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## A FISCHER INDOLIZATION STRATEGY TOWARD THE TOTAL SYNTHESIS OF (–)-GONIOMITINE

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*This manuscript is dedicated to Prof. Masakatsu Shibasaki for his 70th birthday.*

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**Abstract** – A Fischer indolization strategy toward the core of (–)-goniomitine is reported. Initial investigations into the Pd-catalyzed asymmetric allylic alkylation of dihydropyrido[1,2-*a*]indolone (DHPI) substrates are also discussed.

(–)-Goniomitine (**1**, Figure 1), isolated from the bark of *Gonomia Malagasy*, is differentiated from other *Aspidosperma* alkaloids (e.g., **2–4**) by its unique aminal-containing tetracyclic core.<sup>1</sup> There are currently seven reported total syntheses of (±)-goniomitine (**1**),<sup>2</sup> along with three asymmetric total syntheses.<sup>3</sup> We anticipated that sufficiently rapid assemblage of the highlighted tricyclic subunit, combined with our group's expertise in the asymmetric synthesis of all-carbon quaternary centers,<sup>4</sup> would facilitate an efficient catalytic enantioselective synthesis of (–)-goniomitine (**1**).

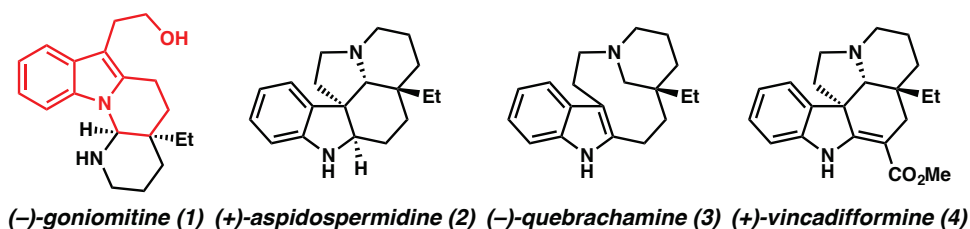
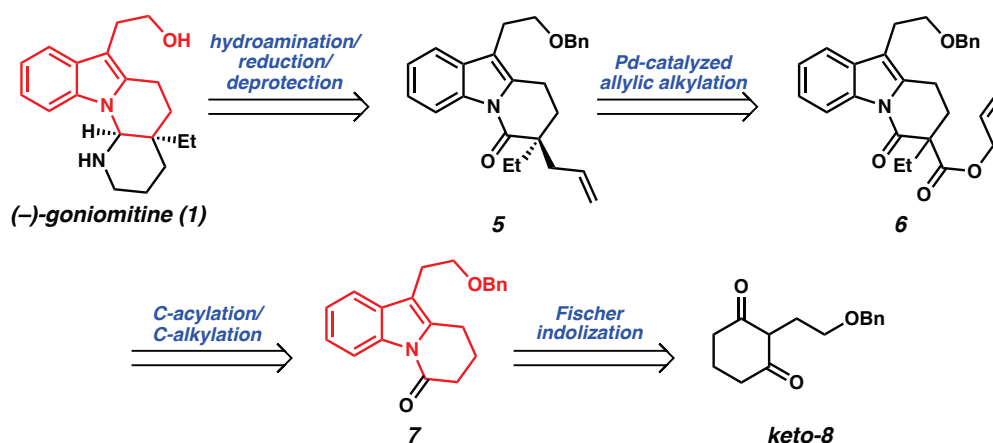


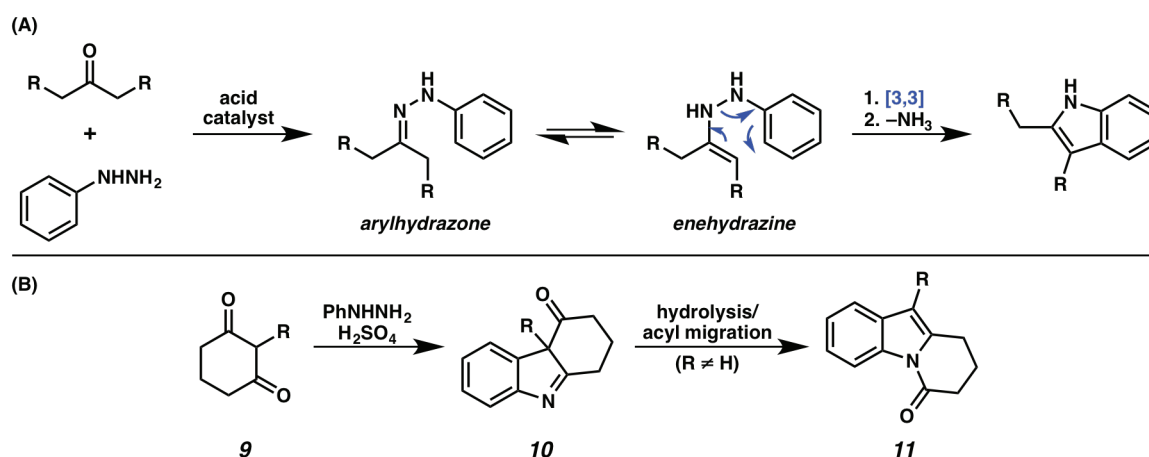
Figure 1. Representative *Aspidosperma* Alkaloids

In our initial retrosynthetic analysis of (–)-goniomitine (**1**), we believed that late-stage redox manipulations and alcohol deprotection could furnish the natural product from lactam **5** (Scheme 1). We expected the quaternary center in lactam **5** could arise from the enantioselective Pd-catalyzed decarboxylative allylic alkylation of racemic β-amidoester **6**. Importantly, we believed that

enantioconvergent construction of the quaternary center would offer significant improvement over the comparatively poor stereocontrol featured in previous enantioselective syntheses of (–)-goniomitine (**1**).<sup>3</sup> Disconnection of the ethyl and alloc groups revealed key dihydropyrido[1,2-*a*]indolone (DHPI) **7**, which we anticipated could be accessed via the Fischer indolization of 1,3-cyclohexanedione **8**.



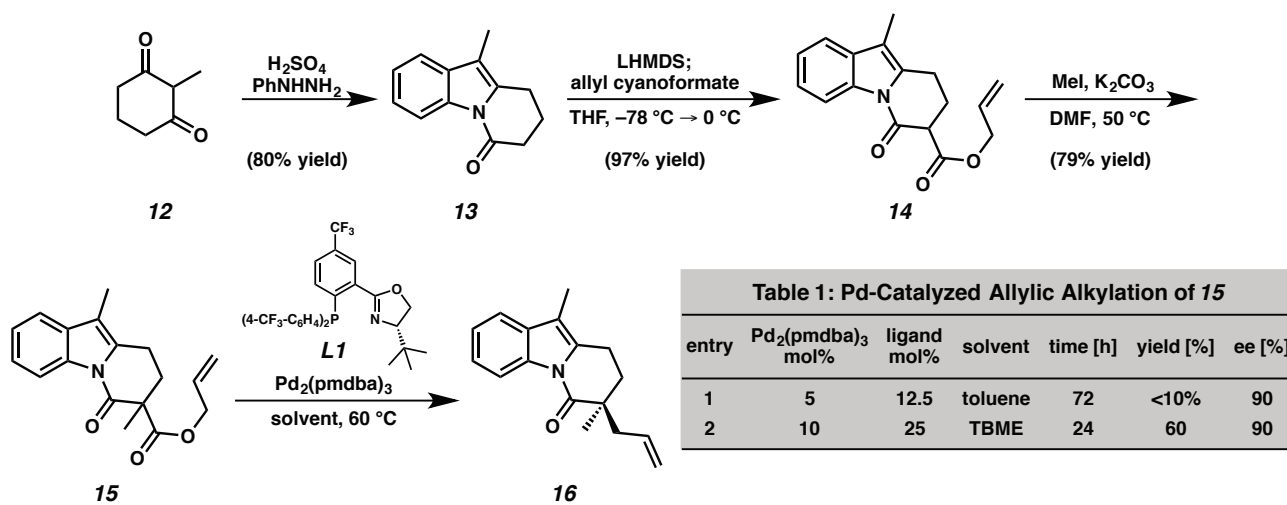
The acid-promoted Fischer indolization reaction, first discovered in 1883, is one of the most robust and widely utilized methods for the synthesis of substituted indoles from carbonyl precursors.<sup>5</sup> Ketones and aldehydes can be converted to the respective arylhydrazones under either Brønsted or Lewis acidic conditions (Scheme 2A). The arylhydrazone intermediate undergoes tautomerization to the corresponding enehydrazine, followed by a [3,3]-sigmatropic rearrangement and finally elimination of ammonia to deliver an indole product. This venerable transformation has seen widespread use in the realm of total synthesis,<sup>6</sup> and has been rendered enantioselective in an elegant desymmetrization reaction of *meso* cyclic ketones.<sup>7</sup> Of particular relevance to our synthetic plan toward (–)-goniomitine (**1**) was a report from Teuber and co-workers describing a Fischer indolization protocol for the synthesis of DHPI products



Scheme 2. A) General Fischer Indolization Reaction. B) DHPI Synthesis via Fischer Indolization of 1,3-Cyclohexanediones

(Scheme 2B).<sup>8</sup> They found that treatment of 2-substituted 1,3-cyclohexanediones (**9**) with phenylhydrazine and sulfuric acid first gives tricycle **10**, which undergoes sequential hydrolysis and N-acylation to furnish DHPI **11**.

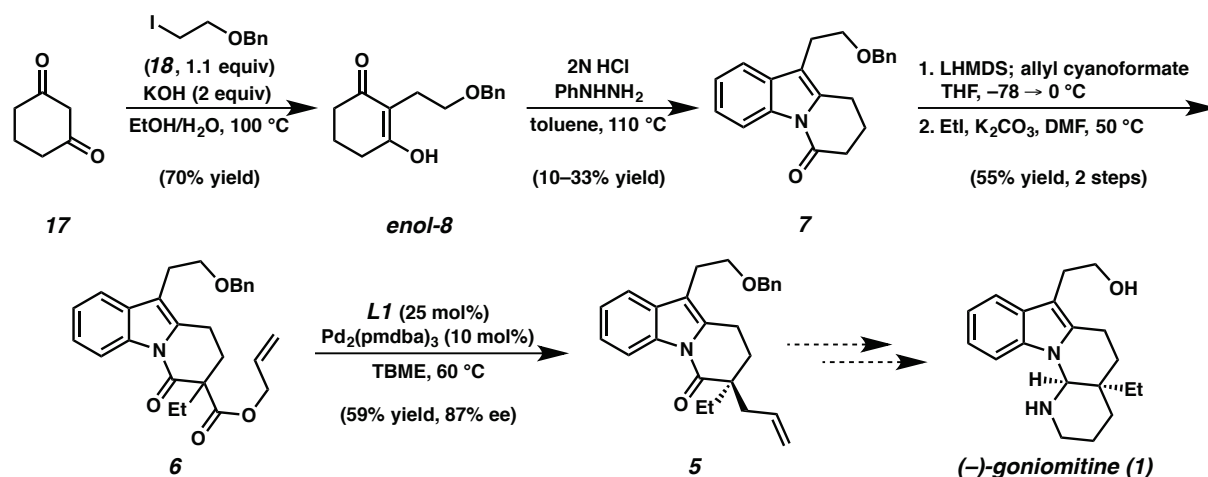
Our studies on the Pd-catalyzed allylic alkylation of the previously unexplored DHPI substrate class commenced with C3-methyl DHPI **13**, which is readily available from 2-methyl-1,3-cyclohexanedione (**12**, Scheme 3).<sup>8</sup> DHPI **13** was smoothly acylated using LHMDS and allyl cyanoformate. Subsequent site-selective alkylation with iodomethane delivered racemic  $\beta$ -amidoester **15** in 77% overall yield from **13**. We found that subjecting **15** to the catalyst complex derived from Pd<sub>2</sub>(pmdba)<sub>3</sub> (5 mol%) and (*S*)-(CF<sub>3</sub>)-*t*-BuPHOX (**L1**, 12.5 mol%) in toluene at 60 °C resulted in minimal conversion, despite prolonged reaction times (Table 1, Entry 1). Full consumption of starting material was only achieved after switching from toluene to TBME as solvent, and raising the loading of Pd<sub>2</sub>(pmdba)<sub>3</sub> and ligand to 10 mol% and 25 mol%, respectively (Entry 2). Under these conditions, we were able to isolate  $\alpha$ -quaternary DHPI **16** in 60% yield and 90% enantiomeric excess.



Scheme 3. Synthesis of C3-Methyl  $\alpha$ -Quaternary DHPI **16**

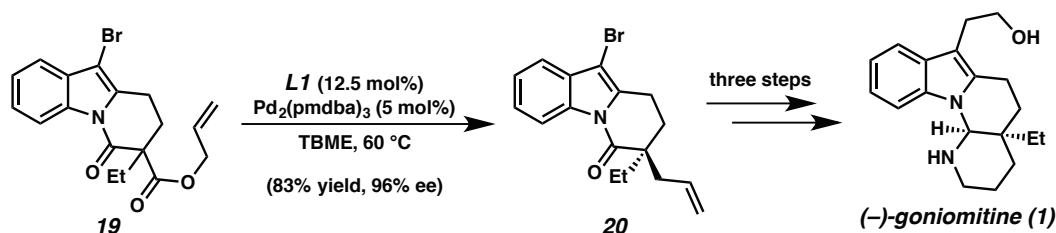
Regarding the total synthesis of (–)-goniomitine (**1**), our first challenge was to establish a regioselective C-alkylation of 1,3-cyclohexanedione (**17**) with (2-benzyloxy)ethyl iodide (**18**). Although Ma and co-workers have previously reported this transformation, we were unsuccessful in our attempts to reproduce their work.<sup>9</sup> We discovered that slightly different conditions afforded the desired C-alkylated product **8** in 70% yield as the enol tautomer (Scheme 4). After investigating several conditions for the Fischer indolization reaction, it was discovered that subjecting *enol-8* to 2N HCl in refluxing toluene furnished key DHPI **7**, albeit in an unsatisfactory range of 10–33% yield. Nevertheless, we were able to synthesize  $\beta$ -amidoester **6** from DHPI **7** in 55% yield over a two-step sequence analogous to that

described above (cf. Schemes 3 and 4), which put us in position to test the allylic alkylation chemistry on the real system. Once again, we observed that TBME as solvent, along with high catalyst loading, was required to deliver  $\alpha$ -quaternary allylic alkylation product **5** in a disappointing 59% yield and 87% enantiomeric excess.



Scheme 4. Synthesis of  $\alpha$ -Quaternary DHPI **5** Toward (-)-Goniomitine (**1**)

Previous studies by our group have revealed that electron-withdrawing substituents on the lactam nitrogen atom provide the best results in the allylic alkylation chemistry.<sup>4b</sup> We therefore hypothesized that a C3-alkyl substituent might be too electron-donating, and thus reevaluated our synthetic plan. Gratifyingly, C3-brominated substrate **19** performed exceptionally well in the Pd-catalyzed allylic alkylation, delivering  $\alpha$ -quaternary DHPI **20** in 83% yield and 96% ee (Scheme 5). We were then able to advance this compound to (-)-goniomitine (**1**) in just three steps and 29% overall yield.<sup>10</sup>



Scheme 5. Strategic Bromination Enables a Total Synthesis of (-)-Goniomitine (**1**)

To summarize, we employed a Fischer indolization protocol to synthesize a key tricyclic DHPI intermediate (**7**) toward (-)-goniomitine (**1**) in three steps from commercial materials. While this transformation failed to deliver the product in good yield, sufficient material was made available to study the Pd-catalyzed enantioselective allylic alkylation of the DHPI substrate class. As a result, we discovered a critical electronic effect at the C3 position of the indole moiety that led to the first catalytic enantioselective total synthesis of (-)-goniomitine (**1**).

## EXPERIMENTAL

Unless stated otherwise, reactions were performed at ambient temperature (23 °C) in flame-dried glassware under an argon atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina).<sup>11</sup> Commercially available reagents were used as received. Reactions requiring external heat were modulated to the specified temperatures using an IKA Mag temperature controller. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 pre-coated plates (250 nm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. Silicycle SiliaFlash P60 Academic Silica gel (particle size 40-63 nm) was used for flash chromatography. (*S*)-(CF<sub>3</sub>)-*t*-BuPHOX,<sup>12</sup> and tris(4,4'-methoxydibenzylideneacetone)-dipalladium(0) [Pd<sub>2</sub>(pmdba)<sub>3</sub>]<sup>13</sup> were prepared by known methods. Phenyl hydrazine was purified immediately before use. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Varian Inova 500 (500 MHz and 126 MHz, respectively) and are reported in terms of chemical shift relative to CHCl<sub>3</sub> (δ 7.26 and 77.16, respectively). Data for <sup>1</sup>H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm<sup>-1</sup>). Analytical chiral SFC was performed with a Mettler SFC supercritical CO<sub>2</sub> analytical chromatography system with Chiralcel OB-H column obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode, or from the Caltech Center for Catalysis and Chemical Synthesis using an Agilent 6200 series TOF with an Agilent G1978A Multimode source in mixed (Multimode ESI/APCI) ionization mode. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm.

**List of Abbreviations.** TBME – *tert*-butyl methyl ether, ee – enantiomeric excess, LHMDS – lithium bis(trimethylsilyl)amide, SFC – supercritical fluid chromatography, THF – tetrahydrofuran, TLC – thin-layer chromatography, DMF – *N,N*-dimethylformamide, DHPI – dihydropyrido[1,2-*a*]indolone.

**Allyl 10-methyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (14):** A flame-dried round bottom flask was charged with LHMDS (670 mg, 4.0 mmol, 1.9 equiv) and a magnetic stirring bar in a N<sub>2</sub>-filled glove box. The flask was sealed, removed from the glovebox, fitted with an argon line, and suspended in a dry ice/acetone bath. THF (11 mL) was added slowly to the flask and allowed to stir until the LHMDS had been completely dissolved. A solution of DHPI **13** (420 mg, 2.1 mmol, 1.0 equiv) in THF (2.5 mL) was added dropwise, and the reaction was allowed to stir for 30 min at –78 °C. Allyl cyanofornate (270 mg, 2.43 mmol, 1.15 equiv) was then added dropwise, and the reaction was allowed to

warm slowly to 0 °C over 4 h. Once the cooling bath temperature reached 0 °C, 100 mL of saturated aqueous NH<sub>4</sub>Cl was then added slowly and the mixture stirred for 20 min before being extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude residue was purified by flash column chromatography (SiO<sub>2</sub>, 15% acetone in hexanes) to give tertiary β-amidoester **14** (580 mg, 97% yield) as a faintly yellow oil: R<sub>f</sub> = 0.41 (3:1 hexanes:acetone eluent); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.45–8.41 (m, 1H), 7.45–7.41 (m, 1H), 7.32–7.27 (m, 2H), 5.94 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1H), 5.35 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.26 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.72 (dq, *J* = 5.7, 1.5 Hz, 2H), 3.82 (dd, *J* = 8.0, 5.0 Hz, 1H), 3.04 (dddd, *J* = 16.4, 8.1, 4.7, 1.1 Hz, 1H), 2.90 (dddd, *J* = 16.3, 8.3, 4.7, 1.2 Hz, 1H), 2.55–2.45 (m, 1H), 2.33 (ddt, *J* = 13.1, 8.0, 4.8 Hz, 1H), 2.19 (t, *J* = 1.0 Hz, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 169.2, 164.9, 134.8, 132.1, 131.6, 131.3, 124.6, 124.2, 119.0, 118.0, 116.6, 113.3, 66.4, 51.1, 25.0, 19.8, 8.6; IR (Neat Film, NaCl) 3050, 2943, 2359, 1741, 1698, 1627, 1459, 1396, 1383, 1370, 1338, 1308, 1269, 1246, 1220, 1172, 1156, 1128, 1104, 1028, 989, 750 cm<sup>-1</sup>; HRMS (ESI/APCI) *m/z* calc'd for C<sub>17</sub>H<sub>18</sub>NO<sub>3</sub> [M+H]<sup>+</sup>: 284.1281, found 284.1287.

**Allyl 7,10-dimethyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (15):** To a solution of β-amidoester **14** (107 mg, 0.38 mmol, 1.0 equiv) in DMF (1.2 mL) were added K<sub>2</sub>CO<sub>3</sub> (61 mg, 0.45 mmol, 1.2 equiv) and MeI (28 mL, 0.45 mmol, 1.2 equiv). The reaction mixture was heated to 50 °C with stirring. After 5 h, starting material was completely consumed as determined by TLC analysis. Saturated aqueous NH<sub>4</sub>Cl (10 mL) was added, followed by extraction with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. Flash column chromatography (SiO<sub>2</sub>, 15% acetone in hexanes) afforded quaternary β-amidoester **15** (88 mg, 79% yield) as a clear colorless oil: R<sub>f</sub> = 0.47 (3:1 hexanes:acetone eluent); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.49–8.44 (m, 1H), 7.45–7.41 (m, 1H), 7.33–7.27 (m, 2H), 5.84 (ddt, *J* = 17.2, 10.4, 5.5 Hz, 1H), 5.24 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.18 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.64 (dq, *J* = 5.5, 1.5 Hz, 2H), 3.06–2.96 (m, 1H), 2.87 (dddd, *J* = 16.8, 11.0, 4.8, 1.4 Hz, 1H), 2.58 (ddd, *J* = 13.4, 5.4, 4.8 Hz, 1H), 2.18 (dd, *J* = 1.1, 0.7 Hz, 3H), 2.07 (ddd, *J* = 13.5, 11.0, 4.8 Hz, 1H), 1.68 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 172.1, 168.5, 135.0, 132.3, 131.5 (2C),<sup>14</sup> 124.5, 124.1, 118.7, 118.0, 116.7, 112.9, 66.3, 52.6, 32.9, 21.7, 19.1, 8.5; IR (Neat Film, NaCl) 2939, 1735, 1700, 1628, 1458, 1385, 1345, 1364, 1267, 1240, 1060, 971, 934, 752 cm<sup>-1</sup>; HRMS (FAB+) *m/z* calc'd for C<sub>18</sub>H<sub>20</sub>NO<sub>3</sub> [M+H]<sup>+</sup>: 298.1438, found 298.1435.

**(*S*)-7-Allyl-7,10-dimethyl-8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one (16):** An oven-dried 20 mL scintillation vial was charged with Pd<sub>2</sub>(pmdba)<sub>3</sub> (14 mg, 12.7 mmol, 0.1 equiv), (*S*)-(CF<sub>3</sub>)<sub>3</sub>-*t*-BuPHOX (**L1**, 18.8 mg, 31.8 mmol, 0.25 equiv), and a magnetic stirring bar in a N<sub>2</sub>-filled glove box. The vial was then charged with TBME (3.2 mL) and stirred at 23 °C for 30 min, generating a dark purple solution. To the preformed catalyst solution was added a solution of **15** (55 mg, 0.127 mmol, 1.0 equiv) in TBME (0.64 mL). The vial was sealed, removed from the glovebox, and placed in a preheated 60 °C heating

block with stirring. Full consumption of starting material was achieved after 24 h, as determined by TLC analysis. The crude reaction mixture was stripped onto silica gel, and purified by flash column chromatography (SiO<sub>2</sub>, 30% CH<sub>2</sub>Cl<sub>2</sub> in hexanes) to afford  $\alpha$ -quaternary lactam **16** (19.5 mg, 60% yield) as a clear colorless oil:  $R_f = 0.41$  (1:1 hexanes:CH<sub>2</sub>Cl<sub>2</sub> eluent); 90% ee,  $[\alpha]_D^{25} -75.8$  ( $c$  0.42, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.48–8.44 (m, 1H), 7.44–7.40 (m, 1H), 7.30–7.26 (m, 2H), 5.88–5.78 (m, 1H), 5.17–5.13 (m, 1H), 5.13–5.11 (m, 1H), 2.96 (dddt,  $J = 16.5, 8.0, 5.6, 1.3$  Hz, 2H), 2.66–2.60 (m, 1H), 2.42 (ddt,  $J = 13.8, 7.7, 1.1$  Hz, 1H), 2.18 (t,  $J = 1.0$  Hz, 3H), 2.09 (ddd,  $J = 13.7, 8.5, 5.4$  Hz, 1H), 1.87 (ddd,  $J = 13.5, 7.3, 5.2$  Hz, 1H), 1.36 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  174.3, 134.9, 133.5, 133.0, 131.5, 124.2, 123.7, 119.0, 117.8, 116.6, 112.0, 43.1, 42.3, 31.7, 23.3, 18.3, 8.5; IR (Neat Film, NaCl) 3074, 2968, 2933, 2864, 1694, 1625, 1455, 1382, 1360, 1336, 1311, 1291, 1247, 1190, 1121, 1060, 1015, 999, 916, 803, 753 cm<sup>-1</sup>; HRMS (ESI/APCI)  $m/z$  calc'd for C<sub>17</sub>H<sub>20</sub>NO [M+H]<sup>+</sup>: 254.1539, found 254.1547; SFC conditions: 5% *i*-PrOH, 2.5 mL/min, Chiralcel OB-H column,  $\lambda = 210$  nm,  $\tau_R$  (min): major = 7.55, minor = 5.97.

**2-(2-(Benzyloxy)ethyl)-3-hydroxycyclohex-2-en-1-one (enol-8)**: A flask was charged with a magnetic stirring bar, 1,3-cyclohexanedione (**17**, 336 mg, 3.0 mmol, 1.0 equiv), and KOH (170 mg, 3.0 mmol, 1.0 equiv). EtOH (1.3 mL) and H<sub>2</sub>O (0.2 mL) were added at 23 °C with stirring, followed by (2-benzyloxy)ethyl iodide (**18**, 870 mg, 3.3 mmol, 1.1 equiv). The flask was fitted with a reflux condenser, placed in an oil bath, and the reaction was heated to 110 °C with stirring. After 18 h, an additional portion of KOH (170 mg, 3.0 mmol, 1.0 equiv) was added and the reaction was stirred for 1 h at which point full consumption of starting material was determined by TLC analysis. The reaction mixture was then removed the oil bath and allowed to cool to 23 °C. The reaction mixture was poured onto EtOAc (50 mL) and washed with H<sub>2</sub>O (2 x 25 mL). The combined aqueous layers were acidified to pH 2 using 1N HCl and were then extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. Flash column chromatography (SiO<sub>2</sub>, 45% EtOAc in hexanes) afforded **enol-8** (515 mg, 70% yield) as a colorless amorphous solid:  $R_f = 0.25$  (1:1 hexanes:EtOAc eluent); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  9.68 (s, 1H), 7.39–7.28 (m, 5H), 4.58 (s, 2H), 3.63–3.59 (m, 2H), 2.73–2.67 (m, 2H), 2.46 (t,  $J = 6.3$  Hz, 2H), 2.34 (dd,  $J = 7.2, 6.1$  Hz, 2H), 1.91 (dt,  $J = 12.6, 6.5$  Hz, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  198.3, 174.8, 136.6, 128.8, 128.4, 128.1, 114.1, 73.8, 72.1, 36.6, 29.5, 22.7, 20.7; IR (Neat Film, NaCl) 3059, 3029, 2934, 2867, 2664, 1574, 1453, 1372, 1266, 1191, 1095, 856, 735, 697 cm<sup>-1</sup>; HRMS (ESI/APCI)  $m/z$  calc'd for C<sub>15</sub>H<sub>19</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 247.1329, found 247.1324.

**10-(2-(Benzyloxy)ethyl)-8,9-dihydropyrido[1,2-*a*]indol-6(7H)-one (7)**: A flask was charged with a magnetic stirring bar, **enol-8** (370 mg, 1.5 mmol, 1.0 equiv), PhNHNH<sub>2</sub> (162 mg, 1.5 mmol, 1.0 equiv), and toluene (3 mL). Aqueous HCl (2N, 1.5 mL) was then added at 23 °C. The flask was fitted with a reflux condenser, placed in an oil bath, and the reaction was heated to 100 °C with stirring. After 24 h, the

reaction mixture was cooled to 23 °C, diluted with H<sub>2</sub>O (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. Flash column chromatography (SiO<sub>2</sub>, 15% EtOAc in hexanes) afforded DHPI **7** (158 mg, 33% yield) as an orange oil: R<sub>f</sub> = 0.3 (3:2 hexanes:Et<sub>2</sub>O eluent); spectroscopic data were consistent with those reported in the literature.<sup>15</sup>

## ACKNOWLEDGEMENTS

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