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A New Asymmetric Synthesis of the Anti-Tumor Alkaloid (*R*)-(+)-Crispine A

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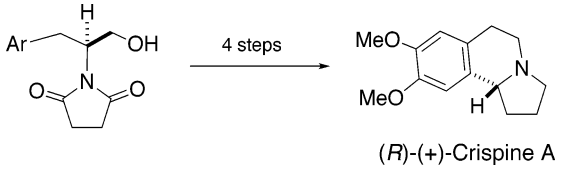
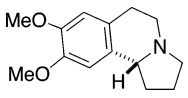


(*R*)-(+)-Crispine A

We report a novel, facile, and asymmetric approach for the synthesis of the anti-tumor alkaloid (+)-crispine A via a highly diastereoselective *N*-acyliminium cyclization reaction as a key synthetic step.

The pyrroloisoquinoline alkaloid (+)-crispine A, **1**, isolated in 2002 from *Clathrus crispus* by Zhao and co-workers, shows important biological activity against SKOV3, KB, and HeLa human cancer cell lines.[1] To date, syntheses of racemic crispine A have been achieved by Knolker and Agarwal,[2] Meyer and Opatz,[3] and more recently, by King.[4] The first enantioselective synthesis of this alkaloid was reported by Czarnocki and co-workers on the basis of the use of asymmetric transfer hydrogenation as a key synthetic step.[5]



Crispine A, **1**

Our own group has had considerable success in the development of asymmetric routes to several important heterocyclic templates, including the pyrroloisoquinoline system.[6] There has been considerable interest in the synthesis of the pyrroloisoquinoline core over recent years, with many approaches involving *N*-acyliminium chemistry in the key ring-forming step, of which several have also addressed the important question of stereocontrol in the cyclization.[7] In this current paper, we report the successful application of our own *N*-acyliminium strategy in an efficient new asymmetric synthesis of (+)-crispine A, **1**.

Our approach to crispine A began with the synthesis of imide **2**, prepared as previously reported from (2*S*)-2-amino-3-(3,4-dimethoxyphenyl)propan-1-ol and succinic anhydride.[6] Subjecting imide **2** to sodium borohydride reduction, as described in Scheme 1, resulted in direct and highly diastereoselective cyclization to give tricyclic lactam **3** as a single diastereoisomer (as determined by 400 MHz ^{1}H NMR spectroscopy), in excellent yield (91%). Presumably, under the acidic reaction conditions, the electron-rich methoxy-substituted aryl ring is able to cyclize onto the *N*-acyliminium intermediate that is generated in situ. We have been able to confirm the relative stereochemistry of this advanced intermediate by single-crystal X-ray analysis.[6b] The relative stereochemistry observed in product **3** is as expected on the basis of the conformational models previously proposed by our group to rationalize such highly diastereoselective cyclization reactions onto *N*-acyliminium intermediates.[6]

Our completion of the total synthesis of crispine A required us to remove the hydroxymethyl auxiliary group, and to this end, we have investigated two alternative procedures. The most direct route to achieve this transformation would be the application of a method originally developed by Kraft,[8] and more recently applied by Martin,[9] involving a Raney nickel induced decarbonylative removal of the hydroxymethyl functionality. Martin has successfully applied this methodology in the synthesis of pumiliotoxin 251D from an advanced bicyclic lactam intermediate.[9] According to Kraft, primary alcohols undergo oxidation to aldehydes and are then subsequently decarbonylated when treated with Ra-Ni in refluxing toluene.[8] The quality of the Raney nickel used in this approach is known to be a critical factor in its success. In our hands, the Ra-Ni induced removal of the hydroxymethyl substituent from intermediate **3** proceeded smoothly as reported, and in an excellent yield of 98%, to give the corresponding lactam, **4**. Reductive

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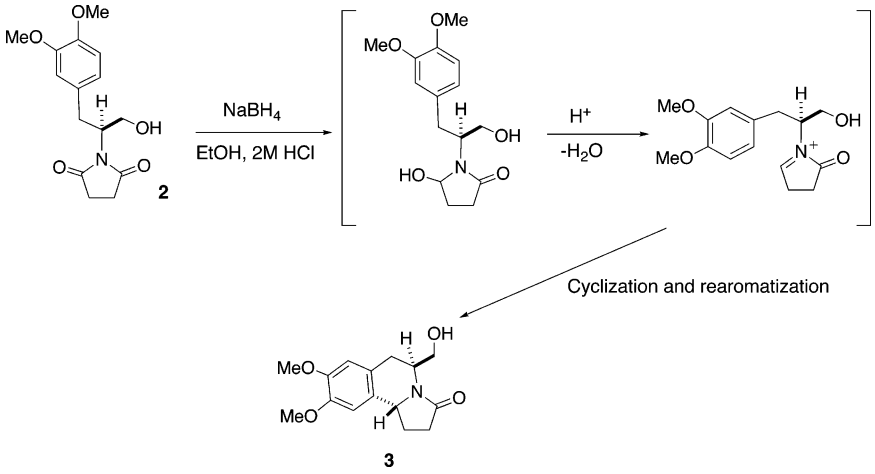
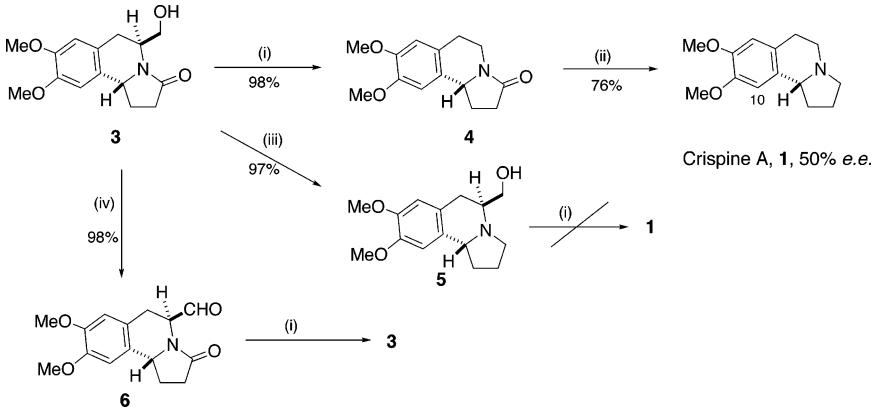
SCHEME 1



SCHEME 2[a]



[a] Key: (i) Ra-Ni (W2), toluene, Δ; (ii) LAH, THF, Δ, 3 h, then rt, 12 h; (iii) LAH, THF, Δ, 3 h, then rt, 12 h; (iv) IBX, EtOAc, Δ, 4 h.

removal of the lactam carbonyl group was achieved using LAH in THF, thus completing the synthesis of crispine A (Scheme 2). In the recent enantioselective synthesis of this alkaloid, reported by Czarnocki and Drabowicz,[5] the enantiomeric excess of the alkaloid was determined by NMR spectroscopic methods using (*R*)-(+)-*tert*-butylphenylphosphinothiolic acid as a chiral additive. This research team were kind enough to furnish us with an amount of this chiral reagent for use in our own studies, and the determinations of product ee described in this paper are thus based on an identical NMR spectroscopic procedure. Use of this thioacid as a chiral shift reagent allowed the determination of the ee of our product, which was shown to have a disappointingly low value of 50% ee. The diagnostic signal in the ^{1}H NMR spectrum used in the determination is the aromatic C(10) proton which, in the presence of the chiral shift reagent, shows distinct, well-separated singlet peaks for the enantiomers at 6.39 and 6.22 ppm. In our case, although the level of product ee was moderate, the major enantiomer was confirmed to be the desired (*R*)-crispine A, as expected. Although the use of Ra-Ni (W2) for removal of the hydroxymethyl group allows for rapid and relatively high-yielding access to crispine A, in only three synthetic steps from imide **2**, epimerization of the benzylic stereocentre was occurring at some point in the two-step sequence shown in Scheme 2 and thus compromising the enantiomeric purity of the final product.

As an alternative approach, we chose to reverse the order of synthetic transformations and first removed the lactam carbonyl using LAH to yield amine **5**, followed by the Ra-Ni reaction. Unfortunately we were unable to achieve the removal of the hydroxymethyl group by following this alternative scheme of events, observing only decomposition of amine **5**.

As noted above, the literature precedent for the use of Ra-Ni is suggestive of an initial oxidation of the hydroxymethyl group to an aldehyde intermediate before subsequent decarbonylation.[8] Based on this proposed mechanism, we decided to investigate the use of the aldehyde derivative **6** as a substrate for the Ra-Ni reaction, reasoning that the aldehyde may undergo direct decarbonylation. In our hands, however, compound **6** was simply reduced back to the hydroxymethylated substrate **3** under the usual reaction conditions. Since lactam removal to access **5** proceeded without affecting the diastereoisomer ratio (i.e., **5** was obtained as a single diastereoisomer), we propose that racemization of substrate **3** is taking place during the Ra-Ni procedure (step i, Scheme 2).

This issue was ultimately overcome through the application of a Rh-induced decarbonylation sequence previously applied by us in our work on the *Erythrina* alkaloid series.[10] Compound **3** was oxidized to aldehyde **6** in good yield using IBX in ethyl acetate, followed by Rh-induced decarbonylation using our previously developed procedure.[10] Amide **4** was again trans-

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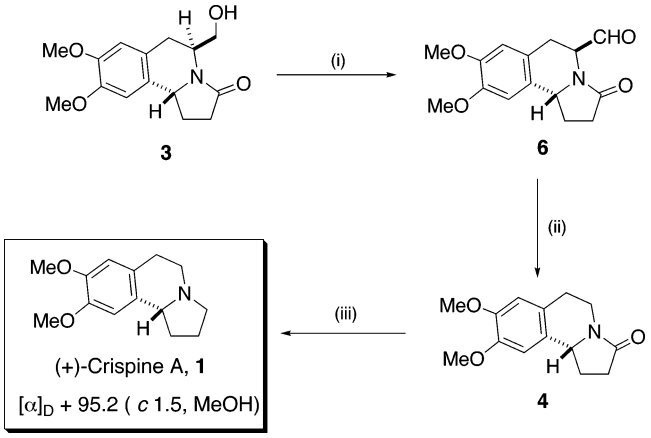
SCHEME 3[a]



[a] Key: (i) IBX, EtOAc, Δ, 4 h (98%); (ii) $Rh(PPh_3)_2(CO)Cl$, dppp, xylene, Δ, 240 h (46%); (iii) LAH, THF, 20 h (58%).

formed into the target, (*R*)-(+)-crispine A, **1**, in 58% yield by LAH reduction in THF (Scheme 3).

Compound **1**, obtained as detailed in Scheme 3, was shown to have an ee of 95% by using the ^{1}H NMR chiral shift experiment described above. The optical rotation of our product was determined to be +95.2 (*c* 1.5, MeOH) and was comparable to that reported by Zhao and co-workers for the natural product isolate [+91.0 (MeOH)].[1] Czarnocki and Drabowicz observed a rotation of + 100.4 (*c* 1) using chloroform as solvent, due to apparent problems of dissolution when using methanol.[5]

In summary, we report a new, efficient, and highly stereoselective synthesis of the anti-tumor alkaloid (+)-crispine A in four synthetic steps from a readily available enantiomerically pure imide substrate **2** in an overall yield of 24%.

Experimental Section

1-(2*S*)-[2-(3,4-Dimethoxyphenyl)-1-hydroxymethylethyl]pyrrolidine-2,5-dione, 2. Succinic anhydride (2.56 g, 25.60 mmol) and (2*S*)-2-amino-3-(3,4-dimethyloxy)phenyl)propan-1-ol (4.92, 23.27 mmol) were stirred in toluene (100 mL) under an atmosphere of nitrogen. Triethylamine (4 mL) was added to the resultant solution and the mixture heated at reflux for 18 h. After 18 h, the reaction was cooled to room temperature and solvent removed by rotary evaporator to yield a yellow oil. The crude product was adsorbed onto silica gel and chromatographed using silica gel as absorbent and ethyl acetate as eluent to produce a colorless solid (4.87 g, 71%): mp 124−125 °C; $[\alpha]_D$ −73.2 (*c* = 1.01 in CH_2Cl_2); ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1700 (CO), 2938 (aliphatic CH) and 3447 (OH); δ_H (400 MHz, $CDCl_3$) 2.51−2.61 (4 H, m, $COCH_2CH_2CO$), 2.95−3.10 (2 H, m, $ArCH_2CHN$), 3.79−3.85 (1 H, m, CH(*H*)OH), 3.83 (3 H, s, OCH_3), 3.84 (3 H, s, OCH_3), 4.03 (1 H, dd, J 8.0, 11.6 Hz, CH(*H*)OH), 4.47−4.52 (1 H, m, $ArCH_2CHN$) and 6.67−6.80 (4 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 27.8 (CH_2), 27.8 (CH_2), 33.1 (CH_2), 55.6 (CH), 55.8 (OCH_3), 55.8 (OCH_3), 61.8 (CH_2), 111.0 (CH), 111.9 (CH), 121.0 (CH), 129.6 (C), 147.6 (C), 148.7 (C), 178.3 (CO) and 178.3 (CO); MS (FAB) *m*/*z* 294 [(M + H)$^+$, 4.0] ((M + H)$^+$, 294.1344, $C_{15}H_{19}NO_5$ requires 294.1342).

(5*S*,10b*R*)-5-Hydroxymethyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one, 3. 1-(2*S*)-[2-(3,4-Dimethoxyphenyl)-1-hydroxymethylethyl]pyrrolidine-2,5-dione **2** (4.09 g, 13.94 mmol) was dissolved in absolute ethanol (100 mL) and cooled to 0 °C. Sodium borohydride (5.28 g, 139.4 mmol) was then added with stirring. A 2 M solution of HCl in absolute ethanol (6.97 mL, 13.94 mmol) was then slowly added via syringe over a 3 h period. The resultant solution was acidified to pH 1−3 by the addition of a 2 M solution of HCl in absolute ethanol over a 15 min period. This afforded a white suspension, which was stirred for a further 20 h. The reaction was quenched with sodium hydrogen carbonate and extracted with dichloromethane (3 × 40 mL). The dichloromethane layers were then combined and dried over anhydrous magnesium sulfate and solvent removed by rotary evaporation to yield the target cyclized compound as a single diastereoisomer, which was purified by column chromatography using silica gel as absorbent and 5% methanol/dichloromethane as eluent to yield a white solid (3.01 g, 78%): mp 177−179 °C; $[\alpha]_D$ +133.6 (*c* = 1.03 in CH_2Cl_2); ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1666 (CO), 2939 (aliphatic CH) and 3369 (OH); δ_H (400 MHz, $CDCl_3$) 1.91−1.98 (1 H, m, CH(*H*)CH_2CO), 2.46−2.52 (1 H, m, CH_2CH(*H*)CO), 2.61−2.69 (3 H, m, CH(*H*)CH_2CO, CH_2CH(*H*)CO and ArCH(*H*)CHN), 3.00 (1 H, dd, *J* 6.8, 16.0 Hz, ArCH(*H*)CHN), 3.62−3.73 (2 H, m, CH_2OH), 3.87 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 4.47−4.50 (1 H, m, $ArCH_2CHN$), 4.76 (1 H, t, *J* 7.6 Hz, NC*H*Ar), 6.59 (1 H, s, Ar*H*) and 6.63 (1 H, s, Ar*H*), (OH not visible); δ_C (100 MHz, $CDCl_3$) 27.1 (CH_2), 29.1 (CH_2), 31.7 (CH_2), 49.5 (CH), 54.2 (CH), 55.9 (OCH_3), 56.1 (OCH_3), 63.2 (CH_2), 107.3 (CH), 111.7 (CH), 124.1 (C), 128.4 (C), 148.0 (C), 148.2 (C) and 175.1 (CO); MS (FAB) *m*/*z* 278 [(M + H)$^+$, 27.5] ((M + H)$^+$, 278.1395, $C_{15}H_{19}NO_4$ requires 278.1392).

(10b*R*)-8,9-Dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one, 4, by Raney-Ni Route. Freshly prepared Raney nickel (W-2) (7.08 g) was washed with water (3 × 20 mL) followed by 2-propanol (2 × 20 mL). 2-Propanol was decanted, the Raney nickel was taken up in toluene, and the residual water and 2-propanol were azeotropically removed using a Dean−Stark trap. A solution of (5*S*,10b*R*)-5-hydroxymethyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one **3** (1.18 g, 6.49 mmol) in toluene (60 mL) was added, and the reaction was refluxed under Dean−Stark conditions for 4 h. The resulting solution was filtered through a Celite pad, washed with methanol, and evaporated under reduced pressure to yield the target compound as a yellow oil (1.03 g, 98%): $[\alpha]_D$ +175.8 (*c* = 3.09 in $CHCl_3$); ν_{max} (thin film, $CHCl_3$)/cm^{-1} 1681 (CO) and 2934 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.82−1.90 (1 H, m, CH(*H*)CH_2CO), 2.45−2.71 (4 H, m, CH(*H*)CH_2CO, CH_2CH_2CO and ArCH(*H*)CH_2N), 2.85−2.93 (1 H, m, ArCH(*H*)CH_2N), 2.99−3.06 (1 H, m, $ArCH_2$CH(*H*)N), 3.87 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 4.31 (1 H, ddd, *J* 2.4, 6.0, 12.8 Hz, $ArCH_2CH$(*H*)N), 4.74 (1 H, t, *J* 8.0 Hz, NC*H*Ar), 6.58 (1 H, s, Ar*H*) and 6.63 (1 H, s, Ar*H*); δ_C (100 MHz, $CDCl_3$) 27.8 (CH_2), 28.1 (CH_2), 31.8 (CH_2), 37.1 (CH_2), 55.9 (OCH_3), 56.0 (OCH_3), 56.6 (CH), 107.6 (CH), 111.6 (CH), 125.5 (C), 129.3 (C), 147.9 (C), 148.0 (C) and 173.4 (CO); MS (FAB) *m*/*z* 248 [(M + H)$^+$, 31.3] ((M + H)$^+$, 248.1287, $C_{14}H_{17}NO_3$ requires 248.1287).

(*R*)-(+)-Crispine A, 1, by Raney-Ni Route. Lithium aluminum hydride (1 M solution in tetrahydrofuran) (4.5 mL, 4.49 mmol) was added to a predried flask fitted with a reflux condenser under a nitrogen atmosphere. Anhydrous tetrahydrofuran (100 mL) was added and the solution cooled to 0 °C. (10b*R*)-8,9-Dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one **4** (1.05 g, 4.49 mmol) in anhydrous tetrahydrofuran (50 mL) was added dropwise to the hydride solution at 0 °C and the resulting solution heated under reflux for 3 h and then stirred for a further 12 h at room temperature. Diethyl ether (50 mL) was added, and reaction was quenched by the careful addition of saturated sodium potassium tartate. The mixture was stirred for a further 1 h before the addition of anhydrous magnesium sulfate prior to filtration through a Celite pad. The filtrate was evaporated under reduced pressure, and the resultant yellow solid was purified by column chromatography using silica gel as absorbent and 10:1 chloroform/methanol as eluent to yield a colorless solid (752 mg, 76%): mp 88−89 °C (lit.[1] mp 88−89 °C); $[\alpha]_D$ + 43.9 (*c* = 1.14 in CH_3OH) [lit.[1] $[\alpha]_D$ +91.0 (CH_3OH)]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 2934 (aliphatic CH); δ_H

(400 MHz, $CDCl_3$) 1.72−1.79 (1 H, m, CH(*H*)CH_2CH_2N), 1.86−1.96 (2 H, m, $CH_2CH_2CH_2$N), 2.31−2.37 (1 H, m, CH(*H*)CH_2-CH_2N), 2.60−2.79 (3 H, m, CH_2CH_2CH(*H*)N, ArCH(*H*)CH_2N and $ArCH_2CH$(*H*)N), 2.98−3.11 (2 H, m, CH_2CH_2CH(*H*)N and ArCH-(*H*)CH_2N), 3.18 (1 H, ddd, *J* 2.8, 5.6, 10.8 Hz, $ArCH_2CH$(*H*)N), 3.50 (1 H, t, *J* 8.4 Hz, NC*H*Ar), 3.84 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 6.57 (1 H, s, Ar*H*) and 6.61 (1 H, s, Ar*H*); δ_C (100 MHz, $CDCl_3$) 22.3 (CH_2), 27.9 (CH_2), 30.6 (CH_2), 48.3 (CH_2), 53.2 (CH_2), 55.9 (OCH_3), 56.0 (OCH_3), 62.9 (*C*H), 108.8 (*C*H), 111.3 (*C*H), 126.1 (*C*), 130.5 (*C*), 147.3 (*C*) and 147.4 (*C*); MS (FAB) *m*/*z* 232 [MI, 66.6] (MI, 233.1419, $C_{14}H_{19}NO_2$ requires 233.1416). The ee of crispine A obtained via this method was determined to be ca. 50% by the ^{1}H NMR chiral shift experiments described in the discussion.

(10b*R*)-8,9-Dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one, 4, by Rh-Decarbonylation Route. Bis-(triphenylphosphine)rhodium(I) carbonyl chloride (0.012 g, 0.018 mmol) was added to anhydrous xylene (10 mL) under a nitrogen atmosphere. The mixture was then stirred at 80 °C for 15 min. 3-Bis(diphenylphosphino)propane (0.019 g, 0.046 mmol) was then added and the mixture stirred for a further 30 min at this temperature. To the stirred mixture was then added aldehyde **6** (0.102 g, 0.371 mmol) in anhydrous xylene (10 mL), and the resulting mixture was heated under reflux for a further 240 h. The solvent was removed under reduced pressure. The crude product was then adsorbed onto silica and purified by flash column chromatography over silica with 3:1 ethyl acetate/hexane as the eluent to produce the **4** as an oil (0.042 g, 46%). Spectral analysis of compound **4** obtained via this route was identical to that reported above.

(*R*)-(+)-Crispine A, 1, by Rh-Decarbonylation Route. Treatment of amide **4**, obtained via Rh-decarbonylation chemistry, as described above using LAH gave crispine A, **1**, in 58% yield and was shown to have an ee of >95% by ^{1}H NMR chiral shift experiments as described in the discussion. Spectral analysis of compound **1** obtained via this route was identical to that reported above. The optical rotation of this product was determined to be +95.2 (*c* 1.5, MeOH) and was comparable to that reported by Zhao and co-workers for the natural product isolate [+91.0 (MeOH)].[1]

(5*S*,10b*R*)-(8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo-[2,1-*a*]isoquinolin-5-yl)methanol, 5. Lithium aluminum hydride (1 M solution in tetrahydrofuran) (3.61 mL, 3.61 mmol) was added to a predried flask fitted with a reflux condenser under a nitrogen atmosphere. Anhydrous tetrahydrofuran (50 mL) was added and the solution cooled to 0 °C. (5*S*,10b*R*)-8,9-Dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one, **3** (500 mg, 1.80 mmol), in anhydrous tetrahydrofuran (20 mL) was added dropwise to the hydride solution at 0 °C and the resulting solution heated under reflux for 3 h and then stirred for a further 12 h at room temperature. Diethyl ether (20 mL) was added, and the reaction was quenched by the careful addition of saturated sodium potassium tartrate. The mixture was stirred for a further 1 h before the addition of anhydrous magnesium sulfate prior to filtration through a Celite pad. The filtrate was evaporated under reduced pressure, and the resultant yellow solid was purified by column chromatography using silica gel as absorbent and 10:1 chloroform/methanol as eluent to yield a colorless solid (460 mg, 97%): $[\alpha]_D$ +79.1 (*c* = 1.83 in $CHCl_3$); ν_{max} (thin film, neat)/cm^{-1} 2934 (aliphatic CH) and 3374 (OH); δ_H (400 MHz, $CDCl_3$) 1.78−1.89 (3 H, m, C$H_2CH_2CH_2$N and CH_2CH(*H*)CH_2N), 2.41−2.46 (2 H, m, CH_2CH(*H*)CH_2N and ArCH(*H*)CHN), 2.76−2.81 (1 H, m, CH_2CH_2CH(*H*)N), 2.96 (1 H, dd, *J* 5.2, 16.0 Hz, ArCH(*H*)CHN), 3.05−3.09 (1 H, m, CH_2CH_2-CH(*H*)N), 3.13−3.16 (1 H, m, $ArCH_2CH$N), 3.22 (1 H, br, s, O*H*), 3.42 (1 H, dd, *J* 8.0, 10.4 Hz, CH(*H*)OH), 3.52 (1 H, dd, *J* 5.2, 10.4 Hz, CH(*H*)OH), 3.85 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 4.22 (1 H, t, *J* 6.4 Hz, NC*H*Ar) and 6.56 (2 H, s, Ar*H*); δ_C (100 MHz, $CDCl_3$) 24.0 (CH_2), 26.3 (CH_2), 33.5 (CH_2), 51.9 (CH_2), 55.6 (*C*H), 55.6 (OCH_3), 55.8 (OCH_3), 62.6 (CH_2), 109.0 (*C*H), 111.2 (*C*H), 112.3 (CH), 124.9 (*C*), 130.9 (*C*), 147.3 (*C*) and 147.6 (*C*); MS (FAB) *m*/*z* 264 [(M + H)$^+$, 14.2] ((M + H)$^+$, 264.1596, $C_{15}H_{21}$-NO_3 requires 264.1600).

(5*S*,10b*R*)-8,9-Dimethoxy-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbaldehyde, 6. *o*-Iodoxybenzoic acid (4.48 g, 16.12 mmol) was added to a solution of (5*S*,10b*R*)-5-hydroxymethyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one, **3** (1.49 g, 5.37 mmol), in ethyl acetate (75 mL), and the reaction was heated under reflux for 4 h. The resulting mixture was cooled to room temperature, filtered through a sinter funnel, and evaporated to a crude brown residue. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 3:1 light petroleum/ethyl acetate as eluent to isolate the target compound as a yellow foam (1.46 g, 99%): $[\alpha]_D$ +66.5 (*c* = 1.3 in $CHCl_3$); ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1672 (CO) and 2937 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.85−1.93 (1 H, m, CH(*H*)CH_2CO), 2.47−2.55 (1 H, m, CH_2CH(*H*)CO), 2.68−2.75 (2 H, m, CH(*H*)CH_2CO and CH_2CH(*H*)CO), 3.06 (1 H, dd, *J* 7.2, 16.0 Hz, ArCH(*H*)CHN), 3.22 (1 H, dd, *J* 2.4, 16.4 Hz, ArCH-(*H*)CHN), 3.85 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 4.91 (1 H, t, *J* 6.8 Hz, NC*H*Ar), 5.01 (1 H, dd, *J* 2.4, 7.2 Hz, $ArCH_2CH$N), 6.53 (1 H, s, Ar*H*), 6.65 (1 H, s, Ar*H*) and 9.62 (1 H, s, C*H*O); δ_C (100 MHz, $CDCl_3$) 26.5 (CH_2), 28.2 (CH_2), 31.4 (CH_2), 54.7 (*C*H), 55.7 (*C*H), 56.0 (OCH_3), 56.1 (OCH_3), 107.5 (*C*H), 111.5 (*C*H), 122.3 (*C*), 128.1 (*C*), 148.2 (*C*), 148.5 (*C*), 174.4 (*C*O) and 198.9 (*C*HO); MS (FAB) *m*/*z* 276 [(M + H)$^+$, 22.2] ((M + H)$^+$, 276.1240, $C_{15}H_{17}NO_4$ requires 276.1236).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **1**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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