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One-Pot Synthesis of (±)-Crispine A and Its C-Ring-Substituted Analogs

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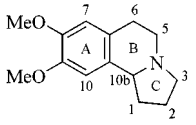
A straightforward access to crispine A and C-ring-substituted analogs by 1,4-addition of a deprotonated α-amino nitrile to α,β-unsaturated carbonyl compounds is described. If the reduction step is omitted, substituted 5,6-dihydropyrrolo[2,1-*a*]isoquinolines can be obtained.

Introduction

Despite the success of both combinatorial and rational approaches in the process of drug development, natural products still represent a rich source of novel pharmaceutically active compounds. Particularly ingredients of plants used in traditional medicine are attractive candidates for the discovery of new lead structures. In Chinese folk medicine, the welted thistle (*Carduus crispus*) was used for the treatment of cold, stomach ache and rheumatism. Pharmacological screening of its extracts revealed a cytotoxic activity against some human cancer cell lines.[1] The search for the antiproliferative principle of the plant led to the discovery of five novel isoquinoline alkaloids, among them the hexahydropyrrolo[2,1-*a*]isoquinoline alkaloid crispine A[1] (Figure 1).



(±)-Crispine A

Figure 1. Structure of crispine A.

Due to the renewed interest in this molecule, two total syntheses have recently been published by Knölker et al. and Szawkalo et al.[2,3] Herein, we report on a facile one-pot synthesis of (±)-crispine A and analogs based on the conjugate addition of a deprotonated α-amino nitrile to α,β-unsaturated carbonyl compounds. This simple approach not only allows the introduction of various substituents but also permits the formation of pyrrole derivatives. The latter method represents an improvement of the von Miller–Plöchl pyrrole synthesis.[4–6]

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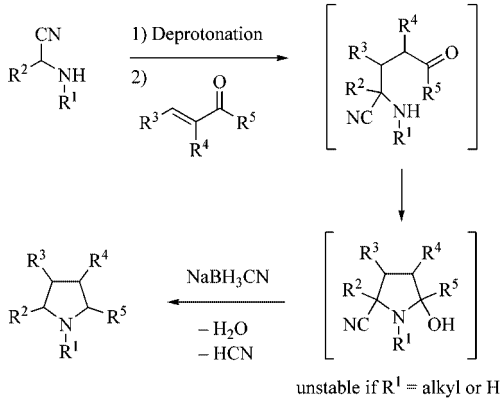
Results and Discussion

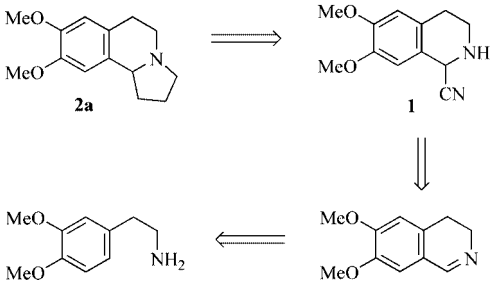
Deprotonated *N*-mono or *N*-unsubstituted α-amino nitriles can be used as nucleophiles in 1,4- and 1,2-addition reactions. As previously reported by our group, they can serve as key intermediates in a convenient one-pot synthesis of highly substituted pyrrolidines[7,8] and 1,2-diamines[9] (Scheme 1).



Scheme 1. Synthesis of pyrrolidines from α-amino nitriles.

Encouraged by the simplicity and efficiency of this method, we sought for possible applications in the construction of polycyclic fused ring systems. Crispine A should be easily accessible by the above mentioned method using 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**1**) as a precursor. This amino nitrile can be synthesized from *N*-formylhomoveratrylamine by Bischler-Napieralski cyclization, followed by addition of HCN to the resulting dihydroisoquinoline[10] (Scheme 2).

Deprotonation of amino nitrile **1** by KHMDS in THF at –78 °C, 1,4-addition to acrolein and one-pot reduction of the resulting unstable intermediate by sodium cyanoborohydride in acidic solution furnishes (±)-crispine A. However, the yield of the desired product was only 13% and unfortunately, neither the addition of crown ethers nor the

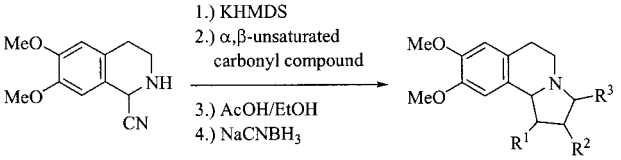


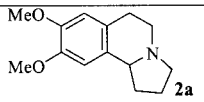
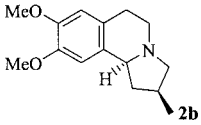
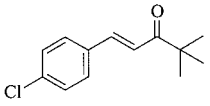
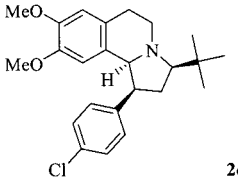
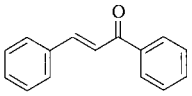
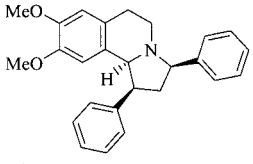
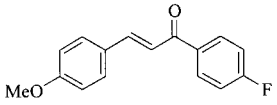
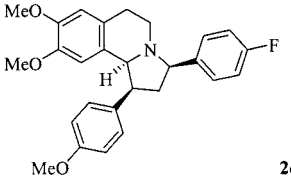
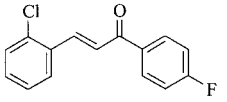
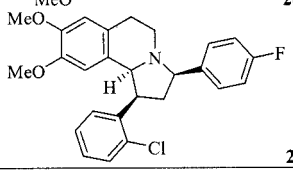
Scheme 2. Retrosynthetic analysis of (±)-crispine A.

use of different solvents allowed to improve the obtained yield. Our previous findings in the synthesis of simple pyrrolidines from deprotonated Strecker products indicate that acrolein tends to give somewhat lower yields than other Michael acceptors. On the other hand, the base-induced elimination of HCN from **1**, which may compete with the desired α-deprotonation, could also account for the low yield. When switching to methacrolein as the electrophile, 2-methyl-substituted crispine A (**2b**) was obtained as a 4.5:1 diastereomeric mixture in favor of the *cis* product in 41% yield. The reaction of deprotonated **1** with 1-(4-chlorophenyl)-4,4-dimethylpent-1-en-3-one furnished the 1,3-disubstituted crispine derivative **2c** in 87% yield as a single diastereomer, the relative configuration of which could be assigned by NOE measurements to be all-*cis*. These results clearly indicate that deterioration of **1** in the deprotonation step does not occur to a significant extent. The results of the reaction of **1** with various Michael acceptors are summarized in Table 1.

In the case of the products derived from substituted chalcones (**2d**–**2f**), again the all-*cis* diastereomers are formed exclusively. Besides the introduction of substituents

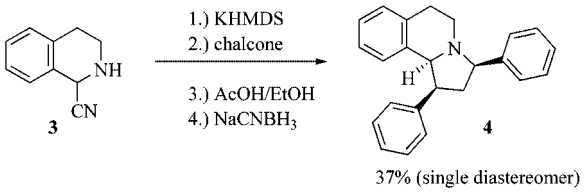
Table 1. Preparation of C-ring-substituted analogs of crispine A.



Electrophile	Major product	dr[a]	Isolated yield
	 **2a**	–	13%
	 **2b**	*cis*/*trans* = 4.5:1	41%
	 **2c**	single diastereomer	87%
	 **2d**	single diastereomer	53%
	 **2e**	single diastereomer	29%
	 **2f**	single diastereomer	41%

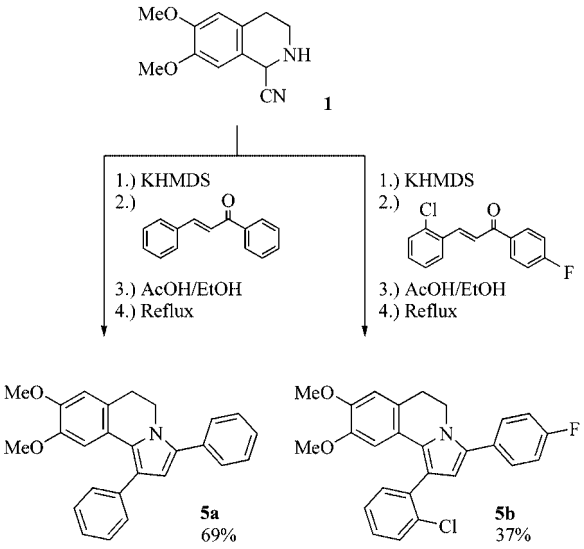
[a] Determined by ^{1}H NMR spectroscopy.

to the C-ring, the described synthetic method also allows the variation of the A-ring if different 1,2,3,4-tetrahydroisoquinoline-1-carbonitriles are used. As an example, compound **4** can be obtained from amino nitrile **3**[11,12] (Scheme 3).



Scheme 3. One-pot synthesis of 1,3-diphenyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline.

It turned out to be necessary to hydrolyze amine–borane complexes formed in the reduction step by addition of ethanolamine or citric acid to the reaction mixture.[13,14] By omission of the reduction step, the corresponding 5,6-dihydropyrrolo[2,1-*a*]isoquinolines can be obtained. Acetic acid and ethanol are added to the reaction mixture in order to promote the eliminiation of the hydroxy and the nitrile function (Scheme 4).



Scheme 4. Synthesis of 5,6-dihydropyrrolo[2,1-*a*]isoquinolines.

Conclusions

In summary, we present a simple one-pot synthesis of crispine A and some C-ring-substituted analogs. A- and C-ring-substituted products can conveniently be obtained by variation of the building blocks. Apart from the synthesis of the saturated C-ring, the formation of the unsaturated pyrrole ring is also possible. The reported transformations demonstrate the extension of the synthesis of simple pyrrolidines and pyrroles from α-amino nitriles to the preparation of polycyclic fused ring systems.

Experimental Section

General: All reactions were carried out under argon unless stated otherwise. THF was dried by distillation from Na/benzophenone. Cinnamaldehyde and benzaldehyde were distilled before use. All other solvents and reagents were purchased from commercial suppliers and were used without further purification. TLC was performed on TLC aluminium sheets (silica gel 60 F_{254}, E. Merck or alumina N/UV_{254}, Macherey–Nagel). Preparatvie TLC was performed on PSC glass plates (silica gel 60 F_{254}, 2 mm, 20 × 20 cm, with concentration zone, E. Merck). If not otherwise stated, flash chromatography was carried out on silica gel (32–63 μm, 60 Å, MP Biomedicals GmbH). Alternatively, alumina N (50–200 μm, Acros) was used. Preparative RP-HPLC separations were performed with Knauer MiniStar K-500 pumps and a Knauer variable-wavelength monitor. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker AC 300, AMX 400 or DRX 400 instrument, chemical shifts were referenced to the residual solvent signal ($CDCl_3$: δ_H = 7.26 ppm; δ_C = 77.0 ppm). Where indicated, signals were assigned based on DEPT, gs-COSY or gs-HMQC experiments. Some of the spin-spin coupling constants were determined by Lorentz-Gauss transformation of the FID. The relative configurations of the products were assigned with the aid of transient NOE experiments. ESI mass spectra were recorded with a Finnigan Navigator instrument from a solution of the analyte in MeCN/H_2O (70:30), ESI-HR mass spectra were measured with a Waters Q-TOF-Ultima 3 (NaO_2CH as internal reference), or with the same apparatus equipped with a LockSpray interface (NaO_2CH or NaI/CsI as external reference). FD mass spectra were recorded with a Finnigan MAT 95 at a desorption voltage of 5 kV and a heater current ramp of 10 mA/min. IR spectra were recorded with a Perkin–Elmer 1760X FTIR spectrometer. Melting points were measured with a Dr. Tottoli apparatus and are uncorrected. Elemental analyses were performed with a Vario Micro Cube (Elementar).

Preparation of the Isoquinolines 2. Typical Procedure: To a stirred solution of the α-amino nitrile (1.24 mmol) in dry THF (13 mL) was added a freshly prepared solution of KHMDS (1.36 mmol, 1.1 equiv.) in dry THF (1.2 mL) at –78 °C under argon. After 1–3 min, a solution of the α,β-unsaturated carbonyl compound (1.36 mmol, 1.1 equiv.) in dry THF (1.2 mL) was added and the mixture was stirred at –78 °C for 30 min. A mixture of ethanol (4.7 mL, 60 equiv.) and acetic acid (0.42 mL, 6 equiv.) was added, the cooling bath was removed and solid $NaBH_3CN$ (234 mg, 3 equiv.) was added immediately. The mixture was stirred at room temperature overnight. After addition of ethanolamine (1.19 mL, 16 equiv.) and stirring for 3 h, the reaction mixture was diluted with ethyl acetate, washed with water and brine and dried with Na_2SO_4. Evaporation of the solvent in vacuo gave a crude product which was further purified by column chromatography.

(±)-Crispine A (2a): The reaction was conducted according to the general procedure. Reagents: 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**1**) (182 mg, 0.83 mmol) in THF (7.6 mL), KHMDS (183 mg, 0.92 mmol) in THF (0.7 mL), acrolein (61.9 μL, 0.92 mmol) in THF (0.7 mL), ethanol (3.1 mL), acetic acid (0.28 mL), $NaCNBH_3$ (156 mg, 2.48 mmol). Before extractive workup, ethanolamine (0.9 mL) was added and the reaction mixture was stirred at room temperature for 3 h. The organic phase was washed twice with 1 N NaOH, and the organic layer was extracted three times with 1 N HCl. The combined aqueous layers where adjusted to pH = 12 by addition of NaOH. Extraction with CH_2Cl_2 (3×), drying with Na_2SO_4 and evaporation of the solvent in vacuo gave the crude product (186.1 mg) as a brown oil. A portion of the crude product (152.7 mg) was purified by flash

chromatography [cyclohexane/ethyl acetate, 1:4 + 1% (v/v) $EtNMe_2$] to yield crispine A as a colorless oil (20.4 mg, 13%). Spectroscopic data are in accordance with data from the literature.[2] ^1H NMR (300 MHz, $CDCl_3$): δ = 6.60, 6.56 (2 s, 2 H, 7-H, 10-H), 3.84 (s, 6 H, 2 OCH_3), 3.42 (t, 1 H, $^3J_{H,H}$ = 8.1 Hz, 10b-H), 3.17 (ddd, 1 H, $^3J_{H,H}$ = 10.9, 6.1, 2.7 Hz, 5-H-a), 3.11–2.93 (m, 2 H, 3-H-a, 6-H-a), 2.78–2.48 (m, 3 H, 3-H-b, 5-H-b, 6-H-b), 2.38–2.24 (m, 1 H, 1-H-a), 1.99–1.80 (m, 2 H, 2-H-a,b), 1.80–1.63 (m, 1 H, 1-H-b) ppm.

Preparation of *cis*-8,9-Dimethoxy-2-methyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (2b): The reaction was conducted according to the general procedure. Reagents: 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**1**) (171 mg, 0.78 mmol) in THF (5.6 mL), KHMDS (178 mg, 0.89 mmol) in THF (1.0 mL), methacrolein (71 µL, 0.86 mmol) in THF (1.0 mL), ethanol (2.9 mL), acetic acid (0.27 mL), $NaCNBH_3$ (152 mg), ethanolamine (0.76 mL). The reaction yielded a yellow oil (198.9 mg). Purification of a portion (184 mg) of the crude product by flash chromatography [cyclohexane/ethyl acetate, 1:6 + 1% (v/v) $EtNMe_2$] gave a diastereomeric mixture (*cis*/*trans* = 4:1) of 2-methyl-substituted crispine A (73 mg, 41%) as a yellowish amorphous solid. IR (film): $\tilde{\nu}$ = 2952, 1610, 1511, 1464, 1377, 1263, 1232, 1216, 1141, 1014 cm^{-1}. ^1H NMR, HMQC (400 MHz, $CDCl_3$): δ = 6.60, 6.54 (2 s, 2 H, 7-H, 10-H), 3.84 (s, 6 H, 2 OMe), 3.65 (br. dd, $^3J_{H,H}$ = 8.6 Hz, $^3J_{H,H}$ = 7.4 Hz, 0.8 H, 10b-H^c), 3.45 (m_c, 0.2 H, 10b-H^t), 3.24 (dd, $^3J_{H,H}$ = 9.2 Hz, $^3J_{H,H}$ = 7.7 Hz, 0.2 H, 3-H-a^t), 3.13 (ddt, $^3J_{H,H}$ = 8.3 Hz, $^3J_{H,H}$ = 5.8 Hz, $^3J_{H,H}$ = 2.6 Hz, 0.8 H, 5-H-a^c), 2.94–3.06 (m, 1 H, 5-H-a^t, 6-H^c), 2.77 (t, $^3J_{H,H}$ = 8.5 Hz, 0.8 H, 3-H-a^c), 2.58–2.73 (m, 3 H, 5-H-b^t, 6-H-a,b^t, 3-H-b^c, 5-H-b^c, 6-H-b^c), 2.54 (ddd, $^3J_{H,H}$ = 6.7 Hz, $^3J_{H,H}$ = 7.8 Hz, $^3J_{H,H}$ = 11.8 Hz, 0.8 H, 1-H-a^c), 2.27–2.44 (m, 1 H, 2-H^{c,t}), 2.14 (dd, $^3J_{H,H}$ = 9.3 Hz, $^3J_{H,H}$ = 7.9 Hz, 0.2 H, 3-H-b^t), 1.95–2.04 (m, 0.2 H, 1-H-a^t), 1.87 (ddd, $^3J_{H,H}$ = 11.7 Hz, $^3J_{H,H}$ = 7.1 Hz, $^3J_{H,H}$ = 4.1 Hz, 0.2 H, 1-H-b^t), 1.29 (td, $^3J_{H,H}$ = 11.9 Hz, $^3J_{H,H}$ = 9.2 Hz, 0.8 H, 1-H-b^c), 1.08 (d, $^3J_{H,H}$ = 7.0 Hz, 0.6 H, Me^t), 1.06 (d, $^3J_{H,H}$ = 6.7 Hz, 2.4 H, Me^c) ppm. ^{13}C NMR, HMQC (100.6 MHz, $CDCl_3$): δ = 147.3, 147.2 (C-8, C-9), 131.6, 126.3 (C-6a, C-10a), 111.4, 108.8 (C-7^c, C-10^c), 108.6 (C-7^t, C-10^t), 62.6 (C-10b^c), 62.4 (C-10b^t), 61.9 (C-3^t), 60.3 (C-3^c), 56.0, 55.9 (OMe), 48.6 (C-5^t), 48.2 (C-5^c), 40.8 (C-1^c), 39.2 (C-1^t), 31.4 (C-2^c), 30.2 (C-2^t), 28.1 (C-6^t), 26.9 (C-6^c), 20.5 (CH_3) ppm. Note: The superscripts *c* and *t* denote the *cis* and the *trans* isomer, respectively. ESI-MS: *m*/*z* (%) = 248.3 (100) [M + H]$^+$. HRMS: calcd. for [$C_{15}H_{21}NO_2$ + H]$^+$ 248.1615, found 248.1646.

Preparation of all-*cis*-3-*tert*-Butyl-1-(4-chlorophenyl)-8,9-dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (2c): The reaction was conducted according to the general procedure. Instead of ethanolamine a saturated solution of citric acid was used for the destruction of borane–amine complexes. Reagents: 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**1**) (242 mg, 1.11 mmol) in THF (11.5 mL), KHMDS (243 mg, 1.22 mmol) in THF (1.0 mL), 4,4-dimethyl-1-(4-chlorophenyl)pent-1-en-3-one[15] (271 mg, 1.22 mmol) in THF (1.0 mL), ethanol (4.2 mL), acetic acid (0.38 mL), $NaCNBH_3$ (209 mg, 3.32 mmol). The reduction was conducted for 4 d. After complete reduction, a saturated aq. solution of citric acid (1 mL) was added and the solution was stirred for 1 h. The reaction mixture was adjusted to pH = 14 by addition of NaOH and partitioned between ethyl acetate and a 1:1 mixture of 1 N NaOH/brine. The aqueous phase was reextracted with ethyl acetate and the combined organic phases were dried with Na_2SO_4. The solvent was removed under reduced pressure to yield a brown-white solid (496 mg). A portion (204 mg) of the raw product was dissolved in THF (3 mL) and a saturated aq. solution of citric acid (1 mL) was added. The mixture was left for 12 h and heated to reflux for 1 h. The mixture was adjusted to pH = 14 by addition of NaOH. After addition of ethyl acetate, the organic layer was extracted three times with 1 N NaOH solution. The combined aqueous phases were reextracted with ethyl acetate and the combined organic layers were dried with Na_2SO_4. The amorphous, yellow solid (160 mg, 0.40 mmol, 87%) obtained by removal of the solvent in vacuo did not require chromatographic purification. IR (KBr): $\tilde{\nu}$ = 2959, 1520, 1490, 1474, 1259, 1218, 1131, 1090, 1016, 825 cm^{-1}. ^1H NMR, NOESY (400 MHz, $CDCl_3$): δ = 7.23 (m_c, 2 H, 3′,5′-H), 7.03 (m_c, 2 H, 2′,6′-H), 6.52, 6.09 (2 s, 2 H, 7-H, 10-H), 3.78 (s, 3 H, OCH_3), 3.62–3.71 (m, 2 H, 5-H-a, 10b-H), 3.48–3.54 (m, 4 H, OCH_3, 1-H), contained in this multiplet: 3.51 (s, 3 H, OCH_3), 3.13 (m_c, 1 H, 6-H-a), 2.66 (dd, $^3J_{H,H}$ = 16.1, 3.5 Hz, 1 H, 6-H-b), 2.49 (ddd, $^3J_{H,H}$ = 13.2, 9.9, 8.4 Hz, 1 H, 2-H-a), 2.35 (t, $^3J_{H,H}$ = 8.4 Hz, 1 H, 3-H), 2.28–2.33 (m, 1 H, 5-H-b), 1.60 (ddd, $^3J_{H,H}$ = 13.2, 8.4, 3.5 Hz, 1 H, 2-H-b), 0.99 (s, 9 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 146.6, 146.2 (C-8, C-9), 144.6 (C-1′), 130.9 (C-4′), 130.6 (C-2′,6′), 128.7 (C-6a), 127.7 (C-3′,5′), 127.3 (C-10a), 110.6, 110.0 (C-7, C-10), 72.7 (C-3), 69.9 (C-10b), 55.6 (OCH_3), 50.3 (C-5), 42.5 (C-1), 38.2 (C-2), 33.4 [*C*(CH_3)$_3$], 29.8 (C-6), 28.1 (CH_3) ppm. ESI-MS: *m*/*z* (%) = 422.2 (73) [M + Na]$^+$, 400.2 (100) [M + H]$^+$. HRMS: calcd. for [$C_{24}H_{30}ClNO_2$ + H]$^+$ 400.2043, found 400.2053.

Preparation of all-*cis*-8,9-Dimethoxy-1,3-diphenyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (2d): The reaction was conducted according to the general procedure. Reagents: 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**1**) (139.3 mg, 0.64 mmol) in THF (4.6 mL), KHMDS (141.6 mg, 0.71 mmol) in THF (0.8 mL), chalcone (146.7 mg, 0.70 mmol) in THF (0.8 mL), ethanol (2.4 mL), acetic acid (0.22 mL), $NaCNBH_3$ (120.3 mg, 1.91 mmol), ethanolamine (0.62 mL). The reaction yielded an amorphous yellow solid (243.0 mg). Purification of a portion (224 mg) of the crude product by flash chromatography [petroleum ether/ethyl acetate, 10:1 + 1% (v/v) $EtNMe_2$] gave pure *cis*-1,3-diphenylcrispine A as a yellowish amorphous solid (132 mg, 58%). IR (film): $\tilde{\nu}$ = 2940, 1603, 1519, 1456, 1276, 1216, 1136, 1028, 761, 730, 701 cm^{-1}. ^1H NMR, COSY, HMQC (400 MHz, $CDCl_3$): δ = 7.47 (pseudo-d, $^3J_{H,H} \approx$ 8.2 Hz, 2 H, 2′,6′-H), 7.41 (pseudo-d, $^3J_{H,H} \approx$ 7.0 Hz, 2 H, 2′′,6′′-H), 7.36 (pseudo-t, $^3J_{H,H} \approx$ 7.5 Hz, 2 H, 3′,5′-H), 7.24–7.29 (m, 1 H, 4′-H), 7.13 (pseudo-t, $^3J_{H,H} \approx$ 7.5 Hz, 2 H, 3′′,5′′-H), 7.02 (m_c, 1 H, 4′′-H), 6.54, 6.16 (2 s, 2 H, 7-H, 10-H), 3.79 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, 10b-H), 3.78 (s, 3 H, OMe), 3.72 (ddd, $^3J_{H,H}$ = 9.7 Hz, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 4.2 Hz, 1 H, 1-H), 3.50 (s, 3 H, OMe), 3.46 (t, $^3J_{H,H}$ = 8.5 Hz, 1 H, 3-H), 3.18–3.06 (m, 2 H, 5-H-a, 6-H-a), 2.97 (ddd, $^2J_{H,H}$ = 13.3 Hz, $^3J_{H,H}$ = 9.5 Hz, $^3J_{H,H}$ = 8.0 Hz, 1 H, 2-H-a), 2.66 (m_c, 1 H, 6-H-b), 2.21–2.31 (m, 1 H, 5-H-b), 1.85 (ddd, $^2J_{H,H}$ = 13.3 Hz, $^3J_{H,H}$ = 9.1 Hz, $^3J_{H,H}$ = 4.2 Hz, 1 H, 2-H-b) ppm. ^{13}C NMR, HMQC (100.6 MHz, $CDCl_3$): δ = 146.5, 146.2, 145.8, 142.7 (q-C), 129.2 (C-2′,6′), 128.7 (C-6a/C-10a), 128.5 (C-3′′,5′′), 127.9 (C-3′,5′), 127.7 (C-2′′,6′′), 127.5 (C-6a/C-10a), 127.1 (C-4′′), 125.6 (C-4′), 110.9, 110.3 (C-7, C-10), 69.3 (C-3), 69.1 (C-10b), 55.6 (OMe), 47.9 (C-5), 45.5 (C-2), 44.9 (C-1), 29.8 (C-6) ppm. ESI-MS: *m*/*z* (%) = 386.3 (100) [M + H]$^+$, 384.8 (45) [M – 2 H]$^+$, 248.2 (28). HRMS: calcd. for [$C_{26}H_{27}NO_2$ + H]$^+$ 386.2120, found 386.2130. $C_{26}H_{27}NO_2$ (385.50): calcd. C 81.01, H 7.06, N 3.63; found C 80.94, H 7.07, N 3.58.

Preparation of all-*cis*-3-(4-Fluorophenyl)-8,9-dimethoxy-1-(4-methoxyphenyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (2e): The reaction was conducted according to the general procedure. Instead of ethanolamine, a saturated solution of citric acid was used for the destruction of borane–amine complexes. Reagents: 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**1**)

(271 mg, 1.24 mmol) in THF (13 mL), KHMDS (278 mg, 1.39 mmol) in THF (1.2 mL), 4′-fluoro-4-methoxychalcone (348 mg, 1.36 mmol) in THF (1.2 mL), ethanol (4.7 mL), acetic acid (0.42 mL), $NaCNBH_3$ (234 mg, 3.72 mmol). After complete reduction, a saturated aq. solution of citric acid (3 mL) was added. The mixture was stirred at room temperature for 2 h and heated to reflux 1 h. The solution was cooled, ethyl acetate was added and the reaction mixture was adjusted to pH = 14 by addition of NaOH. The two phases were separated and the organic layer was washed three times with 1 N NaOH. Drying with Na_2SO_4 and evaporation of the solvent yielded a brown oil (477 mg). Purification of a portion (222 mg) of the crude product by flash chromatography (cyclohexane/ethyl acetate, 10:1) yielded a yellowish amorphous solid (72 mg, 29%). IR (film): $\tilde{\nu}$ = 2936, 1610, 1510, 1465, 1246, 1219, 1176, 1136, 1033, 832 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39 (m_c, 2 H, 2′,6′-H), 7.28 (pseudo-d, $^3J_{H,H} \approx$ 8.7 Hz, 2 H, 3′,5′-H), 7.01 (pseudo-t, $^3J_{H,H} \approx$ 8.7 Hz, 2 H, 2′′,6′′-H), 6.65 (pseudo-d, $^3J_{H,H} \approx$ 8.7 Hz, 2 H, 3′′,5′′-H), 6.52, 6.15 (2 s, 2 H, 7-H, 10-H), 3.60–3.79 (m, 8 H, 2 OCH_3, 1-H, 10b-H), contained in this multiplett: 3.76 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 3.51 (s, 3 H, OCH_3), 3.40 (t, $^3J_{H,H}$ = 8.5 Hz, 1 H, 3-H), 2.98–3.14 (m, 2 H, 5-H-a, 6-H-a), 2.92 (ddd, $^3J_{H,H}$ = 13.2 Hz, $^3J_{H,H}$ = 9.3 Hz, $^3J_{H,H}$ = 8.1 Hz, 1 H, 2-H-a), 2.58–2.68 (m, 1 H, 6-H-b), 2.17–2.28 (m, 1 H, 5-H-b), 1.73 (ddd, $^3J_{H,H}$ = 13.2 Hz, $^3J_{H,H}$ = 9.0 Hz, $^3J_{H,H}$ = 4.0 Hz, 1 H, 2-H-b) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 162.0 ($^1J_{C,F}$ = 244.6 Hz, C-4′), 157.4 (C-4′′), 146.5, 146.2 (C-8, C-9), 138.3 ($^4J_{C,F}$ = 3.1 Hz, C-1′), 137.8 (C-1′′), 129.9 (C-2′′,6′′), 129.1 ($^3J_{C,F}$ = 7.9 Hz, C-2′,6′), 128.6, 127.3 (C-6a, C-10a), 115.3 ($^2J_{C,F}$ = 21.2 Hz, C-3′, 5′), 113.2 (C-3′′,5′′), 110.8, 110.2 (C-7, C-10), 68.9, 68.4 (C-3, C-10b), 55.5 (2 OCH_3), 55.0 (OCH_3), 47.8 (C-5), 45.6 (C-2), 43.8 (C-1), 29.7 (C-6) ppm. ESI-MS: *m*/*z* (%) = 456.2 (18) $[M + Na]^+$, 434.2 (100) $[M + H]^+$. HRMS: calcd. for $[C_{27}H_{28}FNO_3 + H]^+$ 434.2131, found 434.2147.

Preparation of all-*cis*-1-(2-Chlorophenyl)-3-(4-fluorophenyl)-8,9-dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (2f): The reaction was conducted according to the general procedure. Instead of ethanolamine, a saturated solution of citric acid was used for the destruction of borane–amine complexes. Reagents: 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**1**) (287 mg, 1.31 mmol) in THF (13.7 mL), KHMDS (290 mg, 1.44 mmol) in THF (1.2 mL), 2-chloro-4′-fluorochalcone (353 mg, 1.44 mmol) in THF (1.2 mL), ethanol (5.0 mL), acetic acid (0.45 mL), $NaCNBH_3$ (247 mg, 3.93 mmol). After complete reduction, a saturated aq. solution of citric acid (3 mL) was added. The mixture was stirred at room temperature for 2 h and heated to reflux for 1 h. The solution was cooled, ethyl acetate was added and the reaction mixture was adjusted to pH = 14 by addition of NaOH. The two phases were separated and the organic layer was washed three times with 1 N NaOH. Drying with Na_2SO_4 and evaporation of the solvent yielded a brown oil (566 mg). Purification of a portion (226 mg) of the crude product by flash chromatography [cyclohexane/ethyl acetate, 10:1 + 1% (v/v) $EtNMe_2$] yielded a yellow amorpohous solid (93 mg, 41%). IR (film): $\tilde{\nu}$ = 2945, 1606, 1509, 1466, 1363, 1219, 1156, 1136, 1036, 838 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.74 (dd, $^3J_{H,H}$ = 7.4 Hz, $^3J_{H,H}$ = 2.2 Hz, 1 H, 3′-H), 7.40 (m_c, 2 H, 2′′,6′′-H), 7.18–7.26 (m, 1 H, aryl), 7.04 (m_c, 2 H, aryl), 6.97 (m_c, 2 H, 3′′,5′′-H), 6.54, 6.20 (2 s, 2 H, 7-H, 10-H), 4.39 (ddd, $^3J_{H,H}$ = 9.8 Hz, $^3J_{H,H}$ = 7.5 Hz, $^3J_{H,H}$ = 4.2 Hz, 1 H, 1-H), 3.84 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, 10b-H), 3.78, 3.58 (2 s, 6 H, OCH_3), 3.47 (t, $^3J_{H,H}$ = 8.5 Hz, 1 H, 3-H), 2.92–3.11 (m, 3 H, 2-H-a, 5-H-a, 6-H-a), 2.61–2.72 (m, 1 H, 6-H-b), 2.20–2.32 (m, 1 H, 5-H-b), 1.71 (ddd, $^3J_{H,H}$ = 13.3 Hz, $^3J_{H,H}$ = 9.0 Hz, $^3J_{H,H}$ = 4.2 Hz, 1 H, 2-H-b) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 162.0 ($^1J_{C,F}$ = 244.9 Hz C-4′′), 146.6, 146.5 (C-8, C-9), 143.0 (C-1′), 138.0 ($^4J_{C,F}$ = 3.1 Hz, C-1′′), 133.5 (C-2′), 131.1 (C-6′), 129.1 ($^3J_{C,F}$ = 7.9 Hz, C-2′′,6′′), 128.3 (C-3′), 128.2, 127.1 (C-6a, C-10a), 126.9 (C-5′), 126.8 (C-4′), 115.3 ($^2J_{C,F}$ = 21.2 Hz, C-3′′, 5′′), 110.9, 109.3 (C-7, C-10), 69.1, 68.4 (C-3, C-10b), 55.6 (OCH_3), 55.5 (OCH_3), 47.7 (C-5), 44.7 (C-1), 39.1 (C-2), 29.7 (C-6) ppm. ESI-MS: *m*/*z* (%) = 460.2 (38) $[M + Na]^+$, 438.2 (100) $[M + H]^+$. HRMS: calcd. for $[C_{26}H_{25}ClFNO_2 + H]^+$ 438.1636, found 438.1636. $C_{26}H_{25}ClFNO_2$ (437.93): calcd. C 71.31, H 5.75, N 3.20; found C 71.40, H 5.73, N 3.10.

1,3-Diphenyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (4): The reaction was conducted according to the general procedure. Reagents: 1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**3**) (62 mg, 0.35 mmol) in THF (2.5 mL), KHMDS (78 mg, 0.39 mmol) in THF (0.4 mL), chalcone (79 mg, 0.38 mmol) in THF (0.4 mL), ethanol (1.3 mL), acetic acid (0.12 mL), $NaCNBH_3$ (65 mg, 1.64 mmol), ethanolamine (0.33 mL). The reaction yields a yellow-orange oil (121.4 mg). A portion (62.6 mg) of the crude product was dissolved in THF (1 mL) and saturated citric acid was added in order to destroy remaining borane–amine complexes. The reaction mixture was adjusted to pH = 14 after 10 d at room temperature and extracted twice with 1 N NaOH. The combined aqueous phases were extracted with ethyl acetate and the combined organic layers were dried with Na_2SO_4. The solvent was removed under reduced pressure. The crude product (56.9 mg) was purified by semipreparative HPLC [Phenomenex Luna C18(2), 10 µ, 250 × 21.2 mm, acetonitrile/water, 90:10, 20 mL/min] to yield a colorless oil (10.0 mg, 37%). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.50 (m, 5 H, aryl), 7.31–7.39 (m, 2 H, aryl), 7.13 (mc, 2 H, aryl), 6.93–7.08 (m, 3 H, aryl), 6.84 (t, $^3J_{H,H}$ = 7.4 Hz, 1 H, aryl), 6.71 (d, $^3J_{H,H}$ = 7.7 Hz, 1 H, aryl), 3.87 (d, $^3J_{H,H}$ = 6.7 Hz, 1 H, 10b-H), 3.73–3.83 (m, 1 H, 1-H), 3.46 (t, 1 H, $^3J_{H,H}$ = 8.5 Hz, 3-H), 3.07–3.28 (m, 2 H, 5-H-a, 6-H-a), 2.98 (ddd, $^3J_{H,H}$ = 13.2 Hz, $^3J_{H,H}$ = 9.5 Hz, $^3J_{H,H}$ = 8.5 Hz, 1 H, 2-H-a), 2.76 (dd, $^3J_{H,H}$ = 15.4 Hz, $^3J_{H,H}$ = 3.7 Hz, 1 H, 6-H-b), 2.23–2.37 (m, 1 H, 5-H-b), 1.84 (ddd, $^3J_{H,H}$ = 13.2, $^3J_{H,H}$ = 8.5 Hz, $^3J_{H,H}$ = 3.9 Hz, 1 H, 2-H-b). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 145.6, 142.6, 136.5, 135.4 (q-C), 129.1 (2 C), 128.4 (2 C), 128.2 (1 C), 127.8 (2 C), 127.7 (2 C), 127.1 (1 C), 126.8 (1 C), 125.4 (1 C), 125.3 (1 C), 125.0 (1 C), 69.3, 69.2 (C-3, C-10b), 47.8 (C-5), 45.2 (C-2), 44.5 (C-1), 30.3 (C-6). ESI-MS: *m*/*z* (%) = 326.2 (100) $[M + H]^+$. HRMS: calcd. for $[M + H]^+$ 326.1909, found 326.1908.

Preparation of the Pyrroles 5. Typical Procedure: To a stirred solution of the α-amino nitrile **1** (0.91 mmol) in dry THF (8.3 mL) was added a freshly prepared solution of KHMDS (1.0 mmol, 1.1 equiv.) in THF (0.8 mL) at –78 °C under argon. After 1–3 min, a solution of the α,β-unsaturated carbonyl compound (1.0 mmol, 1.1 equiv.) in THF (0.8 mL) was added and the mixture was stirred for 30 min. A mixture of ethanol (3.7 mL, 60 equiv.) and acetic acid (0.31 mL, 6 equiv.) was added. The cooling was removed and the reaction mixture was refluxed for 30 min. The reaction mixture was partitioned three times between saturated $NaHCO_3$ solution and ethyl acetate. Drying of the organic layer with Na_2SO_4 and evaporation of the solvent in vacuo gave a crude product, which was further purified by column chromatography.

Preparation of 8,9-Dimethoxy-1,3-diphenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (5a): The reaction was conducted according to the general procedure. Reagents: 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**1**) (219 mg, 1.00 mmol) in THF (9.2 mL), KHMDS (215 mg, 1.10 mmol) in THF (0.8 mL), chalcone (230 mg, 1.10 mmol) in THF (0.8 mL), ethanol (3.8 mL), acetic acid (0.34 mL). The reaction yielded a light brown solid (367 mg). Purification of a portion (64 mg) of the crude product by flash

chromatography [cyclohexane/ethyl acetate, 11:1 + 1% (v/v) $EtNMe_2$] yielded the product as amorphous colorless solid (46 mg, 69%). IR (KBr): $\tilde{\nu}$ = 2905, 1602, 1508, 1488, 1286, 1233, 1214, 1137, 801, 763, 702 cm^{-1}. ^1H NMR, COSY, HMBC, NOESY (400 MHz, $CDCl_3$): δ = 7.55–7.59 (m, 2 H, phenyl), 7.46 (s, 2 H, phenyl), 7.43–7.46 (m, 2 H, phenyl), 7.31–7.43 (m, 3 H, phenyl), 7.28 (m_c, 1 H, phenyl), 6.92 (s, 1 H, 10-H), 6.74 (s, 1 H, 7-H), 6.39 (s, 1 H, 2-H), 4.13 (t, $^3J_{H,H}$ = 6.4 Hz, 2 H, 5-H_2), 3.89 (s, 3 H, 8-OCH_3), 3.46 (s, 3 H, 9-OCH_3), 2.99 (t, $^3J_{H,H}$ = 6.4 Hz, 2 H, 6-H_2) ppm. ^{13}C NMR, HMQC, HMBC (100.6 MHz, $CDCl_3$): δ = 147.3 (C-9), 147.0 (C-8), 137.4 (C-1′ or C-1′′), 133.1 (C-3), 132.6 (C-1′ or C-1′′), 129.3 (2 C), 128.7 (2 C), 128.5 (2 C), 128.3 (2 C), 126.9 (C-4′), 126.2 (C-4′′), 126.0 (C-10b), 124.7 (C-6a), 122.6 (C-10a), 121.4 (C-1), 110.8 (C-7), 110.6 (C-2), 108.0 (C-10), 55.9 (8-OCH_3), 55.3 (9-OCH_3), 42.6 (C-5), 29.8 (C-6) ppm. FD-MS: *m*/*z* (%) = 381.0 (100) $[M]^+$. $C_{26}H_{23}NO_2$ (381.47): calcd. C 81.86, H 6.08, N 3.67; found C 81.88, H 6.04, N 3.67.

Preparation of 1-(2-Chlorophenyl)-3-(4-fluorophenyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (5b): The reaction was conducted according to the general procedure for the pyrroles. Reagents: 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**1**) (199 mg, 0.91 mmol) in THF (8.3 mL), KHMDS (200 mg, 1.00 mmol) in THF (0.8 mL), 2-chloro-4′-fluorochalcone (262 mg, 1.00 mmol) in THF (0.8 mL), ethanol (3.7 mL), acetic acid (0.31 mL). The reaction yielded a slightly brown solid (352 mg). Purification of a portion (143 mg) of the crude product by flash chromatography [cyclohexane/ethyl acetate, 5:1 + 1% (v/v) $EtNMe_2$] gave the product as amorphous white solid (60 mg, 37%). IR (KBr): $\tilde{\nu}$ = 2934, 1508, 1484, 1239, 1214, 1141, 1030, 800, 768 cm^{-1}. ^1H NMR, HMBC (400 MHz, $CDCl_3$): δ = 7.48 (m_c, 2 H, *o*-ClC_6H_4), 7.42 (m_c, 2 H, 2′′,6′′-H), 7.23–7.31 (m, 2 H, *o*-ClC_6H_4), 7.13 (pseudo-t, $^3J_{H,H}$ = 8.7 Hz, 2 H, 3′′,5′′-H), 6.71 (s, 1 H, 7-H), 6.51 (s, 1 H, 10-H), 6.33 (s, 1 H, 2-H), 4.12 (t, $^3J_{H,H}$ = 6.2 Hz, 2 H, 5-H_2), 3.87 (s, 3 H, 9-OCH_3), 3.38 (s, 3 H, 8-OCH_3), 3.00 (t, $^3J_{H,H}$ = 6.2 Hz, 2 H, 6-H_2) ppm. ^{13}C NMR, HMQC (400 MHz, $CDCl_3$): δ = 161.9 ($^1J_{C,F}$ = 247.2 Hz, C-4′′), 147.5 (C-9), 147.0 (C-8), 136.5 (C-2′), 134.3 (C-1′), 132.8 (*o*-ClC_6H_4), 131.6 (C-1), 130.3 ($^3J_{C,F}$ = 7.7 Hz, C-2′′,6′′), 129.7 (*o*-ClC_6H_4), 128.7 ($^4J_{C,F}$ = 3.6 Hz, C-1′′), 128.1 (*o*-ClC_6H_4), 127.0 (C-3), 126.7 (*o*-ClC_6H_4), 124.1 (C-6a), 122.6 (C-10b), 117.8 (C-10a), 115.4 ($^2J_{C,F}$ = 21.5 Hz, C-3′′,5′′), 111.1 (C-2), 110.8 (C-7), 107.2 (C-10), 55.9 (8-OCH_3), 55.2 (9-OCH_3), 42.3 (C-5), 29.6 (C-6) ppm. FD-MS: *m*/*z* (%) = 432.9 (100) $[M]^+$. $C_{26}H_{21}ClFNO_2$ (433.90): calcd. C 71.97, H 4.88, N 3.23; found C 71.93, H 4.91, N 3.32.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of all products.

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