarbazole amides. 6-Chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3**) could be prepared from 4-chloroaniline (**4**) and 2-(hydroxymethylene)cyclohexanone (**5**),[8] a tautomer of 2-formylcyclohexanone, via a cyclohexane-1,2-dione (4-chlorophenyl)hydrazone intermediate.[9] The reaction, known as Borsche synthesis, is a special case of the Fischer indole synthesis.[6f,g]

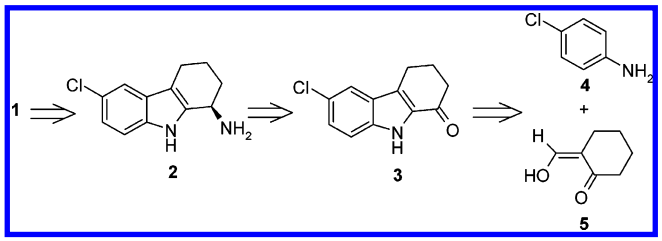
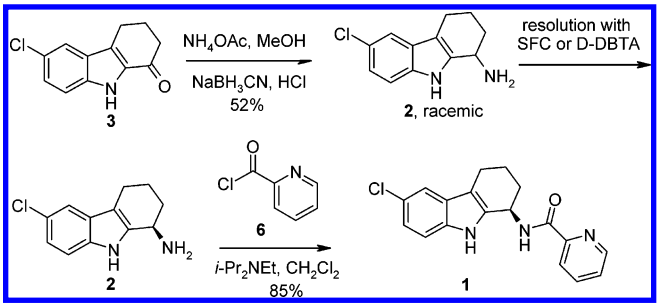


Figure 1. **Strategy for synthesis of 1.**

Our first synthesis was racemic (Scheme 1). Reductive amination of 6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3**) with ammonium acetate and sodium cyanoborohydride provided racemic amine **2** in 52% yield. Imine formation from ketone **3** with ammonium acetate proved difficult, and the reaction required 15 h at 60 °C. A significant amount of tar was generated, presumably due to the acid-catalyzed decomposition of the ketone as well as the amine product, which contributed to the low yield. The racemic amine **2** was resolved by preparative chiral supercritical fluid chromatography (SFC) using 10% MeOH, 10% $CHCl_3$, and 0.5% trifluoroacetic acid (TFA) in carbon dioxide as eluent on a Daicel AS-H column.[10,11] While the chiral separation provided enough material to support early studies, the low solubility of racemic **2** in the mobile phase hampered our efforts to scale up the chiral SFC separation. While separation of racemic **1** was also possible by SFC chromatography,[12] the solubility of racemic **1** in the mobile phase was even worse than that of the racemic amine precursor **2**. We also prepared some other *N*-derivatives such as triisopropylsilyl and trifluoroacetyl analogues of racemic **2**, and attempted the chiral separation utilizing simulated moving bed (SMB) chromatography on a chiral stationary phase. Unfortunately, separation of these *N*-derivatives proved unsatisfactory due to poor separation or low solubility.

Scheme 1



Similarly, chemical resolution with many common chiral acids also failed to give product of high enantiomeric purity in satisfactory yield. The best chemical resolution was obtained using one equivalent of dibenzoyl-D-tartaric acid (D-DBTA) in methanol, which afforded **2** in 93:7 enantiomeric ratio, but only 13% yield. While acylation of the resolved amine (**2**) with 2-picolyl chloride (**6**) in the presence of Hunig's base provided **1** in 80−90% yield, we had yet to identify a method that could provide chiral amine **2** in suitable purity and yield for preclinical development.

The strategy of an enantioselective synthesis utilizing chiral catalysis was then examined. The direct access of **2** from ketone **3** through reductive amination is the most obvious methodology for this strategy. While Noyori reduction has been known for enantioselective reduction of imines, its utility for the synthesis of a primary amine such as **2** is limited, due to the low stability as well as the reversibility of the imine intermediate. Noyori asymmetric hydrogenation with a chiral Ru(II) catalyst and a 5:2 formic acid/triethylamine azeotropic mixture is typically more enantioselective on cyclic imines for the preparation of endocyclic chiral amines.[13a] For the preparation of primary amines such as **2**, Noyori has used an alkyl amine such as benzylamine as the amino source which could then be cleaved by hydrogenolysis to provide a primary amine.[13a] More recently, Kadyrov and

(8) Tishler, M.; Gal, G.; Stein, G. A. *Org. Synth.* **1959**, *39*, 27.

(9) 6-Chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3**) was obtained from Ubichem Research through custom synthesis.

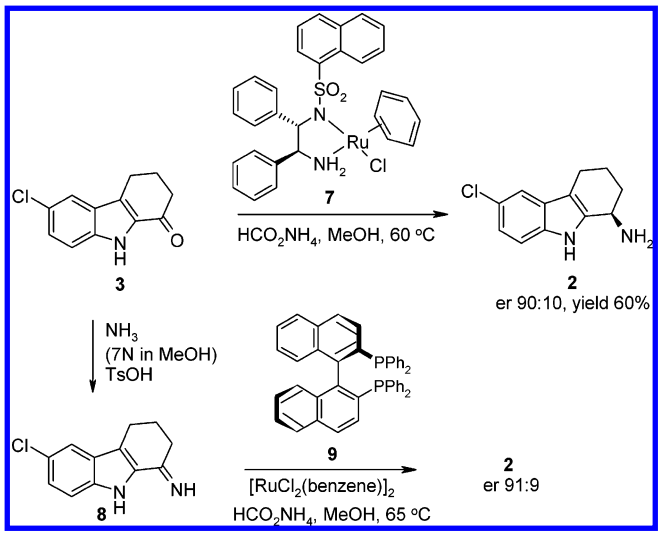
(10) Racemic amine **2** was resolved on a Berger analytical SFC with an HP1100 diode array detector. The sample was monitored at 230 nm under the following conditions: 10% methanol, 10% chloroform, 0.5% trifluoroacetic acid in carbon dioxide with a flow rate of 2 mL/min at 1500 psi, 27 °C on a Daicel AD-H column (3 cm × 25 cm). When the separated enantiomers were run on an analytical column Daicel AD-H (4.6 mm × 250 mm) in 10% methanol, 10% chloroform, 0.5% trifluoroacetic acid in carbon dioxide with a flow rate of 2 mL/min at 1500 psi, 27 °C, the *R*-isomer had a retention time of 5.57 min, and the *S*-isomer a retention time of 8.13 min.

(11) Conditions for chiral analysis of **2** were as follows. Column: Chiracel OD-H, 4.6 mm × 250 mm; mobile phase: 15:85 *i*-PrOH/hexanes (0.1 % Et_2-NH); flow rate: 1 mL/min; detection: 230 nm; temperature: 25 °C; retention time: 28 min for (*S*)-**2**, 12.3 min for enantiomer (*R*)-**2**. The salt form (**13**) was analyzed the same way as for free amine **2** after neutralization with aqueous NaOH and extraction into THF.

(12) Racemic final product **1** was resolved on a Berger analytical SFC with an HP1100 diode array detector. The sample was monitored at 230 nm under the following conditions: 30% methanol in carbon dioxide with a total flow rate of 2 mL/min at 1500 psi, 40 °C on a Daicel AS-H column (4.6 mm × 250 mm), to give the *R*-isomer (retention time 5.08 min) and the *S*-isomer (retention time 7.45 min).

(13) (a) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916. (b) Kadyrov, R.; Riermeier, T. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5472.

Scheme 2



co-worker reported enantioselective hydrogen-transfer reductive amination with ammonium formate and Ru(II)−BINAP catalysts for preparation of primary amines.[13b]

We pursued both types of catalyst and achieved modest success (Scheme 2). The Noyori transfer hydrogenation was performed on ketone **3** with 2 mol % of Noyori's Ru(II) catalyst **7**[13a] and 6 equiv of ammonium formate in methanol at 60 °C under nitrogen atmosphere for 18 h. This modified Noyori condition provided amine **2** in 9:1 enantiomeric ratio and 60% isolated yield. Alternatively, the transfer hydrogenation could be performed on the preformed imine **8** with the catalyst prepared in situ from (*R*)-BINAP (**9**) and benzeneruthenium(II) chloride dimer.[13b] Imine **8** was formed in 7 N ammonia in methanol with catalytic amount of *p*-toluenesulfonic acid. This method provided **2** in similar enantioselectivity (91:9) but of unacceptable chemical purity.

While the possibility of improving the yield from the Noyori transfer hydrogenation existed, we did not have a good method to enhance the enantiomeric purity from the 80% ee delivered by the chiral reduction to a level acceptable for pharmaceutical development (>98% ee). The cost of the chiral Ru(II) catalysts was also an issue for the industrial production we were pursuing. Therefore, our efforts shifted to an approach based on asymmetric reduction directed with a chiral auxiliary. For this approach, we focused on chiral benzyl amines that are known surrogates for the amino group and available on scale at low cost.[14] Liégeois and co-workers used (*S*)- and (*R*)-α-methylbenzylamines in their efforts towards synthesis of pirlindole from a 6-methyl tetrahydrocarbazolone via reductive amination, although the stereoselectivity was not verified.[14a]

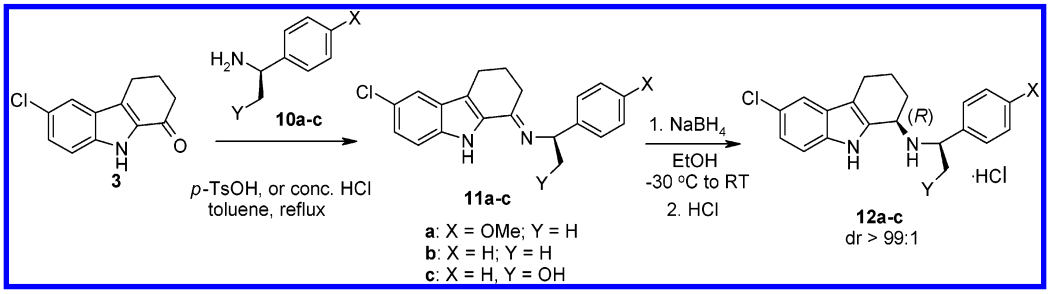
Table 1. **Selectivity Observed with Various Chiral 1-(Phenyl)ethylamines**

entry	chiral auxiliary	diastereo ratio from reduction	diastereo ratio after salt crystallization	isolated product	isolated yield from ketone **3** (%)
1	**10a**	96:4	>99.5:0.5	**12a**	82
2	**10b**	95:5	>99.5:0.5	**12b**	86
3	**10c**	88:12	99.3:0.7	**12c**	70

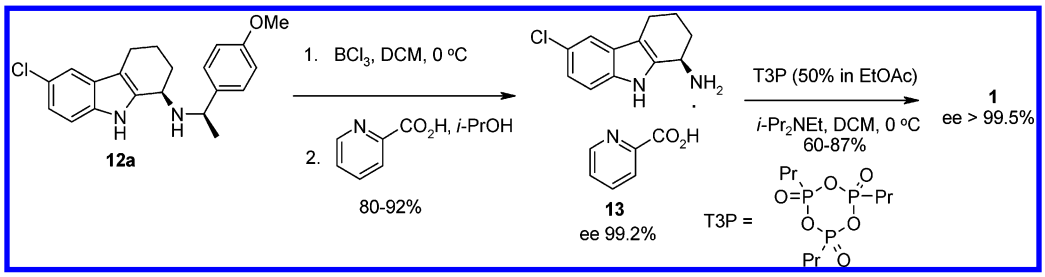
We were delighted to find that several chiral (phenyl)ethylamines gave high diastereofacial selectivity in the reductive amination of tetrahydrocarbazolone **3** as shown in Scheme 3. The reductive amination could be carried out in one pot with the ketone and reagents mixed in dichloromethane or 1,2-dichloroethane. However, the reactions on large scale were found to be more reproducible when performed in two sequential steps: imine formation with catalytic amount of *p*-TsOH or HCl in toluene at 105 °C, followed by reduction of the resultant imine intermediates (**11a**−**c**) in a mixture of toluene and ethanol at −30 °C to room temperature. As shown in Table 1, the best selectivity was achieved with (*R*)-1-(4-methoxyphenyl)ethylamine (**10a**, 96:4), and with (*R*)-1-(phenyl)ethylamine (**10b**, 95:5), while (*S*)-phenylglycinol (**10c**) gave a poorer ratio (88:12).[15] In all cases, the crude amino product was treated with HCl and isolated as a HCl salt. The formation and crystallization of the HCl salt enhanced the diastereomeric purity of the isolated product to over 99% as determined by analysis by HPLC.[15] The undesired diastereo isomer was essentially removed in just one crystallization. The reduction of the methoxy compound (**11a)** was selected for scale-up because of the more facile cleavage of the chiral auxiliary (vide infra). On scale-up, **12a** was isolated in 82% yield and 99.6% diastereomeric purity on a 300-gal scale. The yield approached 90% in smaller fixed equipment.

With the preparation of the "protected" chiral amines (**12a**−**c**) achieved in high yield and excellent selectivity, deprotection and amide formation were the two remaining steps. Cleavage of the chiral auxiliaries to give the desired chiral amine **2** proved difficult. Hydrogenolysis with various metal catalysts (Pd, Ru, and Rh) is the most common method for *N*-debenzylation,[16] but it led to loss of the chloro substituent as well as decomposition of the tetrahydrocarbazole moiety in all cases (**12a**−**c**). Three equivalents of $AlCl_3$ in dichloromethane worked to some extent in benzyl cleavage of the benzyl groups of **12a** and **12b**. However,

Scheme 3



Scheme 4



the low stability of the tetrahydrocarbazole moiety in the presence of the large amount of strong acids generated in the difficult acidic workup led to only about 30% isolated yield of the HCl salt of **2**. For the hydroxyl compound **12c**, we found that the phenylglycinol moiety could be removed with $NaIO_4$. Eventually, we found that BCl_3 and BBr_3 gave the cleanest *N*-debenzylation for **12a** and **12b**. The boron reagents worked particularly well for **12a** because of the stabilization effect on the purported benzyl cationic intermediate from the *p*-methoxy group. Compound **12a** was chosen for scale-up in the pilot plant (Scheme 4). The *N*-debenzylation progressed smoothly with 2−3 equiv of BCl_3 in dichloromethane. However, isolation of free base **2** could not be achieved consistently with satisfactory purity and yield. After extensive screening of various acids for the salt formation and crystallization, we were rewarded with a pleasant surprise. The only crystalline salt with acceptable isolated purity and yield turned out to be the 1:1 salt (**13**) from **2** and 2-picolinic acid; the same acid that was to be incorporated into the target **1** in the last step. In scale-up to 200 gallons, salt **13** was isolated in 81% yield and 99.2% ee. With a second crop, the total yield was as high as 92%.

While typical acylation conditions such as *O*-benzotriazole activation and acid chloride worked for the formation of the amide from **13**, the most practical method utilized 1-propylphosphonic acid cyclic anhydride (T3P) and Hunig's base in dichloromethane (Scheme 4).[17] The carboxylic acid, activated via a purported mixed anhydride with a 1-propylphosphonic acid moiety, reacted with the amine (**2**) cleanly and nearly instantaneously with ice cooling. The target active pharmaceutical ingredient (API) **1** was isolated as a crystalline solid in up to 87% yield in ≥99.5% ee.[18] The sequence as described herein has been scaled up in pilot-plant reactors and has produced multikilograms of **1**. Assignment of the absolute stereochemistry of **1** was accomplished by X-ray analysis of a single crystal of **1** as shown in Figure 2.

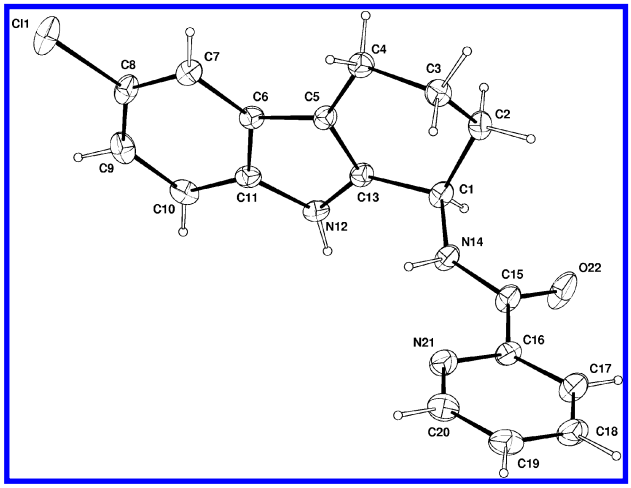


Figure 2. **ORTEP view of X-ray structure of 1.**

Conclusion

An efficient asymmetric synthesis of *N*-[(1*R*)-6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-yl]-2-pyridinecarboxamide has been achieved. Three generations of synthesis were explored: a racemic synthesis followed by a resolution through chiral chromatography or crystallization of the salt of the amine with a chiral acid, an enantioselective asymmetric synthesis through a reductive amination via chiral transfer hydrogenation catalyzed by two Noyori chiral Ru (II) complexes, and a chiral (phenyl)ethylamine-directed diastereo or facial selective synthesis. The latter was the most efficient and most selective. The synthesis also featured isolation of the 2-picolinic acid salt of (1*R*)-6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine and application of 1-propylphosphonic acid cyclic anhydride (T3P) for the convenient amide formation from the two components of the salt. This practical stereoselective synthesis has been scaled up in 200-gallon reactors for delivery of multikilograms of the target compound in over 99.5% enantiomeric purity.

Experimental Section

(1*R*)-6-Chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine (2). *1. Racemic Synthesis Followed by Resolution by Chiral Column. Racemic Amine.* To a solution of 6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3**) (500 mg, 2.3 mmol) and ammonium acetate (1.8 g, 23 mmol) in methanol (9 mL) was added sodium cyanoborohydride (720 mg, 11.5 mmol).

(14) (a) Tullio, P. d.; Felikidis, A.; Pirotte, B.; Liégeois, J.-F.; Stachow, M.; Delarge, J. *Helv. Chim. Acta* **1998**, *81*, 539. (b) Gutman, A. L.; Etinger, M.; Nisnevich, G.; Polyak, F. *Tetrahedron: Asymmetry* **1998**, *9*, 4369.

(15) HPLC conditions for analysis of diastereomers **12a-c** with HPLC were as follows: Column: Luna C_{18}(2) 50 mm × 2 mm, 3 μm; mobile phase A: H_2O (0.05% TFA), mobile phase B: MeCN (0.05% TFA); gradient: 0−95% B over 8 min; detection: 220 nm; temperature: 40 °C; retention time: 4.45 min for **12a** and 4.55 min for its diastereomer; 4.38 min for **12b** and 4.49 min for its diastereomer; 4.21 min for **12c** and 4.32 min for its diastereomer.

(16) (a) Rylander, P. N. *Catalytic Hydrogenation in Organic Synthesis*; Academic Press: London, 1979. (b) Frahm, A. W.; Knupp, G. *Tetrahedron Lett.* **1981**, *22*, 2633. (c) Speckenbach, B.; Pisel, P.; Frahm, A. W. *Synthesis* **1997**, 1325.

(17) (a) Wissmann, H.; Kleiner, H., J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 133. (b) Helal, C. J.; Kang, Z.; Lucas, J. C.; Bohall, B. R. *Org. Lett.* **2004**, *6*, 1853.

(18) HPLC conditions for chiral analysis of **1** were as follows. Column: Chiracel OD-H, 4.6 mm × 250 mm; mobile phase: 10:90 *i*-PrOH/hexanes (0.1% Et_2NH); flow rate: 1 mL/min; detection: 230 nm; temperature: 25 °C; retention time: 9.3 min for enantiomer (*S*)-**1**, 11.2 min for enantiomer (*R*)-**1**.

After heating at 60 °C for 15 h, the mixture was cooled and treated with concentrated hydrochloric acid until pH = 1. The organics were removed under reduced pressure, and the resulting precipitate was collected by filtration, dissolved in 30 mL of ethyl acetate and 5 mL of methanol, and washed with 20 mL of saturated aqueous sodium carbonate. The phases were separated, and the organic phase was concentrated to yield racemic 6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine (**2**, racemic) (260 mg, 52% yield) as a light-brown solid. ^{1}H NMR (DMSO-d_6) δ 10.90 (s, 1H), 7.34 (m, 1H), 7.27 (d, 1H), 6.97 (dd, 1H), 3.90 (t, 1H), 2.54 (m, 2H), 2.04−1.89 (m, 2H), 1.66 (m, 1H), 1.50 (m, 1H); MS *m*/*z* 221 (M + 1); HRMS (ESI): calcd for $C_{12}H_{11}ClN$ (M − NH_2)$^+$ 204.0580, found 204.0570.

2. Enantioselective Synthesis through Chiral Transfer Hydrogenation. A mixture of 220 mg (1.00 mmol) of ketone **3**, 380 mg (6.00 mmol) of ammonium formate, and 12 mg (0.020 mmol) of Noyori's catalyst[13a] in 5 mL of methanol was heated to 60 °C under nitrogen atmosphere for 18 h. The mixture was cooled to ambient temperature and quenched with 20 mL of 2 M HCl in water. The mixture was washed with 10 mL of CH_2Cl_2. Layers were separated. The aqueous phase was made basic with 2 M NaOH in water and extracted with 15 mL of CH_2Cl_2 twice. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum to give 132 mg (60%) of product **2** as a gray solid: enantiomeric ratio 9:1;[11] purity by HPLC 98%. For the final synthetic route, amine **2** was isolated and characterized as a salt with 2-picolinic acid. See the procedure for compound **13**.

(1*R*)-1-(5-Chloro-3-propyl-1*H*-indol-2-yl)-*N*-{(1*R*)-1-[4-(methoxy)phenyl]ethyl}ethanamine (12a). To a 300-gal reactor with a condenser and built-in Dean−Stark trap were successively added 17.2 kg (78.3 mol) of 6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3**), 206 L of toluene, 12.4 kg (82.0 mol) of (*R*)-(+)-1-(4-methoxyphenylethyl)amine (**10a**), and 276 g (2.78 mol) of concentrated HCl. The reaction was brought to reflux and was stirred for 10 h. After being cooled to room temperature, the mixture containing imine intermediate **11a** was drained to an addition vessel. The reactor was rinsed with 21.5 L of toluene which was added to the addition vessel.

The reactor was then charged with 172 L of ethanol and cooled to −30 °C, followed by addition of 2.92 kg (77.3 mol) of sodium borohydride in three portions. The crude imine from the addition vessel was added over about 4 h with temperature maintained at about −30 °C. After being stirred for 12 h, the reaction was warmed to room temperature over 1 h. The reaction was then treated with 8.6 L of acetone and stirred for 30 min. The volume of the reaction mixture was reduced to about 70 L with vacuum distillation, followed by addition of 258 L of ethyl acetate and 103 L of water. The layers were separated. The organic layer was successively washed with 85 L of water and 85 L of 10 wt % brine. Analysis by HPLC showed the diastereomeric ratio of 96:4 for free base of **12a** and its diastereomer at this point.[15]

For the salt formation in the same reactor, the crude amine prepared as above was diluted with 34.4 L of methanol and 51.6 mL of toluene. After being cooled to −5 °C, the mixture was treated with 7.05 kg (101 mol) of concentrated HCl over 30 min and stirred for additional 30 min. The solid salt was filtered, and the filter cake was washed with 6.9 L of methyl *tert*-butyl ether (MTBE). The filter cake was dried at 60 °C under vacuum to provide 25.1 kg (82% overall yield from ketone **3**) of HCl salt **12a** as a white crystalline solid: diastereomeric ratio 99.6:0.4;[15] $[\alpha]^{22}_D$ +89.9 (*c* 0.55, MeOH); ^{1}H NMR (DMSO-d_6) δ 11.9 (s, 1H), 10.0 (m, 1H), 9.35 (m, 1H), 7.70 (d, J = 8.7 Hz, 2H), 7.52 (s, 1H), 7.40 (d, J = 8.7 Hz, 1H), 7.13 (d, J = 8.6 Hz, 1H), 7.00 (d, J = 8.7 Hz, 2H), 4.69 (m, 1H), 4.54 (m, 1H), 3.75 (s, 3H), 2.62 (m, 2H), 2.14 (m, 1H), 2.01 (m, 2H), 1.76 (m, 1H), 1.67 (d, J = 8.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 159.5, 134.3, 130.1, 129.9, 129.6, 127.1, 123.4, 122.1, 117.8, 114.0, 113.1, 112.9, 55.2, 55.0, 49.1, 25.7, 20.1, 19.7, 18.8. HRMS calcd for $C_{21}H_{24}ClN_2O$ (M + H)$^+$ 355.1577, found, 355.1577. Anal. Calcd for $C_{21}H_{23}ClN_2O$·HCl: C, 64.45; H, 6.18; N, 7.16; Cl, 18.12. Found: C 64.26; H, 6.12; N, 7.15; Cl, 18.40.

(1*R*)-1-(5-Chloro-3-propyl-1*H*-indol-2-yl)-*N*-[(1*R*)-1-phenylethyl]ethanamine (12b). To a 20-L reactor with a condenser and built-in Dean−Stark trap were successively added 1.00 kg (4.55 mol) of 6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3**), 16 L of toluene, 552 g (4.55 mol) of (+)-α- methylbenzylamine (**10b**), and 60.5 g (318 mmol) of *p*-TsOH·H_2O. The mixture was heated at reflux for 12 h. The reaction mixture was partially concentrated to 4 L under vacuum. The crude imine in toluene was diluted with 12 L of EtOH, cooled to −17 °C. To the mixture (which might be a slurry at this point) was added 1.37 L (2.74 mol) of 2 M $NaBH_4$ in triglyme over 1 h between −17 °C to −20 °C. A solution formed after the addition of the $NaBH_4$. The mixture was stirred at −15 °C for 10 h. The reaction mixture was sampled for analysis by HPLC which showed a diastereomeric ratio of 95:5 favoring the desired diastereomer **12b**.[15] The reaction mixture was warmed to room temperature over 1 h, and 0.5 L of acetone was added over 30 min. The mixture was concentrated to 4 L, followed by addition of 14 L of ethyl acetate and 5 L of 4% $NaHCO_3$ aqueous solution. Layers were separated, and the organic layer was successively washed with 4 L of water and 4 L of 10% brine and concentrated to 8 L under vacuum.

After being diluted with 5 L of ethyl acetate and 2 L of MeOH, 1.50 L (6.00 mol) of 4 N HCl in 1,4-dioxane was added over 20 min. The resultant slurry was stirred for 1 h at ambient temperature and filtered. The filter cake was washed with 2 L of EtOH and dried under vacuum at 60 °C for 24 h to provide 1.41 kg (86% overall yield from ketone **3**) of HCl salt **12b** as a white crystalline solid: diastereomeric ratio 100:0;[15] $[\alpha]^{22}_D$ +149 (*c* 1.23, MeOH); ^{1}H NMR (DMSO-d_6) δ 11.7 (s, 1H), 9.93 (m, 1H), 9.34 (m, 1H), 7.82 (d, J = 8.7 Hz, 2H), 7.50 (s, 1H), 7.47 (m, 3H), 7.18 (d, J = 8.7 Hz, 2H), 4.77 (m, 1H), 4.61 (m, 1H), 2.67 (m, 2H), 2.53 (m, 3H), 2.20 (m, 1H), 2.02 (m, 2H), 1.85 (m, 1H), 1.73 (d, J = 8.6 Hz, 3H); HRMS (ESI): calcd for $C_{20}H_{22}ClN_2$ (M + H)$^+$ 325.1472, found 325.1474. Anal. Calcd for

$C_{20}H_{21}ClN_2$·HCl: C, 66.49; H, 6.14; N, 7.75; Cl, 19.62. Found: C, 66.21; H, 6.18; N, 7.70; Cl, 19.54.

(2*S*)-2-{[(1*R*)-1-(5-Chloro-3-propyl-1*H*-indol-2-yl)ethyl]-amino}-2-phenylethanol (12c). To a three-neck round-bottom flask equipped with a condenser and Dean−Stark trap were added 2.00 g (9.02 mmol) of 6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3**), 20 mL of toluene, 1.40 g (9.47 mmol) of (*S*)-phenylglycinol (**10c**), and 90.0 mg (0.500 mmol) of *p*-toluenesulfonic acid. The reaction was brought to reflux and was stirred for 24 h. After being cooled to room temperature, the mixture containing imine intermediate **11c** was concentrated to 8 mL.

A second round-bottom flask was charged with 10 mL of methanol and cooled to −45 °C, followed by addition of 385 mg (9.47 mmol) of sodium borohydride. The crude imine from the addition vessel was added with temperature maintained at approximately −45 °C. Once addition of the imine was complete the reaction was warmed to −15 °C. After being stirred for 2 h, the reaction was warmed to room temperature. The reaction was then treated with 1 mL of acetone and stirred for 30 min. The reaction mixture was concentrated to about 8 mL under vacuum, followed by addition of 28 mL of ethyl acetate and 5 mL of 5% sodium chloride in water. The layers were separated, and the organic layer was washed with 5 mL of 10 wt % brine. Analysis by HPLC showed the diastereomeric ratio of 88:12 at this point.[15]

For the salt formation in the same reactor, the free base of **12c** as described above was diluted with 4 mL of methanol and 10 mL of ethyl acetate. The mixture was treated with 3 mL (11.8 mmol) of HCl in 1,4-dioxane over 5 min and stirred for additional 20 min. The solid was filtered, and the filter cake was washed with 4 mL of methyl *tert*-butyl ether (MTBE) followed by 4 mL of ethyl acetate. The filter cake was dried at 60 °C under vacuum to provide 2.46 g (70% overall yield from ketone **3**) of HCl salt **12c** as a crystalline solid: diastereomeric ratio 99.3:0.7.[15] ^{1}H NMR (DMSO-d_6) δ 11.6 (s, 1H), 9.83 (m, 1H), 9.49 (m, 1H), 7.74 (d, J = 8.7 Hz, 2H), 7.50 (s, 1H), 7.43 (m, 3H), 7.14 (d, J = 8.7 Hz, 2H), 5.59 (br s, 1H), 4.72 (m, 2H), 4.11 (m, 1H), 3.87 (m, 1H), 3.50 (br s, 1H), 2.64 (m, 2H), 2.30 (m, 1H), 2.01 (m, 2H), 1.75 (m, 1H). HRMS (ESI): calcd for $C_{20}H_{22}ClN_2O$ $(M + H)^+$ 341.1421, found 341.1418.

(1*R*)-6-Chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-ammonium 2-picolinate (13). To a 200-gal reactor were successively added 13.5 kg (34.5 mol) of **12a** and 67.5 L of dichloromethane. With reaction temperature maintained at about 25 °C, 86.3 L (86.3 mol) of 1 M BCl_3 in dichloromethane was added over about 30 min. After being stirred at 25 °C for 3 h, the reaction was cooled to 10 °C and stirred overnight. The reaction was quenched with 135 kg (10 weights of **12a**) of 20 wt % aqueous KOH over about 1 h such that the first two weights were added with vigorous stirring over 30 min to maintain the temperature at about 10 °C. The mixture was warmed to 25 °C. Layers were separated, and the aqueous layer was extracted with 135 L of 9:1 mixture of dichloromethane/methanol. The combined organic layers were washed with 135 L of 10 wt % brine to give crude free amine **2** as a solution in dichloromethane.

To the crude amine as described above was added 4.73 kg (38.3 mol) of 2-picolinic acid. The solution was concentrated to about 95 L via atmospheric distillation. After being diluted with 95 L of isopropanol, the mixture was further concentrated to about 95 L via atmospheric distillation. The mixture was cooled to 10 °C and stirred for 1 h. The mixture was filtered, and the filter cake was washed with 27 L of 2:1 mixture of isopropyl alcohol/dichloromethane. The filter cake was dried at 60 °C under vacuum to provide 9.6 kg (81%) of the 2-picolinic acid salt **13** as a crystalline solid: enantiomeric ratio 99.6:0.4;[11] $[\alpha]^{22}_D$ +159 (*c* 0.53, MeOH); ^{1}H NMR (DMSO-d_6): δ 8.61 (s, 1H), 8.00 (d, J = 7.8 Hz, 1H), 7.85 (m, 1H), 7.46 (s, 1H), 7.40 (d, H = 4.3 Hz, 1H), 7.09 (d J = 4.3 Hz, 1H), 4.43 (s, 1H), 2.62 (m, 2H), 2.14 (m, 1H), 1.98 (m, 1H), 1.79 (m, 2H). HRMS (ESI): calcd for $C_{12}H_{11}ClN$ $(M - NH_2)^+$ 204.0580, found 204.0576.

***N*-[(1*R*)-6-Chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-yl]-2-pyridinecarboxamide (1).** To a 200-gal reactor was successively added 12.9 kg (37.5 mol) of salt **13**, 90 L of dichloromethane, and 16.0 kg (7.68 mol) of Hunig's base. To ensure a complete reaction, 464 g (3.76 mol, 0.1 equiv to **13**) of 2-picolinic acid was added. After being cooled to 0 °C, the slurry was treated with 33.4 kg (52.5 mol) of 50 wt % solution of 1-propylphosphonic acid cyclic anhydride (T3P) in EtOAc over 30 min while maintaining the temperature at 0−10 °C. The off-white slurry became a clear brown solution and was stirred at 0 °C for about 2 h. The reaction was quenched by addition of 90 L of water at below 25 °C and stirred for 30 min. Layers were separated, and the aqueous layer was extracted with 65 L of dichloromethane. The combined organic layers were successively washed with 90 L of water and 90 L of 15 wt % brine.

The organic layer was concentrated to about 52 L via atmospheric distillation to azeotropically reduce water content to below 0.21 wt % by Karl Fisher analysis. This distillation was repeated if necessary in order to achieve the target water level. The solution was diluted with 65 L of ethanol and concentrated to about 65 L under vacuum. The resultant slurry was treated with 206 L of ethanol to make a solution at 76−80 °C. A hot clarification filtration was carried out on the solution containing **1**. The filtrate was cooled to 20−25 °C and treated with 13 L of water over 1 h with stirring. The mixture was cooled to 0 °C and stirred for 2 h. The resultant white slurry was filtered. The filter cake was washed with 65 L of 1:1 mixture of ethanol−water, dried at 80 °C under vacuum to provide 9.7 kg (79%) of target compound **1** as a white crystalline solid: enantiomeric ratio >99.8:0.2;[18] $[\alpha]_D$ = + 192 (*c* 1.16, CH_2Cl_2); ^{1}H NMR (DMSO-d_6): δ 10.93 (s, 1H), 8.78 (d, 1H), 8.61 (m, 1H), 8.12 (m, 1H), 8.02 (m, 1H), 7.61 (m, 1H), 7.43 (m, 1H), 7.26 (d, 1H), 7.01 (dd, 1H), 5.34 (m, 1H), 2.64 (m, 2H), 2.00 (m, 3H), 1.82

(m, 1H); ^{13}C NMR (DMSO-d_6): δ 164.1, 150.6, 149.1, 138.4, 136.4, 135.3, 128.5, 127.2, 123.7, 122.7, 121.5, 117.8, 113.4, 111.2, 44.0, 30.8, 21.5, 21.0. HRMS (ESI): calcd for $C_{18}H_{17}ClN_3O$ $(M + H)^+$ 326.1060, found 326.1061. Anal. Calcd for $C_{18}H_{16}ClN_3O$ with 1/4 H_2O: C, 65.45; H, 5.04; N, 12.72. Found: C, 65.67; H, 4.91; N, 12.66.

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