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A Facile Preparation of an Octahydropyrrolo[2,3-*c*]pyridine Enantiomer

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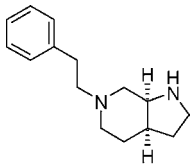
Abstract:

A facile synthesis of octahydro-pyrrolo[2,3-*c*]pyridine 1 using an intramolecular [3+2]-cycloaddition of an azomethine ylide as the key step and employing DW-therm heat-transfer fluid as a solvent is disclosed. Enantiomerically pure 1 was obtained either via a chromatographic separation of the diastereoisomers 12 and 13 resulting from the cycloaddition with a chiral appendage or by a classical resolution of racemate 19.

Inhibitors of apoptosis proteins (IAPs) have been implicated as having a role in cancer by blocking the activity of caspases, thereby preventing programmed cell death of these diseased cells. A proapoptotic mitochondrial protein, Smac, is capable of neutralizing IAPs by binding to a peptide binding pocket on the surface of a key domain (BIR3) of the IAPs thereby precluding their interaction with Caspase 9.[1] Utilizing structure-based drug design we have considered and synthesized several peptidomimetic scaffolds of the Smac ligand which exhibit good in vitro activity in multiple tumor cell lines. One highly potent compound, contains the bicyclic amine core structure **1**, which presented a considerable synthetic challenge. The research synthesis, which will be discussed in a subsequent publication, was sufficient for preparing small quantities of the compound. Further refinement of the procedure has permitted the production of the desired compound on large scale for further studies. The culmination of our effort is the subject of this communication.

The initial synthesis of bicyclic amine **1** involved the use



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of bicyclic lactam **2** as the key intermediate.[2] Bicyclic amines such as **2** are often prepared on small scale via cycloaddition of azomethine ylides (**3**) which are formed by thermolysis of aziridines **4** (Scheme 1).[2−7] This protocol (320−350 °C in a sealed tube) is not convenient for scale-up purposes. Lower temperature (e.g., 110 °C) led to significant decomposition of aziridine **4** as reported earlier.[4b,7]

We utilized a two-pronged approach to provide the supply of **1** in sufficient quantities. The first approach involved the use of a chiral appendage to facilitate the chromatographic separation of diastereomeric isomers resulting from the cycloaddition. The second method was the use of classical resolution for separating the enantiomers.

Approach Using a Chiral Appendage. Synthesis of **1** (Scheme 2) started with the alkylation of 4-bromo-1-butene (**5**) with 2-phenylethylamine (**6**) in the presence of potassium carbonate affording pure **7** (69%) as an oil after distillation (70 °C/0.25 mmHg). For the second piece, alkylation of 2,3-dibromopropionate (**8**) with (*R*)-naphthylethylamine (**9**) using potassium carbonate as the base furnished aziridine ester **10** (96% yield) as an oil after purification by silica gel chromatography. A three-step, one-pot operation involving saponification of ester **10** with potassium trimethylsilanoate, reaction of the resulting potassium carboxylate with pivaloyl chloride, and condensation of the mixed anhydride formed in situ with amine **7** generated aziridine amide **11** in quantitative yield. For the cycloaddition reaction, we chose to utilize an unconventional solvent DW-therm,[8] typically used as a commercial heat-exchange fluid. DW-therm, a mixture of triethoxyalkylsilanes, is a nonviscous, nonhazardous liquid with reported boiling and flash points of 240 °C and 101 °C, respectively. From safety and temperature-control points of view, this liquid is an ideal solvent for the desired cycloaddition reaction. Heating **11** in DW-therm at

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(8) DW-therm, a heat transfer fluid for Huber Cooling and Heating Unistats, was purchased from the Huber Corporation of Germany at www.huber-online.com.

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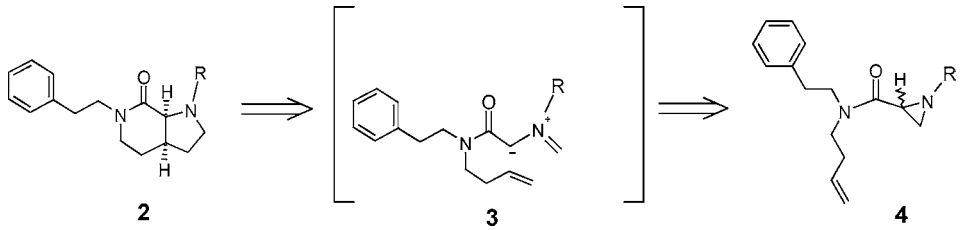
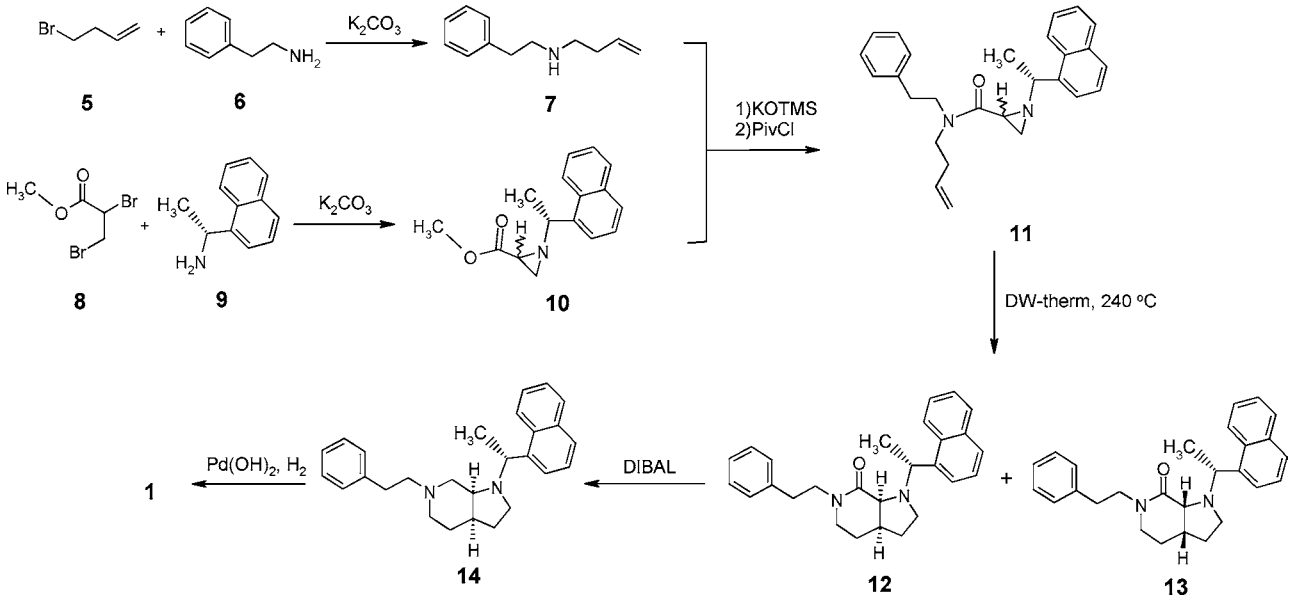
Scheme 1



Scheme 2



240 °C (refluxing conditions) under a nitrogen atmosphere for 20 min afforded a mixture of diastereoisomers **12** and **13** (1:1 ratio) in approximately 90% yield, superior to most of the yields reported for this type of cycloaddition. After the reaction, DW-therm was separated from the products by vacuum distillation and, consistent with green chemistry principles, could be reused. About 2 kg of the diastereomeric mixture of **12** and **13** were produced in five runs using a typical 5-L, three-necked reaction flask. The desired isomer **12** was isolated by silica gel chromatography in 94% diasteromeric excess. Further purification by recrystallization from *tert*-butyl methyl ether/heptane furnished lactam **12** with 99.5% optical purity and an overall yield of 61% of the theoretical yield from **10**. The absolute configuration of **12** was confirmed by a single-crystal X-ray (Figure 1). It is noteworthy that the outcome of this cycloaddition employing other high-boiling solvents such as DMSO (180 °C), 1,3,5-triisopropylbenzene (230 °C), mineral oil (250 °C), or tetramethylethylene sulfone (250−270 °C) was not satisfactory.

Reduction of optically pure **12** with DIBAL, followed by quenching with EtOAc and sat. aqueous $NaHCO_3$ solution furnished **14** as an oil in quantitative yield. This quench procedure generates a granular aluminum salt that is easily separated from the product by filtration. Oily **14** was purified by silica gel chromatography to remove any residual metal that could poison the subsequent catalytic hydrogenation reaction. This resulted in an 84% recovery of **14** which solidified upon standing. Removing the chiral appendage by hydrogenation with $Pd(OH)_2$ as the catalyst furnished octahydro-pyrrolo[2,3-*c*]pyridine **1** in 85% yield with high chemical (>99%) and optical (>99.9%) purity.

Resolution Approach. As observed above, the chiral appendage employed in the first approach did not provide any selectivity in favor of the desired isomer **12.** Rather, the only role it served was to enable the chromatographic separation of the enantiomers **12** and **13**. Therefore, we turned our attention to a simpler strategy: using a racemic precursor for the cycloaddition in anticipation that the final octahydro-pyrrolo[2,3-*c*]pyridine **1** could be obtained by a simple resolution of the corresponding racemate. Aziridine amide **16** (Scheme 3) was prepared in good yield using a similar approach to the preparation of **11**. Cycloaddition of

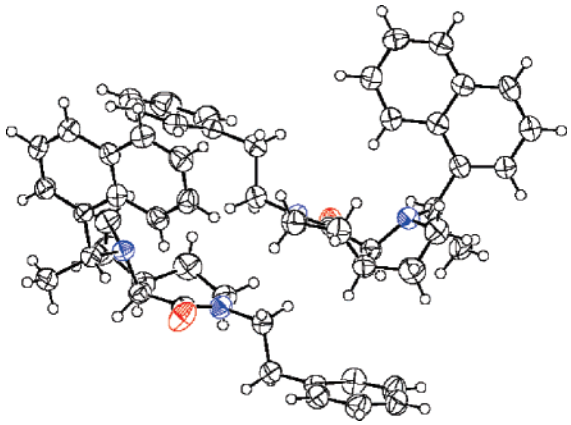
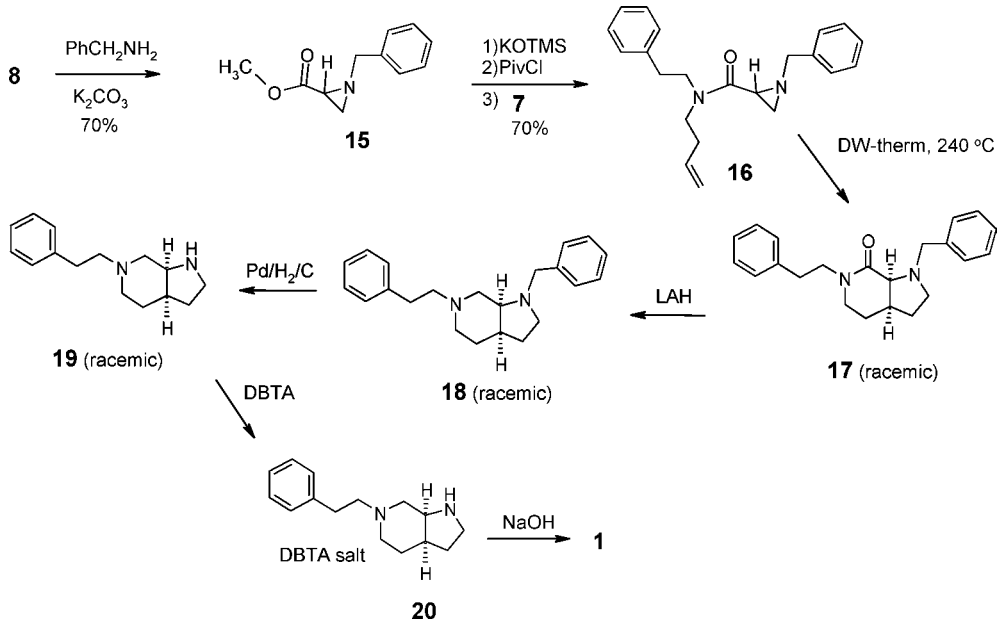


Figure 1.

Scheme 3



16 in DW-therm at 240 °C furnished *cis*-bicyclic amide **17** in 80% yield as a racemic mixture. Reduction of **17** with lithium aluminum hydride, and subsequent removal of the benzyl group by hydrogenation provided the racemic octahydro-pyrrolo[2,3-*c*]pyridine **19** in 64% yield over two steps. Resolution of **19** using (+)-dibenzoyl-D-tartaric acid afforded the tartrate salt **20** with 99% ee in 92% of the theoretical yield. Treating the tartrate salt with aqueous NaOH solution afforded **1** in 97% yield and 99% ee.

In conclusion, we have developed a simple and efficient (90% yield) protocol for the intramolecular [2+3] cycloaddition of azomethine ylides using commercially available DW-therm as a solvent and requiring no special equipment. This methodology was employed successfully for manufacturing large quantities of enantiomerically pure octahydro-pyrrolo[2,3-*c*]pyridine, **1**, an important intermediate in the preparation of IAP inhibitors.[2]

Experimental Section

General. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AVANCE DPX-500 spectrometer (^{1}H NMR at 500 MHz). Reactions were carried out under an atmosphere of nitrogen.

But-3-enyl-phenethylamine (7). Into a 12-L, four-necked flask equipped with a mechanical stirrer, a thermometer and an addition funnel were charged phenethylamine **6** (2 kg, 16.7 mol), potassium carbonate (766 g, 5.6 mol, 325 mesh), and acetonitrile (8 L) under a nitrogen atmosphere. 4-Bromo-1-butene **5** (576 g, 5 mol) was added slowly at 20−25 °C over a period of 30 min. After the addition, the mixture was heated to 50 °C and stirred for an additional 3 h. The mixture was cooled to rt and stirred for an additional 12 h. The stirrer was stopped, and any solid was allowed to settle. The supernatant (organic solution) was separated from the solid by siphoning. The remaining solid was filtered through a pad of Celite, which was rinsed with acetonitrile (1 L). The organic phases containing **7** were combined and evaporated under vacuum. The remaining concentrate was distilled under high vacuum to remove excess phenethylamine until its content in the pot residue was 1% or less. The remaining oil, compound **7**, was used as is. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20−7.35 (m, 5H), 5.79 (m, 1H) 5.00−5.10 (m, 2H), 2.92 (m, 2H), 2.84 (t, J = 6.8 Hz, 2H), 2.73 (t, J = 6.8 Hz, 2H), 2.27 (m, 2H).

1-((*R*)-1-Naphthalen-1-yl-ethyl)aziridine-2-carboxylic acid methyl ester (10). Into a 22-L, four-necked flask equipped with a mechanical stirrer, a thermometer, and an addition funnel were charged (*R*)-(+)-1-(1-naphthyl)ethylamine **9** (823 g, 4.8 mol) and acetonitrile (12.5 L) under a nitrogen atmosphere. To this solution were added potassium carbonate (1.33 kg, 9.6 mol) and 2,3-dibromopropionate **8** (1.42 kg, 5.8 mol). The mixture was heated to 60 °C and stirred for an additional 2 h. The mixture was cooled to rt and stirred for another 16 h. Any solid was removed by filtration. The filtrate was concentrated under vacuum to obtain an oily residue. The oil was dissolved into *tert*-butyl methyl ether (2 L) and hexane (1 L), filtered through a pad of Celite, and concentrated under vacuum to yield a brown oil (1.52 kg). The oil was purified by chromatography (silica gel; ethyl acetate/heptane, 35:65) to obtain product **10** as an oil (1.18 kg, 96% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75−8.05 (m, 4H), 7.50 (m, 3H), 3.84 (s, 1.2H), 3.72 (s, 1.8H), 3.35 (m, 1H), 2.50 (s, 0.6H), 2.37 (m, 0.4H), 2.25 (s, 0.4H), 2.10 (m, 0.6H), 1.95 (d, J = 6.4 Hz, 0.6H), 1.60−1.70 (m, 3.4H).

1-((*R*)-1-Naphthalen-1-yl-ethyl)aziridine-2-carboxylic acid but-3-enyl-((3Z,5Z)-3-vinylhepta-3,5-dienyl)-amide (11). Into a 22-L, four-necked flask equipped with a mechanical stirrer, a thermometer, and an addition funnel were charged aziridine **10** (1.11 kg, 4.35 mol) and THF (11 L) under a nitrogen atmosphere. To the solution was added potassium trimethylsilanolate (558 g, 4.35 mol) over a period of 20 min. After the addition, the mixture was stirred at rt

for an additional 16 h. The mixture was concentrated under vacuum at 30 °C to give an oily residue. The oil was dissolved in dichloromethane (11 L) and cooled to 0 °C. Pivaloyl chloride (551 g, 4.6 mol) was added slowly, and the mixture was warmed to rt, and stirred for an additional 1 h. The mixture was cooled to 0−5 °C, and amine **7** (800 g, 4.57 mol) was added. The mixture was warmed to rt and stirred for an additional 16 h. An aqueous solution of 1 N NaOH (5 L) was added. The organic layer was separated, dried over $MgSO_4$, and concentrated under vacuum at 30 °C to obtain aziridine amide **11** as an oil (1.97 kg), which was used for the next step without further purification.

(3aS,7aS)-1-((*R*)-1-Naphthalen-1-yl-ethyl)-6-phenethyl-octahydropyrrolo[2,3-*c*]pyridin-7-one (12). Into a 2-L, four-necked flask equipped with a mechanical stirrer, a thermometer, and an addition funnel was charged DW-therm (900 g, a mixture of triethoxyalkylsilane, purchased from Huber Corporation[8]) under a nitrogen atmosphere. The solvent was heated to 240 °C. A solution of aziridine amide **11** (443 g, 1.1 mol) in DW-therm (400 g) was added over a period of 45 min, maintaining the batch temperature at 240 °C. After the addition, the mixture was stirred for an additional 20 min. The mixture was cooled to rt and allowed to settle into a two-phase solution. The thick bottom layer was separated and purified by chromatography (silica gel; EtOAc/heptane/diethylamine, 40:60:1) to isolate the first crop of product **12** as a solid. This operation was repeated four more times (3 × 443 g and 1 × 200 g). The combined upper layers were concentrated under vacuum at 60−70 °C/0.5 mmHg until only a small amount of DW-therm was present. The residual oil was purified by chromatography (silica gel; EtOAc/heptane/diethylamine, 40:60:1) to isolate the second crop of product **12**. Both crops of **12** were combined and recrystallized from a mixture of *tert*-butyl methyl ether and heptane to afford bicyclic amide **12** as a solid (529 g, 61% yield from **10**): mp 103−106 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (m, 1H), 7.80 (m, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.47 (d, J = 7.3 Hz, 1H), 7.40 (m, 3H), 7.28 (m, 4H), 7.20 (m, 1H), 5.36 (q, J = 6.7 Hz, 1H), 3.76 (m, 1H), 3.65 (m, 1H), 3.51 (d, J = 8.2 Hz, 1H), 3.35 (m, 1H), 2.92−3.05 (m, 3H), 2.45−2.55 (m, 2H), 2.22 (m, 1H), 1.65−1.80 (m, 2H), 1.57 (d, J = 6.7 Hz, 3H), 1.53 (m, 1H), 1.27 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 140.3, 139.7, 134.4, 132.9, 129.3, 129.0, 128.6, 128.7, 126.8, 125.7, 125.65, 125.61, 125.27, 124.0, 61.9, 52.1, 50.3, 45.6, 4.6, 36.7, 34.6, 29.6, 28.9, 9.5.

(3aR,7aS)-1-(*R*)-1-Naphthalen-1-ylethyl)-6-phenethyl-octahydropyrrolo[2,3-*c*]pyridine (14). Into a 3-L, four-necked flask equipped with a mechanical stirrer, a thermometer, and an addition funnel were charged bicyclic amide **12** (40 g, 0.1 mol) and toluene (600 mL) under a nitrogen atmosphere. The solution was cooled to −70 °C, and a solution of 1.5 M DIBAL in toluene (200 mL, 0.3 mol) was added slowly, maintaining the batch temperature at −70 °C. The mixture was warmed to rt over a period of 45 min and stirred for an additional 2 h. Ethyl acetate (200 mL) was added, maintaining the batch temperature at 20−25 °C. A saturated aqueous solution of $NaHCO_3$ (100 mL) was added, keeping the batch temperature at 20−35 °C. After the addition, the batch was stirred at rt for an additional 1 h. Any white solid was removed by filtration and rinsed with EtOAc. The combined filtrate was washed with 15% aqueous solution of NaCl and concentrated under vacuum at 35 °C to yield an oil (44.3 g). The oil was purified by chromatography (silica gel; EtOAc/heptane/diethylamine, 80:20:1) to obtain product **14** as an oil (36.5 g, 95% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.62 (s, 1H), 7.32−7.52 (m, 3H), 7.10−7.32 (m, 5H), 4.56 (m, 1H), 3.15 (s, 1H), 2.48−2.85 (m, 8H), 2.25 (m, 3H), 1.65−1.90 (m, 4H), 1.55 (d, J = 6.1 Hz, 3H).

1-Benzyl-aziridine-2-carboxylic acid methyl ester (15). To a cool solution of benzyl amine (38.37 g, 360 mmol) in methanol (250 mL) at 5−6 °C was slowly added a solution of 2,3-dibromopropionate (25.27 g, 103 mmol) in methanol (75 mL). The reaction mixture was warmed to 20−25 °C and maintained at this temperature for 18 h. The reaction mixture was concentrated; TBME (500 mL) and water (500 mL) were added. The organic layer with washed water, dried over $MgSO_4$, and concentrated to give yellow oil. The crude was further purified with column chromatography on silica gel (EtOAc/hexanes, 1:1) to give 15.43 g of **15** in 78% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28−7.36 (m, 5H), 3.73 (s, 3H), 3.55 (s, 2H), 2.28 (dd, J = 1.9, 3.8 Hz, 1H), 2.23 (d, J = 1.9 Hz, 1H), 1.78 (d, J = 3.8 Hz). MS ($M + H^+$) 192.

1-Benzyl-aziridine-2-carboxylic acid but-3-enyl-phenethyl-amide (16). To a solution of **15** (9.51 g, 49.75 mmol) in THF (200 mL) was added KOTMS (6.38 g, 49.75 mmol). The mixture was stirred overnight at room temperature. The mixture was concentrated and the residue dissolved in dichloromethane (200 mL) and cooled to 0 °C. Trimethylacetyl chloride (5.94 g, 49.25 mmol) was added slowly, and the mixture was warmed to room temperature over 2 h. The mixture was cooled to −78 °C, and but-3-enyl-phenethylamine (**7**, 8.63 g, 49.24 mmol) was added and stirred at −78 °C for 1.5 h. Saturated sodium bicarbonate (100 mL) was added. The mixture was extracted with EtOAc (4 × 100 mL). The organic extracts were combined, dried, and concentrated under vacuum. The residue was purified by flash chromatography (silica gel; hexane/EtOAc, 1:8) to provide 12.5 g (76%) of the title compound **16**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92−7.24 (m, 10H), 5.6 (dd, J = 4.2, 7.9 Hz, 1H), 4.83−4.9 (m, 2H), 3.55 (s, 2H), 3.1 (t, J = 4.2 Hz, 2H), 3H), 2.7 (t, J = 4.2 Hz, 2H), 2.5 (t, J = 3.8 Hz, 2H), 2.4 (t, J = 3.8 Hz, 2H), 2.3 (dd, J = 1.9, 3.9 Hz, 1H), 2.2 (d, J = 1.9 Hz, 1H), 1.78 (d, J = 3.9 Hz, 1H); MS ($M + H^+$) 355.

(3aS,7aS)-6-Phenethyloctahydropyrrolo[2,3-*c*]pyridine (1). A 2.5-L Parr bottle was charged with 20% $Pd(OH)_2$ on carbon (11.2 g, 50% wet) under nitrogen atmosphere. A solution of compound **14** (56 g, 0.15 mol) in methanol (1 L) was added. The mixture was hydrogenated at 50 psi for 16 h until all **14** was consumed. The mixture was filtered through a pad of Celite under a nitrogen atmosphere, and then the filtrate was concentrated under vacuum at 35 °C to give an oil. The oil containing **1** was dissolved in ethyl acetate. A solution of 6 N HCl in isopropyl

alcohol (27 mL) was diluted with EtOAc (60 mL) and added to the solution containing **1** over a period of 40 min at 18−27 °C. After the addition, the mixture was cooled to 0 °C and stirred for an additional 1 h. Any solid was collected by filtration to obtain **1** as a white hydrochloride salt (33 g, 82% yield): mp 172−178 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12−7.32 (m, 5H), 3.50 (s, 1H), 3.15−3.35 (m, 2H), 2.45−2.95 (m, 8H), 2.20 (s, 2H), 1.95 (m, 1H), 1.70 (m, 2H), 1.45 (s, 1H). By treating the hydrochloride salt with aqueous 1 N NaOH solution, the free base of **1** was obtained as an oil: $[\alpha]^{25}_{Na}$ −11.5 (c = 1, CH_3CN); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15−7.35 (m, 5H), 3.05 (m, 1H), 2.96 (q_{AB}, J = 8.2 and 4.0 Hz, 1H), 2.87 (m, 2H), 2.70 (m, 2H), 2.60 (m, 1H), 2.49 (m, 2H), 2.40 (bs, 1H), 2.30 (dd, J = 11.6 and 3.7 Hz, 1H), 2.02 (td, J = 11.0, 3.0 Hz, 1H), 1.88 (m, 1H), 1.77 (m, 1H), 1.52 (m, 2H), 1.36 (m, 1H). ^{13}C NMR (125 Hz, $CDCl_3$) δ 141.0, 129.1, 128.7, 126.3, 60.9, 58.6, 55.0, 53.0, 44.9, 36.6, 34.1, 31.9, 27.8.

1-Benzyl-6-phenethyloctahydropyrrolo[2,3-*c*]pyridine-7-one (17). A solution of **16** (10.7 g, 32 mmol) in DW-therm (8 mL) was added in 15 min to a flask containing DW-therm (10 mL) at 240 °C. The mixture was stirred for an additional 30 min. DW-therm was distilled off under vacuum, and the residue was purified by flash chromatography on silica gel (EtOAc/hexanes) to give racemic **17** as an oil (7.5 g, 70% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.17 (m, 10H), 4.45 (d, J = 13.4 Hz, 1H), 3.76 (m, 1H), 3.62−3.36 (m, 3H), 3.00 (m, 2H), 2.89 (m, 3H), 2,49 (m, 1H), 2.12 (m, 1H), 1.92 (m, 1H), 1.74 (m, 1H), 1.51 (m, 2H); MS (M + H^+) 335.

1-Benzyl-6-phenethyloctahydropyrrolo[2,3-*c*]pyridine (18). A solution of lithium aluminum hydride (30 mmol, 1 M in THF) was slowly added to a solution of **17** (9.94 g, 30 mmol) in THF (220 mL). The mixture was warmed to 60 °C and stirred for 3 h. Water (1.1 g), 15% aqueous solution of NaOH (1.1 mL), and water (3.4 mL) were added in sequence while stirring continued. The resulting suspension was stirred for an additional 20 min. Any solid was removed by filtration through a Celite bed. The filtrate was washed with water and brine. The aqueous layers were combined and extracted with *tert*-butyl methyl ether, and the organic layers were combined and dried with $MgSO_4$. The solvent was removed under vacuum to afford **18** as a clear amber oil (8.79 g, 92%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.15 (m, 10H), 3.87 (d, J = 13.4 Hz, 1H), 3.59 (d, J = 13.4 Hz, 1H), 3.01 (m, 1H), 2.77 (m, 3H), 2.67−2.45 (m, 5H), 2.44−2.35 (m, 2H), 2.15 (m, 1H), 1.80 (m, 1H), 1.72 (dd. J = 11.9 Hz and 6.4 Hz, 2H), 1.58 (m, 1H); MS (M + H^+) 321.

6-Phenethyloctahydropyrrolo[2,3-*c*]pyridine (19). Compound **18 (**8.65 g, 27 mmol) was dissolved in methanol (250 mL) and stirred with 10% palladium-on-carbon catalyst (1.1 g, 50% wet) under H_2 (60 psi) at rt for 16 h. The reaction mixture was filtered, and the solvent was removed under vacuum to obtain **19** as a yellow oil (6.28 g, 84%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (t, J = 7 Hz, 2H), 7.18 (m, 3H), 3.11 (m, 1H), 3.02 (dd, J = 6.4 Hz and 3.7 Hz, 1H), 2.93 (m, 2H), 2.76 (m, 2H), 2.67 (m, 1H), 2.55 (m, 2H), 2.36 (dd, J = 11.9 Hz and 3.7 Hz, 2H), 2.08 (td, J = 11.0 Hz and 2.8 Hz, 1H), 1.94 (m, 1H), 1.83 (m, 1H), 1.57 (m, 2H), 1.43 (m,1H); MS (M + H^+) 231.

(3aS,7aS)-6-Phenethyloctahydropyrrolo[2,3-*c*]pyridine (1). Compound **19** (16.1 g, 70 mol) was dissolved in a solution of 2-propanol (85 mL) and anhydrous ethanol (127 mL). A solution of (+)-dibenzoyl-D-tartaric acid (25.1 g) in ethanol (84 mL) was added slowly, followed by toluene (425 mL). The mixture was stirred at rt for 16 h. Any solid was collected by filtration, rinsed with a solution of 2-propanol/ethanol/toluene (1:2.5:5, 30 mL), and dried under vacuum (50 °C) to furnish the tartrate salt of **20** (19.0 g): HPLC > 99%; $[\alpha]^{25}_{Na}$ +69.4 (c = 1, CH_3CN/H_2O = 1:1). The tartrate salt was stirred in a mixture of aqueous 1 N NaOH solution and *tert*-butyl methyl ether. The organic layer was separated, washed with water, dried with $MgSO_4$, filtered, and concentrated under vacuum to afford **1** (7.23 g, 90% theory) as an oil: specific rotation, ^{1}H- and ^{13}C NMR spectra were consistent with those of the authentic sample.

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