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An Efficient Process for Synthesis of 3-(*R*)-3-(2,3-Dihydrobenzofuran-5-yl)-1,2,3,4-tetrahydropyrrolo[3,4-*b*]quinolin-9-one

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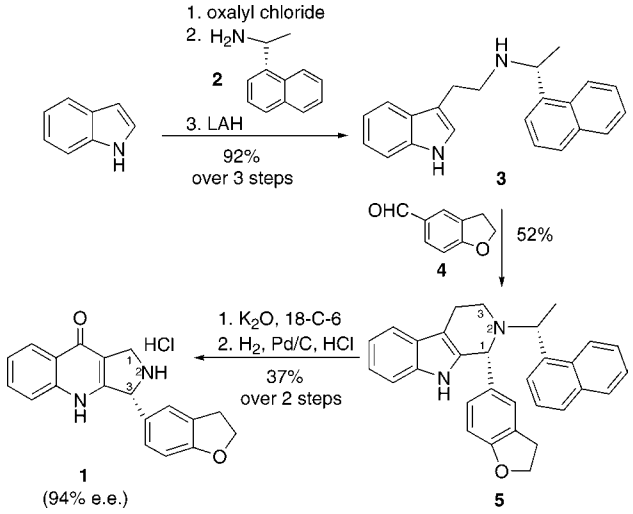
Abstract:

3-(*R*)-3-(2,3-Dihydrobenzofuran-5-yl)-1,2,3,4-tetrahydropyrrolo[3,4-*b*]quinolin-9-one (1) is a key intermediate in the synthesis of pyrroloquinolone analogues, a series of highly potent and selective phosphodiesterase 5 (PDE5) inhibitors. Racemic 1-(2,3-dihydrobenzofuran-5-yl)-2,3,4,9-tetrahydro-1*H*-*β*-carboline (6, Scheme 2) was prepared by Pictet−Spenger condensation in 84% isolated yield with >97% chemical purity. The desired intermediate, 1-(*R*)-1-(2,3-dihydrobenzofuran-5-yl)-2,3,4,9-tetrahydro-1*H*-*β*-carboline *N*-acetyl-D-leucine salt (8), was obtained in 35% isolated yield with high chiral purity (≥ 97% ee) from the chemical resolution of 6 with *N*-acetyl-D-leucine (7). A racemization step was developed for recycling enriched 1-(*S*)-*β*-carboline 9 freebase (8/9, 25 ± 3%/75 ± 3%) to a near racemic mixture (8/9, 47 ± 1%/53 ± 1%). Furthermore, the resolving reagent 7 was recovered in >76% yield, which, together with the recycled racemic mixture (8/9, 47 ± 1%/53 ± 1%), afforded 35% more salt 8 after two recycles (≥97.0% ee). The salt 8 was converted to 1-(*R*)-1-(2,3-dihydrobenzofuran-5-yl)-2-benzyl-2,3,4,9-tetrahydro-1*H*-*β*-carboline (10) in excellent yield (94%). A modified Winterfeldt oxidation of compound 10 using Aliquat 175 as a phase transfer catalyst produced 3-(*R*)-2-benzyl-3-(2,3-dihydrobenzofuran-5-yl)-1,2,3,4-tetrahydropyrrolo[3,4-*b*]quinolin-9-one (12) in moderate 42% yield. Hydrogenolysis of compound 12 gave the desired compound 1 in quantitative yield with retention of chiral purity (≥97.0% ee). This efficient, reproducible, economical, and nonchromatography scale-up process could be used to make multikilogram quantities of compound 1.

Introduction

Recently we reported a series of pyrroloquinolones as highly potent and selective phosphodiesterase 5 (PDE5) inhibitors,[1] for the treatment of male erectile dysfunction (MED).[2] Many of the pyrroloquinolone analogues in this series were derived from the key intermediate, 3-(*R*)-(2,3-dihydrobenzofuran-5-yl)-1,2,3,4-tetrahydropyrrolo[3,4-*b*]-quinolin-9-one (**1**), which was synthesized by an asymmetric Pictet−Spengler reaction (Scheme 1).[3] However, the reported method contained some improvement opportunities for a large scale synthesis: (1) use of a limited and expensive chiral auxiliary starting material, (*R*)-1-naphthalen-1-yl-ethylamine (**2**); (2) several chromatographic purifications were required to purify intermediates as well as the final product **1**; (3) the catalytic hydrogenation conditions used to remove the chiral auxiliary **2** produced 5−15% of an over-reduced byproduct; and (4) the chiral purity of 3-(*R*)-pyrroloquinolinone **1** was 94% ee, which required a final purification by chiral HPLC.[3] Herein, we wish to report a highly efficient synthesis of the key intermediate **1** that is amenable to large-scale production. We focused on a synthetic route using tryptamine and 2,3-dihydrobenzo[*b*]-furan-5-carboxaldehyde (**4**) as starting materials and *N*-acetyl-D-leucine (**7**) as resolving reagent that was prepared from D-leucine. Tryptamine, aldehyde **4**, and D-leucine are all commercially available in large quantities at a reasonable cost.

Scheme 1



Results and Discussion

The Pictet−Spengler reaction was done stepwise, in one pot, by refluxing tryptamine and 2,3-dihydrobenzo[*b*]furan-

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† High Output Synthesis.

‡ Reproductive Therapeutics.

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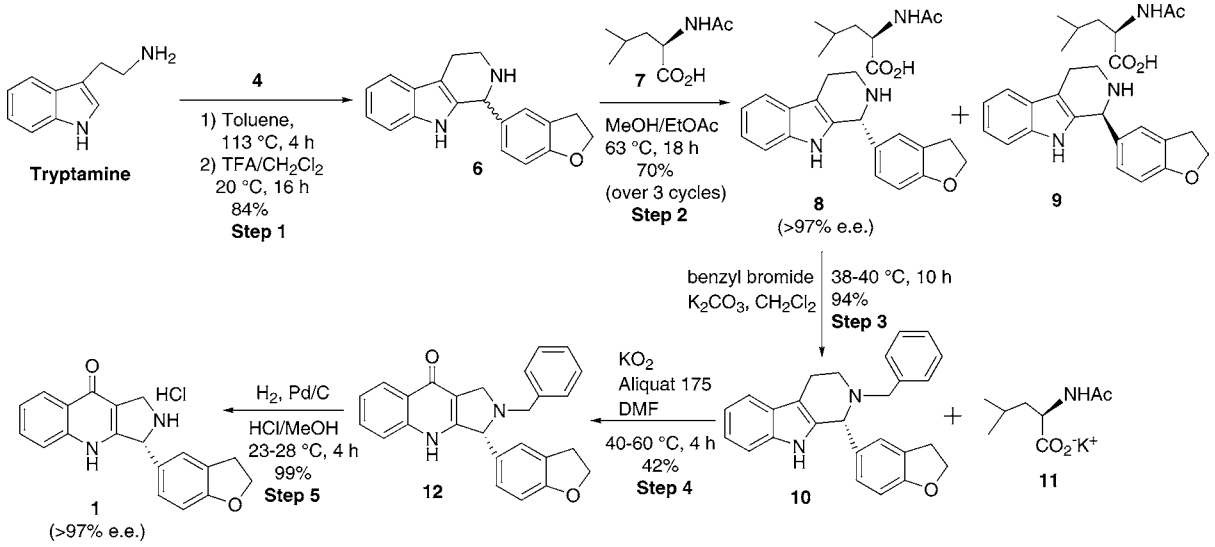
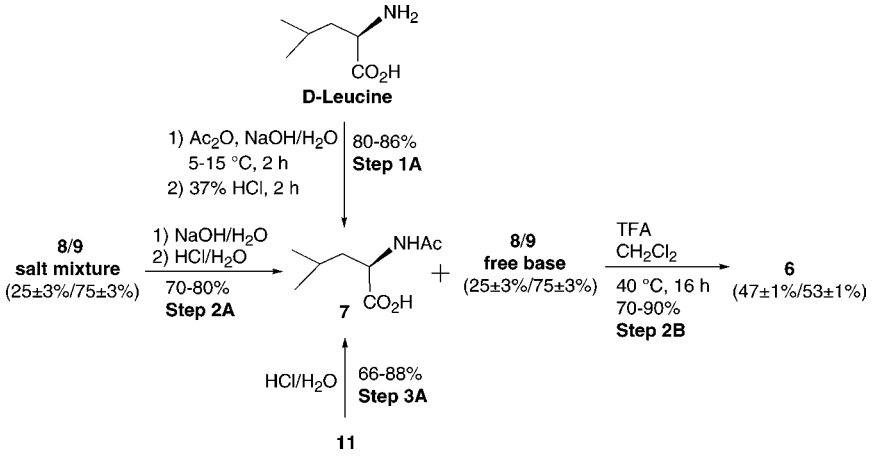
Scheme 2



Scheme 3



5-carboxaldehyde (**4**) in toluene to form the Schiff base in situ, followed by an acid-catalyzed cyclization[3,4] to afford 1-(2,3-dihydrobenzofuran-5-yl)-2,3,4,9-tetrahydro-1*H*-β-carboline (**6**) after recrystallization from EtOAc/hexane (3:5) in good yield (80−84%) and high chemical purity (>97%) (Scheme 2).

A two-step chemical resolution of racemic β-carboline with chiral acids has been reported.[5] However, due to the low yields reported for this method, we decided to investigate a more straightforward and inexpensive method that used *N*-acetyl-D-leucine (**7**) as the chiral resolving agent.[6] The *N*-acetyl material was readily prepared in high chemical yield and optical purity by treatment of D-leucine with acetic anhydride (Scheme 3).[7]

The chemical resolution of β-carboline **6** was originally achieved by the treatment of **6** with 1 equiv of **7** in MeOH to afford the desired 1-(*R*)-β-carboline *N*-acetyl-D-leucine salt **8** in a low yield (21%) but excellent optical purity (≥97% ee, *HPLC Method B*). A drawback to this procedure was that the salt **8** in MeOH was too thick for efficient filtration. This limitation was overcome by the addition of EtOAc, which also increased the isolated yield of **8** to the 32−35% range with the same chiral purity (≥97% ee). A few other solvents (such as EtOAc, acetone, IPA, and EtOH) were also examined for this resolution step in an effort to provide a more fluid and manageable salt. In the case of EtOAc or acetone, no resolution was obtained, while EtOH and IPA gave mixed results. In summary, the treatment of racemic β-carboline **6** with **7** in a mixed MeOH/EtOAc solvent system (4.4/1.0) afforded 1-(*R*)-β-carboline *N*-acetyl-D-leucine salt **8** in 35% yield with high chiral purity (≥97% ee) (Scheme 2). When the enantiomeric purity of the isolated salt **8** dropped below 97% ee, the optical purity could be improved by a MeOH/EtOAc (5.0/1.0) reslurry (see Experimental Section).

To make this process more economical and useful, the filtrate that contained the enriched 1-(*S*)-β-carboline **9**

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mixture (**8**/**9**, 25 ± 3%/75 ± 3%) was recycled. The resolving reagent **7** was recovered after an alkaline/acid treatment (Scheme 3, step 2A) and was obtained in 70−80% yield with the retention of chiral purity (≥97% ee). The β-carboline **8**/**9** free base mixture was readily racemized to a near racemic mixture (47 ± 1%/53 ± 1%) in 70−90% isolated yield after treatment with TFA for 16 h (Scheme 3, step 2B).[3] Both the racemized free base and recycled *N*-acetyl-D-leucine (**7**) were used in the resolution step 2 (Scheme 2) to afford an additional 35% (after two recycles) of 1-(*R*)-salt **8** (≥97% ee). This recycle process could be done at least three times without introducing new impurities. The successful recovery of the resolving reagent **7** and the racemization of the undesired 1-(*S*)-salt **9** allowed this classic resolution route to be an efficient approach for scale-up production of the target 3-(*R*)-pyrroloquinolinone **1**.

The 1-(*R*)-β-carboline *N*-acetyl-D-leucine salt **8** was directly converted to 1-(*R*)-2-benzyl-β-carboline **10** in excellent yield, without interference of the resolving reagent **7** (Scheme 2). Treatment of salt **8** with an excess of K_2CO_3 in CH_2Cl_2 generated 1-(*R*)-β-carboline **8** as its free base in situ; addition of benzyl bromide afforded 1-(*R*)-2-benzyl-β-carboline **10**. This step converts *N*-acetyl-D-leucine (**7**) into the insoluble potassium salt (**11**), which was isolated by simple filtration of the reaction mixture in almost quantitative yield with excellent chemical and optical purity (≥97% ee). The filter cake **11** was dissolved in water and acidified to recover **7** (Scheme 3, step 3A) in 66−88% yield with high chiral purity (≥97% ee). This benzylation reaction was also conducted in nonhalogenated solvents such as acetone or acetonitrile; however, 3−5% of potassium salt **11** was found in the filtrate. Of interest was that the benzylation reaction only took 3 h in acetone vs 10 h in CH_2Cl_2.

The earlier reported oxidation of **10** from our laboratories used *t*-BuOK/O_2/DMF to afford 3-(*R*)-2-benzylpyrroloquinolinone **12** in 45% yield;[3] however, this yield declined to 20% on scale-up, and the product **12** required purification by column chromatography. A modified Winterfeldt condition[8] that used low-cost potassium superoxide (see the cautionary note in the Experimental Section) was reported, and it was suitable for base-sensitive substrates.[9] Some limitations of this procedure were that it required the use of one full equivalent 18-crown-6 as the phase transfer catalyst (PTC), a long reaction time (∼16 h), and the crude product **12** required chromatographic purification.[9] Based on these limitations, it was decided to explore a less expensive PTC reagent, such as Aliquat 175 (methyltributylammonium chloride). This reagent was found to be better than 18-crown-6, Et_4NBr, or Aliquat 366 since only 20 mol % was needed and since it was easy to remove during the workup. In fact, when this reaction was run in DMF, the 1-(*R*)-2-benzyl-β-carboline **10** was completely consumed in 4 h. After workup, the crude mixture that contained 70−82% of the desired 3-(*R*)-2-benzylpyrroloquinolinone **12** was crystallized from MeOH to afford **12** in 36−42% isolated yield with high chemical (>98%) and chiral (≥97% ee) purity (Scheme 2).

Finally, removal of the benzyl group was accomplished by hydrogenolysis using 5% Pd/C (6.6 mol %) in methanol with 1 equiv of HCl. The desired product, 3-(*R*)-pyrroloquinolinone **1**, was isolated quantitatively as its hydrochloride salt. The isolated product **1** had excellent chemical and chiral purity (≥97% ee), and none of the over-reduced product was detected.[3]

Conclusions

In summary, we have developed an efficient, reproducible, and economical process for the large-scale production of 3-(*R*)-pyrroloquinolinone **1**. The yield of desired 1-(*R*)-β-carboline *N*-acetyl-D-leucine salt **8** was significantly improved with the successful recycling of the resolving reagent **7** and racemization of the β-carboline **8**/**9** free base mixture. One synthetic step was removed from the original sequence by direct conversion of *N*-acetyl-D-leucine salt **8** to 1-(*R*)-2-benzyl-β-carboline **10**. The replacement of 18-corwn-6 with Aliquat 175 as PTC in the modified Winterfeldt oxidation not only further reduced the reagent cost but also enabled a nonchromatographic preparation of 3-(*R*)-2-benzylpyrroloquinolinone **12**. Also, there were no chromatographic purifications needed for all intermediates as well as the final product **1**. The overall yield for this five-step synthesis was 22% as compared to the earlier reported six-step asymmetric route that was 18%.[3]

Experimental Section

Starting materials, reagents, and solvents were obtained from commercial suppliers and were used without further purification. Water used in each experiment was deionized water. The phrase "under house vacuum" is ∼160 mmHg of vacuum pressure, except where specified. The aqueous pH was measured by pH indicator strips (colorpHast pH 0−14, EM Science). All melting points were uncorrected and determined on an MEL-TEMP 3.0 apparatus. ^{1}H NMR spectra were recorded at 300 Hz on a Bruker Avance-300 instrument, while mass spectra were recorded on an Agilent Series 1100 LC/MS instrument.

The chemical and optical purities of the intermediates and final product were all determined on an Agilent Series 1100 HPLC system by *Methods A* and *B*, respectively. *Method A* for chemical purity: ZORBAX Ecilipse XDB-Phenyl column (4.6 mm ID × 150 mm, 3.5 micron) at 40 °C with a flow rate of 1.0 mL/min and a run time of 10.0 min. UVmax = 254 and 280 nm. Solvents: A 80% H_2O + 0.05% TFA, B 20% ACN; Gradient: B 20%/0.0 min, 20%/1.0 min, 90%/6.0 min, 90%/8.0 min, 55%/9.0 min, 20%/10.0 min. *Method B* for optical purity: CHIRALPAK AD-RH (4.6 mm ID × 100 mm, 3.5 micron) at 20 °C with a flow rate of 1.0 mL/min and with a run time of 20.0 min. UVmax = 254 and 280 nm. Solvents: A 90% IPA, B 10% hexane. The chemical and optical purities of *N*-acetyl-D-leucine and its potassium or sodium salts were determined by *HPLC Methods C* and *D*, respectively. *Method C* for chemical purity: Supelcosil

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LC-8DB column (4.6 mm ID × 150 mm, 5 micron) at 20 °C with a flow rate of 1.0 mL/min and a run time of 20.0 min. UVmax = 210 nm. Solvents: A H_2O + 0.05% TFA, B MeCN+ 0.05%; Gradient: B 5%/0.0 min, 50%/0−10 min, 50%/10−12 min, 5%/12−13 min, 5%/13−20 min. Retention time 7.0 min/*N*-acetyl-D-leucine. *Method D* for optical purity: CHIRALPAK AD (4.6 mm ID × 250 mm, 3.5 micron) at 20 °C with a flow rate of 1.0 mL/min and with a run time of 15.0 min. UVmax = 210 nm. Solvents: A 25% IPA, B 75% hexane + 0.05% TFA. Retention time 5.1 min/*N*-acetyl-D-leucine, 6.0 min/*N*-acetyl-L-leucine. All reactions were carried out in a 4-neck round-bottom flasks (RBFs, 1−22 L), each equipped with a thermocouple controller, an overhead mechanical stirrer, a condenser, a pressure-equalization addition funnel, a nitrogen inlet/outlet, and, when required, a Dean−Stark trap.

Step 1. 1-(2,3-Dihydrobenzofuran-5-yl)-2,3,4,9-tetrahydro-1*H*-β-carboline (6).[3] A 22-L RBF under nitrogen was charged with toluene (10.0 L) and tryptamine (98%, 980.8 g, 6.0 mol) followed by the addition of 2,3-dihydrobenzo-[*b*]furan-5-carboxaldehyde (**4**) (97%, 916.5 g, 6.0 mol). The mixture was gradually heated to 110−114 °C (beginning azeotropic boiling point was 88 ± 2 °C) and refluxed for 4 h. Water (108 mL) was collected in a Dean−Stark trap. The solvent was removed by distillation under reduced pressure, and the resulting thick yellow semisolid was cooled to 40 °C. Methylene chloride (9.0 L) was added with slow agitation, and the suspension was cooled to 0 °C. TFA (99+%, 1368.2 g, 12.0 mol) was added over a 40-min period. The reaction was then warmed to 20 °C and stirred for 16 h. This mixture was washed with saturated $NaHCO_3$ solution (12.0 L), and the organic phase was separated. The solution was transferred to a 22-L vessel, and the solvents were removed by distillation. To the resulting thick slurry was added EtOAc (3.0 L) at 50 °C with mild stirring followed by the addition of hexane (5.0 L). After the mixture was heated to reflux for 10 min and cooled, it was seeded at 20 °C and the solution was placed in a freezer at 4 °C for 16 h. The crystalline solid was collected by filtration, washed with hexane, and dried in a vacuum oven under house vacuum at 55 °C for 18 h. There was obtained 1469 g (84% yield, HPLC = 97.4%, area%, *Method A*) of β-carboline **6** as a yellowish solid. ^{1}H NMR (300 MHz, *CDCl*$_3$) δ 2.63−3.04 (m, 2 H), 3.08 (t, *J* = 8.3 Hz, 2 H), 3.05−3.21 (m, 1 H), 3.26−3.44 (m, 2 H), 4.51 (t, *J* = 8.6 Hz, 2 H), 5.15 (s, 1 H), 6.74 (d, *J* = 7.8 Hz, 1 H), 6.98−7.28 (m, 5 H), 7.53 (d, *J* = 7.9 Hz, 1 H), 10.1 (s, 1 H). MS: 291 (MH^+), 262, 248.

Step 1A. *N*-Acetyl-D-leucine (7).[7] A 22-L RBF was charged with H_2O (2.45 L) and D-leucine (optical purity 99%, 917.0 g, 7.0 mol). Acetic anhydride (99%, 2142.0 g, 21.0 mol) and 2 N aqueous NaOH (2.45 L, 49.0 mol) were added simultaneously over a 3−4 h period, while the reaction temperature was maintained between 5 and 15 °C (the reaction mixture was always kept slightly alkaline pH = 8−9). After the addition was completed, the mixture was agitated for 1 h and then cautiously acidified with a 37% HCl solution (4.76 L, 49.0 mol) over a 30-min period. A white solid precipitated, and the slurry was stirred for 2 h between 5 and 15 °C. The resulting solid was isolated by filtration, washed with H_2O (2.0 L × 7), dried by air suction for 3 h, and then placed in a vacuum oven under house vacuum at 60 °C for 16 h. There was obtained 1083 g (89%) of *N*-acetyl-D-leucine **7** as a white powdery solid (97.8% ee, *Method B*). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83 (d, *J* = 1.9 Hz, 3 H), 0.91 (d, *J* = 2.0 Hz, 3 H), 1.32−1.50 (m, 2 H), 1.51−1.69 (m, 1 H), 1.85 (s, 3 H), 4.18 (dd, *J* = 1.8, 2.0 Hz, 1 H), 8.06 (d, *J* = 1.2 Hz, 1 H), 12.40 (s, 1 H). MS: 174 (MH^+), 196 (MNa^+), 131.

Step 2. Resolution of β-Carboline 6 with *N*-Acetyl-D-leucine (7). A 22-L RBF was charged with MeOH (6.6 L) and *N*-acetyl-D-leucine **7** (optical purity 97.8%, 904.3 g, 4.96 mol). The resulting clear solution was heated to 50 °C, and β-carboline **6** (97%, 1500 g, 4.96 mol) was added portion-wise over a 2-min period. After the mixture was stirred for 5 min, EtOAc (1.5 L) was added slowly over a 3-min period and then the thick slurry was heated to 62−65 °C for 30 min. The mixture was allowed to gradually cool to 20 °C over a 2−3 h period, seeded with a crystal of 1-(*R*)-1-(2,3-dihydrobenzofuran-5-yl)-2,3,4,9-tetrahydro-1*H*-β-carboline *N*-acetyl-D-leucine salt **8**, and slowly agitated at 20 °C for an additional 18 h. The solid was collected by filtration, and the cake was washed with ice-cold MeOH (0.7 L × 3). The solid was dried by air suction for 1 h under nitrogen and then placed in a vacuum oven under house vacuum at 60 °C for 24 h. There was obtained 727.0 g (32% yield, 98.4% ee, *Method B*) of the salt **8** as an off-white solid. The mother liquor that contained the enriched (*S*)-enantiomer **9** (**8**/**9**, 25 ± 3/75 ± 3) mixture was saved for recycle (see steps 2A and 2B).

If the purity of the 1-(*R*)-β-carboline salt **8** was <97% ee, it was reworked; for example, a 667.0 g amount of 1-(*R*)-β-carboline salt **8** with 95% ee was reslurried in a mixture of MeOH/EtOAc (1.0 L/0.2 L) to afford 610.0 g of pure salt **8** with 98% ee after filtration and drying.

Step 2A. Recovery of *N*-Acetyl-D-leucine (7). After the isolation of the salt **8**, the mother liquor was concentrated to dryness and the resulting material was dissolved in CH_2Cl_2 (6.0 L) and transferred to a 12-L separatory flask. The organic solution was agitated vigorously with 1 N NaOH (3.0 L) for 15 min. After the phase separation, the organic phase was concentrated to dryness and the resulting solid was used for racemization (see step 2B). The aqueous phase (6.0 L) was cooled in an ice bath and carefully acidified to pH ∼1 with concentrated HCl solution (37%, 1.3 L) with rapid agitation. The white solid was isolated by filtration and washed with cold H_2O (0.2 L × 2). The solid was dried by air suction and placed in a vacuum oven under house vacuum at 60 °C for 16 h. There was obtained 628.0 g (73% yield) of recovered *N*-acetyl-D-leucine (**7**) as a white solid, of which the spectroscopic and optical (97.0% ee) properties were identical to that from step 1A. This material was used in the resolution again without further purification.

Step 2B. Racemization of β-Carboline Free Base Mixture (8/9, 25 ± 3%/75 ± 3). A 12-L RBF was charged with β-carboline free base mixture **8/9** (1572 g, 3.39 mol, 23%/77%, recovered from step 2A) and CH_2Cl_2 (6.7 L). The

stirred suspension was cooled in an ice bath to 10 °C, and TFA (99+%, 684.0 g, 6.0 mol) was added dropwise over a 30-min period. After the addition, the reaction was gently heated to reflux at 40 °C for 16 h, and the progress of racemization was determined by chiral HPLC (*Method B*) until complete racemization of **8/9** (free base) was observed. The solution was cooled to 20 °C and vigorously agitated while a 7% NaOH solution (4.3 L, 7.5 mol) was added over a 20-min period. The organic phase was separated, washed with brine (2.0 L), and concentrated to dryness. The resulting material was placed in a vacuum oven under house vacuum at 60 °C for 16 h. There was recovered 912.3 g (93% yield) of racemized product (**8/9**, 48%/52%).

This mixture was resolved with recovered *N*-acetyl-D-leucine **7** (from step 2A) to give an additional 26% yield of the desired 1-(*R*)-*β*-carboline salt **8** with high chiral purity (98.0% ee, *Method B*).

Step 3. 1-(*R*)-1-(2,3-Dihydrobenzofuran-5-yl)-2-benzyl-2,3,4,9-tetrahydro-1*H*-*β*-carboline (10). A 22-L RBF was charged with *N*-acetyl-D-leucine salt **8** (1368 g, 2.95 mol) and CH_2Cl_2 (12.0 L) with stirring under nitrogen. Solid K_2CO_3 (98+%, 913.5 g, 6.49 mol) was added over a 3-min period. After stirring for 10 min at 20 °C, benzyl bromide (98%, 520.0 g, 2.98 mol) was added over a 20-min period and the suspension was agitated at 20 °C for 30 min. The reaction was then gently heated to 38 ± 2 °C and stirred for 10 h. The reaction was cooled to 20 °C, and the white solid was isolated by filtration. The filter cake was washed with CH_2Cl_2 (2.0 L × 2) and saved for step 3A. The combined organic phase was condensed in vacuo, and the resulting off-white yellowish solid was dried in a vacuum oven under house vacuum at 60 °C for 16 h. There was obtained 1054.0 g (94% yield) of 1-(*R*)-2-benzyl-*β*-carboline **10** with 98% chemical purity (*Method A*) and 99% ee (*Method B*). The 2-benzyl compound **10** was used in the next step without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.53−2.61 (m, 1 H), 2.67−2.80 (m, 2 H), 2.98−3.06 (m, 1 H), 3.13 (t, J = 8.4 Hz, 2 H), 3.44 (d, J = 11.8 Hz, 1 H), 3.76 (d, J = 12.2 Hz, 1 H), 4.48 (t, J = 8.2 Hz, 2 H), 4.64 (s, 1H), 6.72 (d, J = 7.8 Hz, 1 H), 6.81−7.03 (m, 2 H), 7.08 (dd, J = 1.1, 7.6 Hz, 1 H), 7.14−7.28 (m, 3 H), 7.29−7.36 (m, 4 H), 7.40 (d, J = 7.5 Hz, 1 H), 10.24 (s, 1H). MS 381 (MH^+), 403 (MNa^+), 276, 262.

Step 3A. Recovery of *N*-Acetyl-D-leucine (7). A 12-L RBF was charged with potassium *N*-acetyl-D-leucine salt **11** from step 3 and H_2O (3.5 L). The solution was cooled to 4 °C in an ice bath, and then a 37% HCl solution (1.5 L) was carefully added over a 30-min period. The agitation was continued for an additional 30 min. The white solid was isolated by filtration and washed with cold H_2O (1 L × 2), and the cake was dried as described in step 2A. There was obtained 410.0 g (80% yield) of recovered *N*-acetyl-D-leucine **7** as an off-white solid, of which the spectroscopic and optical properties were identical to compound **7** made from step 1A.

This material was combined with that from step 2A and used in the resolution of racemate **6** without further purification.

Step 4. 3-(*R*)-2-Benzyl-3-(2,3-dihydrobenzofuran-5-yl)-1,2,3,4-tetrahydro-pyrrolo[3,4-*b*]quinolin-9-one (12).[9] A 5-L RBF was charged with DMF (1.5 L) and potassium superoxide (96%, 255.6 g, 3.6 mol) with agitation under nitrogen followed by Aliquat 175 (methyltributylammonium chloride, 75 wt % in H_2O, 39.1 mL, 0.12 mol). The mixture was warmed to 40 °C for 20 min, and then a solution of 1-(*R*)-2-benzyl-*β*-carboline **10** (228.0 g, 0.60 mol) in DMF (0.5 L) was added over a 30-min period while the reaction temperature was maintained between 40 and 60 °C. After the addition was complete, the heating mantle was replaced with a water bath, and the reaction was agitated at 40−60 °C for 4 h (see **Note** below). The reaction was cooled to 20 °C using an ice−water bath, and the resulting orange slurry was slowly transferred to a 22-L RBF that contained H_2O (3.6 L) and ice (3.6 kg) with rapid agitation. The yellowish slurry was stirred for 30 min and acidified with 3 N HCl solution (0.7 L) to pH = 8−9. The solid was isolated by filtration, washed with H_2O (0.5 L × 2), and dried by air suction. This crude material was placed in a vacuum oven under house vacuum at 60 °C for 16 h. There was obtained 145.0 g (61% yield) of crude compound **12**. Recrystallization of the crude material in refluxing CH_3OH (650 mL) afforded 99.8 g (42% yield) of 1-(*R*)-2-benzylpyrrolidinequinolinone **12** as pale-yellowish solid (97.2% ee; *Method B*), which was used in the next step without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.05−3.22 (m, 2 H), 3.52 (dd, J = 1.4, 9.8 Hz, 1 H), 3.61 (d, J = 12.4 Hz, 1 H), 3.82 (d, J = 12.1 Hz, 1 H), 3.92 (dd, J = 1.1, 9.6 Hz, 1 H), 3.98−4.16 (br s, 1 H), 4.54 (t, J = 8.6 Hz, 2 H), 5.05 (s, 1H), 6.82 (d, J = 7.9 Hz, 1 H), 7.13 (d, J = 7.2 Hz, 1 H), 7.13−7.38 (m, 6 H), 7.48−7.63 (m, 2 H), 8.08 (d, J = 7.8 Hz, 1 H), 11.40 (s, 1H). MS 395 (MH^+), 417 (MNa^+), 811 ($2MNa^+$).

Note: An ARC bomb determination showed that exothermic decomposition starts at 39 °C with increased decomposition at 60 °C and significant pressure buildup at 60−70 °C. Therefore, careful control of the internal reaction temperature below 60 °C is very important.

Step 5. 3-(*R*)-3-(2,3-Dihydrobenzofuran-5-yl)-1,2,3,4-tetrahydropyrrolo[3,4-*b*]quinolin-9-one Hydrogen Chloride Salt (1).[3] A 6-L Parr pressure reactor was charged with **12** (319.2 g, 0.81 mol) and CH_3OH (1.8 L) with stirring under nitrogen. To this mixture was added a 6 N HCl solution (0.136 L) over a 3-min period followed by the addition of 5% Pd/C (115.2 g, 6.6% mol of Pd). The system was closed and purged with nitrogen (× 2) followed by hydrogen (× 2). The reaction was carried out at 23−28 °C under H_2 pressure (50 psi) with moderate agitation (400 rpm) for 4 h. The progress of the reaction was determined by HPLC (*Method A*). After the completion of the reaction, the catalyst was removed by filtration through a Celite 545 short cartridge and the filter cake was washed with CH_3OH (0.2 L × 4). The filtrate was condensed in vacuo, and the resulting material was placed in a vacuum oven under high vacuum (~10 mmHg) at 60 °C for 24 h. There was obtained 275.4 g of 3-(*R*)-quinolinopyrrolidine HCl salt **1** as a greenish solid in excellent yield (99.8%) and optical purity (98.1% ee, *Method B*). ^{1}H NMR (300 MHz, CD_3OD) δ 3.24 (t, J = 8.1

Hz, 2 H), 3.46 (t, J = 8.0 Hz, 2 H), 4.61 (t, J = 8.4 Hz, 2 H), 4.68 (d, J = 6.2 Hz, 2 H), 6.26 (s, 1 H), 6.88 (d, J = 8.0 Hz, 1 H), 7.12 (dd, J = 0.8, 7.0 Hz, 1 H), 7.26 (s, 1 H), 7.52 (dd, J = 6.6, 6.8 Hz, 1 H), 7.65 (d, J = 7.9 Hz, 1 H), 7.71−7.82 (m, 1 H), 8.31 (d, J = 7.8 Hz, 1 H). MS 305 (MH^+), 327 (MNa^+).

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