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Asymmetric Synthesis of Crispine A: Constructing Tetrahydroisoquinoline Scaffolds Using Pummerer Cyclizations

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For the first time, a concise, linear and stereoselective synthesis of both enantiomers of the natural product crispine A has been achieved in six steps with an overall yield of ≥ 20 %, starting from commercially available veratraldehyde. Asymmetric Keck allylation and trifluoroacetic anhydride-mediated Pummerer cyclization were the key transformations used to construct the tetrahydroisoquinoline core structure.

Introduction

Tetrahydroisoquinoline alkaloids with chirality at the C-1 position are widely distributed in nature and significant because of their unique biogenetic origin. Tetrahydroisoquinoline alkaloids, including their unnatural isomers are known to possess diverse biological activities as well as interesting chemical and pharmacological properties.[1] Crispine A (**1**) is a naturally occurring tetrahydroisoquinoline alkaloid isolated from *Carduus crispus* along with four new alkaloids (Figure 1) crispines B–E **2**–**5**. Traditionally, *C. crispus* has been used in Chinese folk medicine for the treatment of colds, stomach-ache and rheumatism.[2] Moreover; some *C. crispus* extracts have been reported to show significant cytotoxic properties against SKOV3, HeLa and KB human cancer cell lines.[2]

Bischler–Napieralski, Pictet–Spengler reactions and introduction of nucleophilic or electrophilic carbon units into the C-1 position of an isoquinoline scaffold are the most often explored strategies by which to construct tetrahydroisoquinoline systems.[1c] Pummerer type cyclization reactions are also established ways to generate tetrahydroisoquinoline cores in Erythrina alkaloids, starting from their corresponding deactivated amide[3] in which additional protection and deprotection transformations are sometimes necessary. The use of basic amines in Pummerer type cyclizations

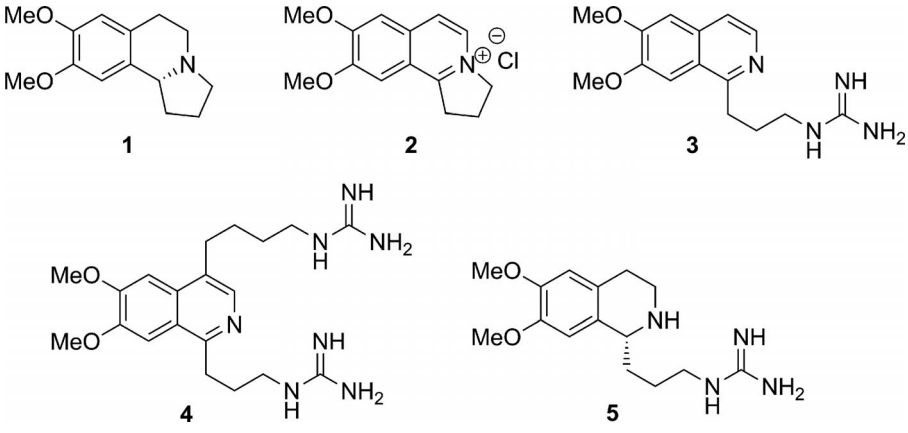

Figure 1. Isoquinoline alkaloids crispine A–E (**1**–**5**).

is rare. Development of new synthetic strategies to construct tetrahydroisoquinoline systems by employing a short synthetic sequence and a protecting group-free asymmetric approach to establish stereochemistry C-1 would be of great interest. In addition to the challenge of making these compounds, their remarkable biological properties and structural diversity have attracted the attention of many synthetic and medicinal chemists. As a consequence, numerous

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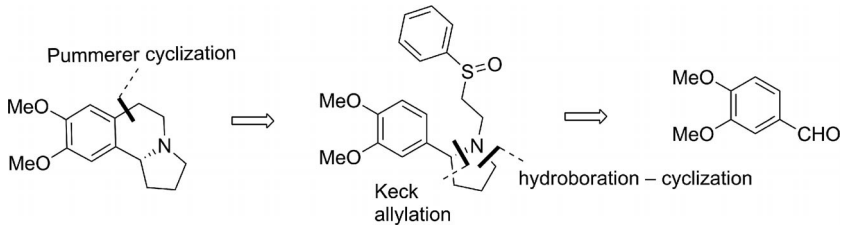


Scheme 1. Retrosynthesis of (+)-crispine A.

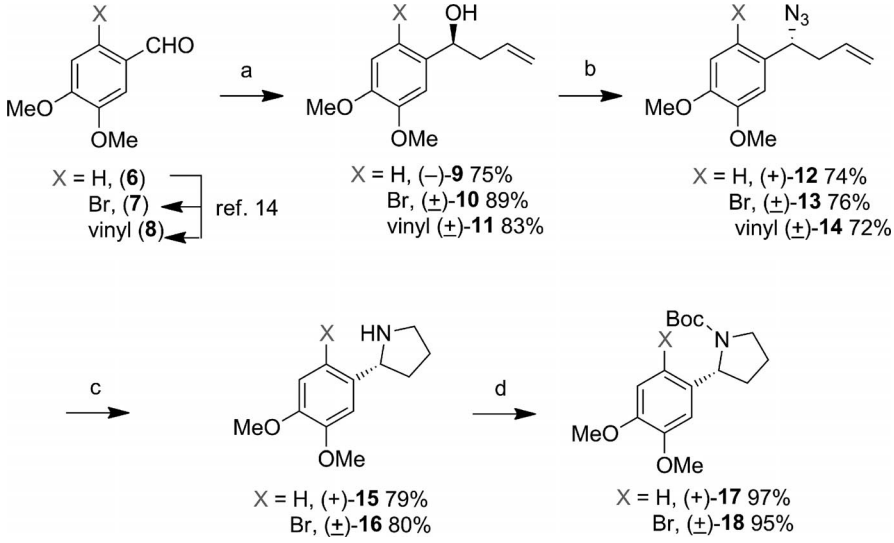
reports of the isoquinoline alkaloids in racemic as well as optically active forms can be found in the literature.[4–13] The majority of these citations detail extensive protection/deprotection schemes. Although there are many reports available; there remains the need for a concise and flexible synthetic approach that enables facile study of structure activity relationships of isoquinoline scaffolds. In this regard, we have developed concise, asymmetric syntheses of both antipodes of crispine A with improved overall yield.

Results and Discussion

Our approach to synthesis of crispine A is based on the retrosynthesis shown in Scheme 1. We envisioned that construction of the piperidine ring in crispine A would result from a Pummerer-type cyclization of a chiral 2-arylpyrrolidine scaffold which could be synthesized using a one-pot hydroboration followed by cyclization.

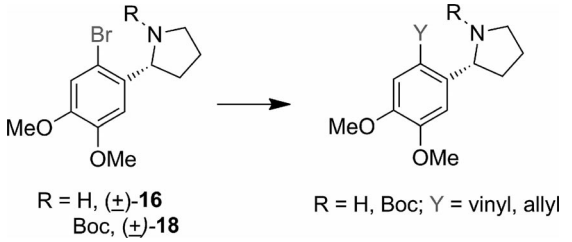
The asymmetric center was thought to be formed by a Keck asymmetric allylation reaction. As shown in Scheme 2, commercially available veratraldehyde (**6**) was converted to bromo derivative **7** and corresponding vinylated aldehydes **8** using a known procedure.[14] Keck asymmetric allylation of veratraldehyde (**6**) furnished the corresponding homoallyl alcohol (–)-**9** in good yield.[15a] The optical rotation of compound (–)-**9** was in agreement with prior reports in the literature.[15b] To test the synthetic feasibility of obvious synthetic approaches, racemic homoallyl alcohols **10** and **11** were synthesized by treating aldehydes **7** and **8** with allylmagnesium bromide. A complex generated from diphenylphosphoryl azide and DBU was treated with homoallyl alcohols [(–)-**9**, (±)-**10** and (±)-**11**] to afford homoallyl azides [(+)-**12**, (±)-**13** and (±)-**14**] with complete inversion of stereochemistry as anticipated.[16] Successful participation of (+)-**12** and (±)-**13** in hydroboration–cycloalkylation[17] led to corresponding pyrrolidines (+)-**15** and (±)-**16**, whereas reaction of compound (±)-**14** resulted in a complex mixture of products. Pyrrolidines (+)-**15** and (±)-**16** were protected with $(Boc)_2O$ to yield the corresponding Boc-protected pyrrolidines (+)-**17** and (±)-**18** in almost quantitative yields thus facilitating structure isolation and characterization.

Next, we turned our attention to functionalization of Ar-Br in (±)-**16** and (±)-**18** by employing Pd-catalysis for effective C–C bond formation. Stille coupling,[14b] using tetravinyl tin in the presence of Pd^0 and a catalytic amount of BHT in toluene, did not yield the required product. Changing the solvent, temperature, ligand and Pd-metal oxidation state did not solve the problem.[18] However, some success was achieved in C–C bond formation by switching our focus to the use of Suzuki coupling conditions. The classical Suzuki coupling partners (boronic acids) for vinylation and



Scheme 2. Synthesis of 2-aryl pyrrolidines **17** and **18**; *reagents and conditions:* a) i) *S*-BINOL, $Ti(OiPr)_4$, 4-Å molecular sieves powder, allyltributyl tin, –20 °C, DCM, 72 h; ii) allylmagnesium bromide, THF, 0 °C-r.t., 1 h; b) DPPA, DBU, toluene, 0 °C-r.t., 3 h; c) dicyclohexylborane, THF, 0 °C-r.t., 12 h, MeOH; d) $(Boc)_2O$, Et_3N, THF, 0 °C-r.t., 2 h.

allylation were not satisfactory. Again, altering solvent, ligand and Pd source failed to yield any beneficial effects. Alternatively, advanced Suzuki reaction with vinyl MIDA boronates[19] gave the required product albeit in poor (20–23%) yields (Scheme 3).

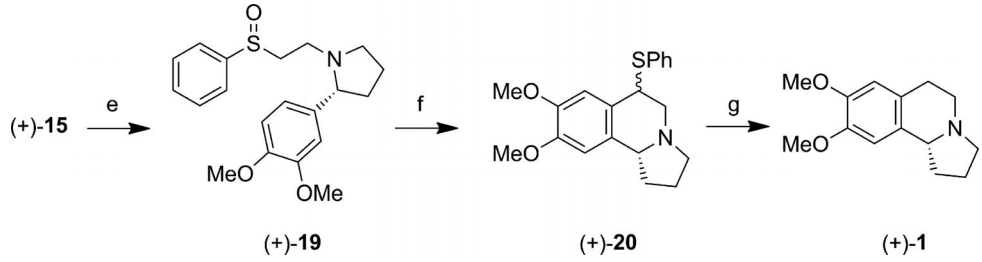


Scheme 3. Pd-mediated coupling reactions; *reagents and conditions:* a) vinyl MIDA, $Pd(OAc)_2$, XPHOS, K_3PO_4, dioxane/H_2O (5:1), 100 °C, 2 h. For the attempted failed reactions, refer to Table S1 in the Supporting Information.

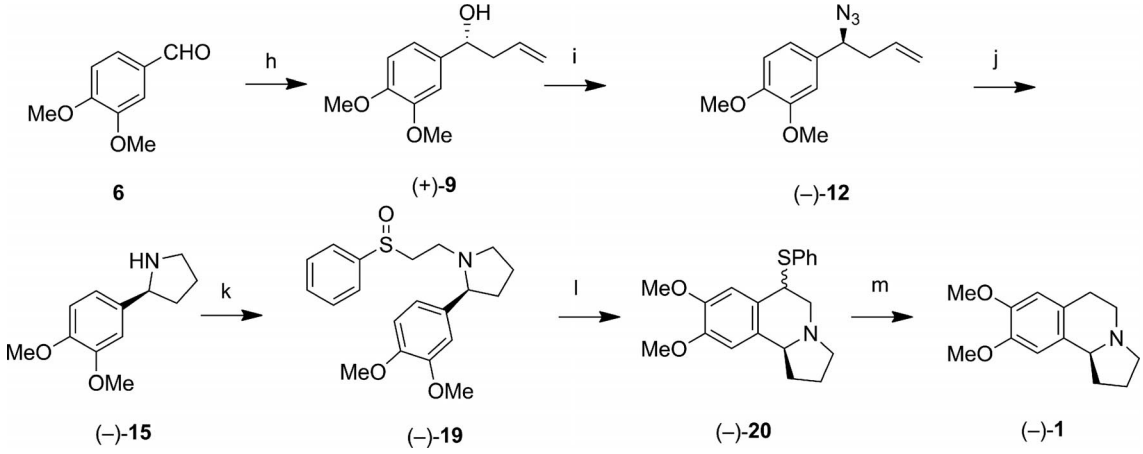
To overcome the unforeseen difficulty in C–C bond formation for the construction of the six-membered ring, a Pummerer type cyclization was attempted. Pummerer type transformations have widespread applications in heterocyclic syntheses, especially in the production of various alkaloid skeletons.[20e,20f] The Pummerer cyclization reaction proceeds through an initially generated thionium ion which is trapped by a nucleophile present in the reaction medium. Michael addition of compound (+)-**15** with phenyl vinyl sulfoxide in the presence of triethylamine was successful and furnished *N*-alkylated product (+)-**19** in good yield. Pummerer cyclization of compound (+)-**19** was tested using various Lewis acidic conditions[20d] and most of the conditions yielded the expected cyclization product (+)-**20** with low to moderate yields (18–45%).[20] After screening various Lewis acids for use in Pummerer cyclization, the combination of TFA and TFAA in DCM was found to afford a better yield (55%). Moreover, excess TFAA in DCM at room temperature was found to be ideal providing the tetrahydroisoquinoline core in very good yield (79%, *de* > 90%).[20c,20d]

Finally, reductive radical elimination of the thiophenyl group using Bu_3SnH and cat. AIBN in toluene at refluxing conditions yielded target compound *R*(+)-crispine A in excellent yield (Scheme 4).[21] The analytical and spectroscopic data of the obtained product was identical to those of the natural product[2] with optical rotation $[\alpha]_D^{25}$ = +93 (*c* = 1, $CHCl_3$) [Reported[2] $[\alpha]_D^{25}$ = +91 (MeOH)].

Similarly, using the same set of reactions, the unnatural isomer (–)-crispine A was also synthesized (In Keck asymmetric allylation *R*-BINOL was employed) with very good overall (19.7%) yield (Scheme 5). Both (+)-crispine A and its precursor (+)-**20** were tested against NCI's 60-cell line



Scheme 4. Synthesis of (+)-crispine A; *reagents and conditions:* e) phenyl vinyl sulfoxide, Et_3N, THF, 0 °C-r.t., 4 h, 81%; f) TFAA (excess), DCM, room temp., 3 h, 79%;g) Bu_3SnH, cat. AIBN, toluene, reflux, 1 h, 80%.



Scheme 5. Synthesis of *S*-(–)-crispine A; *reagents and conditions:* h) *R*-BINOL, $Ti(OiPr)_4$, 4-Å molecular sieves powder, allyltributyl tin, –20 °C, DCM, 72 h, 71%; i) DPPA, DBU, toluene, 0 °C-r.t., 3 h, 77%; j) dicyclohexyl borane, THF, 0 °C-r.t., 12 h, MeOH, 78%; k) phenylvinyl sulfoxide, Et_3N, THF, 0 °C-r.t., 4 h, 77%; l) TFAA (excess), DCM, room temp., 3 h, 76%; m) Bu_3SnH, cat. AIBN, toluene, reflux, 1 h, 79%.

panel. Neither compound showed any promising cytotoxicity in any cell line in the preliminary screening at single dose.[22]

Conclusions

In summary, we have demonstrated a concise (6 steps), asymmetric total synthesis of both enantiomers of crispine A by employing Keck asymmetric allylation and Pummerer cyclization as crucial steps. TFAA-mediated Pummerer cyclization led to the tetrahydroisoquinoline core in high yield and paves way for the synthesis of various structurally similar pyrroloisoquinoline alkaloids in an efficient manner, to investigate their intriguing biological properties.

Experimental Section

General Methods: ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ with a 400 MHz (100 MHz) instrument. Chemical shifts were reported in ppm downfield from tetramethylsilane (δ) as the internal standard and coupling constants are reported in Hertz (Hz). Assignment of proton resonances was confirmed by correlation spectroscopy. IR spectra were recorded using a universal attenuated total reflection sampling accessory with a diamond ATR (attenuated total reflectance) on bench top Cary 630 FT-IR spectrometer. The high-resolution mass spectra (HRMS) were recorded on a Q-Tof Micro mass spectrometer with lock spray source. Optical rotations were measured using an Autopol V automatic polarimeter in a 1 dm or a 5 dm cell. The reaction progress was monitored on precoated silica gel TLC plates. Spots were visualized under 254 nm UV light and/or by dipping the TLC plate into a solution of 2 mL anisaldehyde, 10 mL of glacial acetic acid and 5 mL of H_2SO_4 in 340 mL MeOH followed by heating with a heat gun. Column chromatography was performed with silica gel (230–400 mesh). All solvents (hexanes, EtOAc, CH_2Cl_2, Et_2O) were distilled prior to use. All reactions were performed under an atmosphere of argon using oven-dried glassware and standard syringe/septa techniques. The solvent THF was distilled from sodium-benzophenone, and CH_2Cl_2 was dried with P_2O_5. Triethylamine was distilled from CaH_2.

(–)-(*S*)-1-(3,4-Dimethoxyphenyl)but-3-en-1-ol (9): In a 2 neck 100 mL round-bottomed flask, a mixture of (*S*)-BINOL (0.5 mmol, 0.143 g), 1.0 M $Ti(OiPr)_4$ in DCM (0.5 mmol, 0.1 equiv.) and freshly activated 4-Å molecular sieves powder (2 g) in DCM (10 mL) was refluxed for 1 h. The red brown mixture was cooled to room temperature and veratraldehyde **6** (5 mmol, 0.83 g) was added. After being stirred for 10 min, the contents were cooled to –78 °C and allyltributyl tin (5.5 mmol, 1.76 mL) was added. The reaction mixture was stirred for 10 min and then placed in a –20 °C freezer. After 70 h, saturated $NaHCO_3$ 1.5 mL was then added and contents were stirred for 1 h, dried with anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel using hexane/EtOAc (8.5:1.5) as eluent to give (–)-**9** (0.78 g, 75%) as a white crystalline solid. $[\alpha]_D^{25}$ = –36 (c = 1, $CHCl_3$); m.p. 95–97 °C; IR: $\tilde{\nu}$ = 3393, 2955, 2917, 2855, 1640, 1455 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.90 (d, J = 1.9 Hz, 1 H), 6.85 (dd, J = 8.2, 1.9 Hz, 1 H), 6.81 (d, J = 8.2 Hz, 1 H), 5.78 (ddt, J = 17.2, 10.2, 7.1 Hz, 1 H), 5.18–5.07 (m, 2 H), 4.65 (t, J = 6.5 Hz, 1 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 2.48 (t, J = 6.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149, 148.4, 136.6, 134.6, 118.1, 110.9, 109.0, 73.2, 55.97, 43.8 ppm. HRMS (ESI$^+$) Calcd. for $C_{12}H_{16}NaO_3$ 231.0997, found 231.0997.

(+)-(*R*)-1-(3,4-Dimethoxyphenyl)but-3-en-1-ol (9): Using the same procedure, (*R*)-BINOL as chiral catalyst, compound (+)-**9** was synthesized. Yield obtained was 71%. Spectroscopic data and optical rotation are in full agreement with reported literature.[23] $[\alpha]_D^{25}$ = +33 (c = 1, $CHCl_3$).

(±)-1-(4,5-Dimethoxy-2-vinylphenyl)but-3-en-1-ol (11): In a 100 mL two neck round-bottomed flask, the vinyl aldehyde **8** (5.8 g, 30 mmol) was dissolved in THF (30 mL) and cooled to 0 °C under N_2 atmosphere. To this cold solution, allylmagnesium bromide solution (36 mL, 1.0 M in Et_2O) was added dropwise and stirring continued. After 1 h, saturated NH_4Cl solution was added and the mixture was extracted with diethyl ether (3 × 35 mL). The combined organic layers were dried with anhydrous $MgSO_4$, concentrated and purified by column chromatography using 10% EtOAc in hexanes to yield **11** (5.83 g, 83%) as a viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06 (s, 1 H), 7.04–6.91 (m, 2 H), 5.96–5.79 (m, 1 H), 5.56 (dd, J = 17.2, 1.3 Hz, 1 H), 5.31–5.13 (m, 3 H), 5.06 (dtd, J = 10.8, 6.3, 5.4, 3.0 Hz, 1 H), 3.92 (s, 6 H), 2.57–2.29 (m, 2 H), 2.07 (d, J = 2.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.0, 148.1, 134.6, 133.7, 133.3, 127.7, 118.3, 114.6, 108.7, 108.3, 69.2, 55.9, 55.9, 43.2 ppm. HRMS (ESI$^+$) Calcd. for $C_{14}H_{17}O_2$ [M + H – H_2O] 217.1229, found 217.1226.

(+)-(*R*)-4-(1-Azidobut-3-en-1-yl)-1,2-dimethoxybenzene (12): In a 50 mL round-bottomed flask, a mixture of alcohol (–)-**9** (0.75 g, 3.6 mmol) and diphenylphosphoryl azide (3 g, 10.81 mmol) was dissolved in dry toluene (10 mL). The mixture was cooled to 0 °C under N_2, and neat DBU (1.65 g, 10.81 mmol) was added. The reaction was stirred for 2 h at 0 °C and then at 20 °C for 1 h. The resulting two-phase mixture was diluted with diethyl ether and washed with H_2O (2 X 10 mL) followed by 5% HCl (5 mL). The organic layer was concentrated in vacuo and purified by silica gel chromatography using 95:5 hexane/EtOAc to afford (+)-**12** (0.62 g, 74%) as a colorless oil. $[\alpha]_D^{25}$ = +91 (c = 1, $CHCl_3$); IR: $\tilde{\nu}$ = 2934, 2835, 2091, 1592, 1513, 1463, 1259 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87–6.81 (m, 3 H), 5.73 (ddt, J = 17.1, 10.2, 6.9 Hz, 1 H), 5.11 (m, 2 H), 4.43 (t, J = 7.2 Hz, 1 H), 3.90 (s, 3 H), 3.88 (s, 3 H), 2.68–2.41 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.3, 149.1, 134.0, 119.5, 118.2, 111.1, 109. 9, 65.8, 56.0, 40.7 ppm. HRMS (ESI$^+$) Calcd. for $C_{12}H_{15}O_2$ [M + H – HN_3] 191.1072, found 191.1075.

(–)-(*S*)-4-(1-Azidobut-3-en-1-yl)-1,2-dimethoxybenzene (12): Using the same procedure, compound (–)-**12** was synthesized in 77% yield starting from (+)-**9**. $[\alpha]_D^{25}$ = –86 (c = 1, $CHCl_3$).

(+)-(*R*)-2-(3,4-Dimethoxyphenyl)pyrrolidine (15): To a stirred solution of freshly distilled cyclohexene (1.56 mL, 15.45 mmol) in 10 mL of THF at 0 °C was added dropwise 2.0 M BH_3–Me_2S complex in THF (3.85 mL, 7.72 mmol). The resulting white suspension of dicyclohexylborane was stirred for 1 h at 0 °C and then cooled to –15 °C prior to the addition of azide (+)-**12** (0.6 g, 2.57 mmol) in 5 mL of THF. The resulting mixture was warmed to room temperature. After 12 h, the reaction was quenched with MeOH and diluted with diethyl ether, and the organic layer was extracted with 1 N aqueous HCl. The combined aqueous layers were basified with 30% aqueous NaOH solution until pH 13–14 and then extracted with EtOAc. The combined extracts were dried with anhydrous Na_2SO_4, filtration and concentration furnished a pale yellow viscous liquid (+)-**15** in (79%, 0.453 g), which was pure enough to carry out next reaction. $[\alpha]_D^{25}$ = +49 (c = 1, $CHCl_3$). IR: $\tilde{\nu}$ = 2935, 2834, 1591, 1512, 1450, 1388, 1253, 1136, 1022, 806, 760 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (d, J = 1.9 Hz, 1 H), 6.86–6.82

(dd, J = 8.2, 1.9 Hz, 1 H), 6.76 (d, J = 8.2 Hz, 1 H), 4.01 (d, J = 8.1 Hz, 1 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 3.22 (br. s, 1 H), 3.19–3.11 (m, 2 H), 3.00–2.89 (m, 1 H), 2.17–2.05 (m, 1 H), 1.95–1.74 (m, 4 H), 1.70–1.58 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9, 147.9, 136.2, 118.6, 110.9, 109.9, 62.5, 55.8, 46.6, 34.0, 25.3 ppm. HRMS (ESI$^+$) Calcd. for $C_{12}H_{18}NO_2$ 208.1338, found 208.1341.

(–)-(*S*)-2-(3,4-Dimethoxyphenyl)pyrrolidines (15): Using the same procedure, compound (–)-**15** was synthesized in 78% starting from (–)-**12**. $[\alpha]_D^{25}$ = –54 (c = 1, $CHCl_3$).

(±)-2-(2-Bromo-4,5-dimethoxyphenyl)pyrrolidines (16): By following the above procedure, **(±)-16** (0.88 g, 80%) was prepared from **(±)-13** (1.2 g, 3.84 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (s, 1 H), 6.94 (s, 1 H), 4.40 (t, J = 7.8 Hz, 1 H), 4.03 (br. s, 1 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.19 (ddd, J = 10.0, 7.5, 5.3 Hz, 1 H), 3.03 (ddd, J = 10.0, 8.2, 6.7 Hz, 1 H), 2.34–2.21 (m, 1 H), 1.96–1.72 (m, 2 H), 1.59–1.42 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 148.1, 135.0, 115.2, 112.7, 110.1, 60.9, 56.1, 56.0, 46.5, 32.9, 24.9 ppm. HRMS (ESI$^+$) Calcd. for $C_{12}H_{17}BrNO_2$ 286.0443, found 286.0444.

(+)-*tert*-Butyl (*R*)-2-(3,4-Dimethoxyphenyl)pyrrolidine-1-carboxylate (17): The crude product (+)-**15** (0.06 g, 0.24 mmol) was dissolved in THF (2 mL) and cooled to 0 °C prior to the addition of Boc_2O (+)-**12** (0.15 g, 0.48 mmol) in THF (3 mL). To this cold solution, triethylamine (0.134 mL, 0.96 mmol) was added and stirring continued. After completion of the reaction (monitored by TLC), the whole mixture was concentrated and purified by column chromatography using 30% EtOAc in hexanes to yield **(+)-17** (0.07 g, 97%) as a viscous liquid. $[\alpha]_D^{25}$ = +79 (c = 1, $CHCl_3$) (Mixture of rotamers). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.78 (d, J = 8.1 Hz, 1 H), 6.72–6.65 (m, 2 H), 4.70–4.88 (m, 1 H), 3.84 (s, 6 H), 3.59 (t, J = 6.9 Hz, 2 H), 2.27 (dt, J = 13.5, 7.6 Hz, 1 H), 1.95–1.75 (m, 3 H), 1.45 (s, 3 H), 1.19 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 148.6, 147.4, 137.8, 117.5, 110.7, 108.6, 79.1, 61.0, 55.8, 47.0, 36.0, 28.4, 28.2, 23.1 ppm. HRMS (ESI$^+$) Calcd. for $C_{17}H_{25}NNaO_4$ 330.1681, found 330.1681.

(±)-*tert*-Butyl 2-(2-Bromo-4,5-dimethoxyphenyl)pyrrolidine-1-carboxylate (18): By following the procedure for the preparation of (+)-**17**, compound **(±)-18** (0.37 g, 0.94 mmol) was also prepared starting from **(±)-16** (0.29 g, 1 mmol) and Boc_2O (0.44 g, 2 mmol) in 95% yield. Viscous liquid, mixture of rotamers and major isomer ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.99 (s, 1 H), 6.63 (s, 1 H), 5.02 (dd, J = 8.3, 4.8 Hz, 1 H), 3.86 (s, 3 H), 3.81 (s, 3 H), 3.65 (t, J = 8.6 Hz, 2 H), 2.42–2.32 (m, 1 H), 1.92–1.83 (m, 2 H), 1.81–1.71 (m, 1 H), 1.21 (s, 9 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.4, 148.3, 148.0, 135.9, 115.2, 111.5, 108.8, 79.3, 60.8, 56.1, 56.0, 47.3, 34.2, 28.1, 23.1 ppm. HRMS (ESI$^+$) Calcd. for $C_{17}H_{25}BrNO_4$ 386.0967, found 386.0970.

(+)-(2*R*)-2-(3,4-Dimethoxyphenyl)-1-(2-phenylsulfinyl)ethylpyrrolidine (19): A mixture of compound (+)-**15** (0.414 g, 2 mmol) and triethylamine (0.404 g, 4 mmol) in THF at 0 °C was added dropwise phenyl vinyl sulfoxide (0.365 g, 2.4 mmol) in 2 mL of THF and was warmed to room temperature. After 4 h reaction mixture diluted with EtOAc (10 mL) and washed with H_2O (2 X 5 mL) followed by brine (2 X 5 mL), combined extracts were dried with anhydrous Na_2SO_4. Removal of the solvent in vacuo left a pale yellow liquid, which was purified by silica gel chromatography using 98:2 chloroform/methanol to afford (+)-**19** in (81%, 0. 58 g) yield. $[\alpha]_D^{25}$ = +125 (c = 1, $CHCl_3$); IR: $\tilde{\nu}$ = 3051, 2939, 2793, 1591, 1513, 1462, 1442, 1418, 1260, 1229, 1135, 1024, 729 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.54 (m, 2 H), 7.45 (m, 3 H), 6.98 (d, J = 1.9 Hz, 1 H), 6.83 (dd, J = 8.2, 1.9 Hz, 1 H), 6.77 (d, J = 8.1 Hz, 1 H), 3.89 (s, 3 H), 3.82 (s, 3 H), 3.25 (ddd, J = 19.6, 8.8, 6.4 Hz, 2 H), 3.10 (dt, J = 12.7, 8.2 Hz, 1 H), 2.85–2.77 (m, 2 H), 2.35 (ddd, J = 12.6, 6.3, 4.6 Hz, 1 H), 2.19 (q, J = 8.7 Hz, 1 H), 2.16–2.06 (m, 1 H), 1.96–1.84 (m, 1 H), 1.79 (dddd, J = 12.5, 9.5, 6.6, 3.0 Hz, 1 H), 1.72–1.61 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.3, 148.1, 144.7, 130.8, 129.2, 123.8, 119.6, 110.9, 109.8, 69.9, 57.4, 55.9, 53.2, 47.2, 35.3, 22.2 ppm. HRMS (ESI$^+$) Calcd. for $C_{20}H_{26}NO_3S$ 360.1633, found 360.1630.

(–)-(2*S*)-2-(3,4-Dimethoxyphenyl)-1-[2-(phenylsulfinyl)ethyl]pyrrolidine (19): Using the same procedure as above (for (+)-**19**), compound (–)-**19** was synthesized in 77% with $[\alpha]_D^{25}$ = –118 (c = 1, $CHCl_3$).

(+)-(10b*R*)-8,9-Dimethoxy-6-(phenylthio)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (20): To a stirred solution of compound (+)-**19** (0.54 g, 1.5 mmol) in 5 mL of dry DCM at room temperature, excess TFAA (3 mL) was added in a dropwise manner and allowed to stir for 3 h at same temperature. Solvent was evaporated in vacuo; the remaining residue was basified with sat. $NaHCO_3$ solution and extracted with EtOAc (3 × 25 mL). Combined organic layers were dried with Na_2SO_4, concentrated in vacuo and purified by silica gel column chromatography using 98:2 chloroform/methanol to afford (+)-**20** in (79%, 0. 4 g) yield. $[\alpha]_D^{25}$ = +52 (c = 1, $CHCl_3$); IR: $\tilde{\nu}$ = 2923, 2851, 1511, 1462, 1252, 1213, 1137, 1023, 744 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.37 (m, 2 H), 7.34–7.20 (m, 3 H), 7.02 (s, 1 H), 6.53 (s, 1 H), 4.64–4.51 (m, 1 H), 4.10–4.03 (m, 1 H), 3.84 (s, 3 H), 3.79 (s, 4 H), 3.71–3.57 (m, 2 H), 3.38 (dd, J = 11.9, 5.6 Hz, 1 H), 3.06–2.93 (m, 1 H), 2.80 (tt, J = 17.7, 8.4 Hz, 2 H), 2.39–2.20 (m, 1 H), 1.95–1.80 (m, 3 H), 1.80–1.67 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major isomer): δ = 148.1, 147.4, 132.2, 131.4, 129, 128.9, 127.3, 125.4, 111.1, 108.3, 77.2, 62.3, 55.80, 55.7, 53.2, 45.3, 30.6, 22.0 ppm. ^{13}C NMR (100 MHz, $CDCl_3$, minor isomer): δ = 148.4, 147.5, 134.4, 130.5, 128.9, 128.6, 127.1, 124.5, 111.6, 108.2, 76.6, 62.8, 55.8, 55.7, 53.1, 46, 30.3, 21.8 ppm. HRMS (ESI$^+$) Calcd. for $C_{20}H_{24}NO_2S$ 342.1528, found 342.1526.

(–)-(10b*S*)-8,9-Dimethoxy-6-(phenylthio)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (20): Using the same procedure as above (for (+)-**20**), compound (–)-**20** was synthesized in 76% yield starting from (–)-**19**. $[\alpha]_D^{25}$ = –60 (c = 1, $CHCl_3$).

(+)-(*R*)-8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline [(+)-crispine] (1): To a solution of thioether (+)-**20** (34 mg, 0.1 mmol) in toluene (2 mL) was added tri-*n*-butyltin hydride (58 mg, 0.2 mmol) and a few crystals of 2, 2′-azobis(isobutyronitrile). The solution was degassed by means of two freeze-pump-thaw cycles, and then stirred at 100 °C for 30 min. After cooling, the mixture was concentrated under reduced pressure and the residue was directly purified by chromatography on silica gel (chloroform/methanol/triethylamine, 98:1.5:0.5) to give 18 mg of crispine-A (+)-**1** (80%) as a colorless semi-solid which solidified on long standing. $[\alpha]_D^{25}$ = +93 (c = 1, $CHCl_3$); IR: $\tilde{\nu}$ = 2933, 2794, 1610, 1510, 1463, 1374, 1252, 1212, 1128, 1161, 1012, 856, 747 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.59 (s, 1 H), 6.55 (s, 1 H), 3.83 (d, J = 1.7 Hz, 6 H), 3.43 (t, J = 8.3 Hz, 1 H), 3.16 (ddd, J = 11.3, 6.2, 3.0 Hz, 1 H), 2.72 (dt, J = 16.2, 3.8 Hz, 1 H), 2.67–2.60 (m, 1 H), 2.56 (q, J = 8.6 Hz, 1 H), 2.37–2.24 (m, 1 H), 1.97–1.78 (m, 3 H), 1.77–1.64 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.3, 147.2, 130.8, 126.1, 111.2, 108.7, 62.9, 56.0, 55.9, 53.1, 48.3, 30.5, 28.0, 22.2 ppm. HRMS (ESI$^+$) Calcd. for $C_{14}H_{20}NO_2$ 234.1494, found 234.1493.

(–)-(*S*)-8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline [(–)-crispine] (1): Using the same procedure as above (for (+)-**1**) compound (–)-**1** was synthesized in 79% yield. Spectroscopic

data and optical rotation are in full agreement with reported in literature.[12] $[\alpha]_D^{25}$ = –88 (*c* = 1, $CHCl_3$). [Reported[12] $[\alpha]_D^{20}$ = –95 (*c* = 1.3, $CHCl_3$)].

Supporting Information (see footnote on the first page of this article): Copies of NMR and HRMS for all synthesized intermediates leading to crispine. Details for the failed reactions in Table 1 and NCI screening data are also available.

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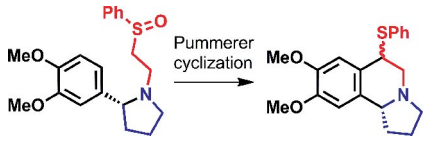
For the first time, a concise, linear and stereoselective synthesis of both enantiomers of crispine A has been achieved in six steps with an overall yield of ≥ 20%, starting from commercially available veratraldehyde.



Keywords: Asymmetric synthesis / Natural products / Alkaloids / Allylation / Cyclization

