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Concise Enantiospecific, Stereoselective Syntheses of (+)-Crispine A and Its (−)-Antipode

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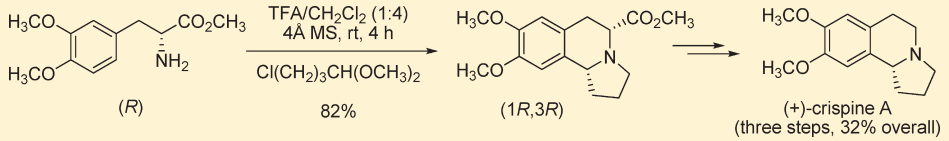
Supporting Information

ABSTRACT:



An enantiospecific and stereoselective total synthesis of the natural product (+)-crispine A has been demonstrated employing a Pictet−Spengler bis-cyclization reaction between commercially available (*R*)-(−)-methyl 2-amino-3-(3,4-dimethoxyphenyl)-propanoate and 4-chloro-1,1-dimethoxybutane to preferentially provide the *cis* tricyclic adduct. Decarboxylation by a convenient two-step protocol provided the enantiopure natural product in three steps with an overall isolated yield of 32% from the amino acid. The unnatural antipode (−)-crispine A was similarly prepared in three steps from the commercially available (*S*)-(+)-amino acid.

The pyrroloisoquinoline alkaloid (+)-crispine A [(*R*)-(+)-**1**, Figure 1] was first isolated in 2002 from the Mongolian thistle *Carduus crispus*[1] and has since emerged as a natural product target of interest, due largely to reports of its cytotoxic activity and similarity to known congeners shown to exhibit antidepressant-like activity.[2] Within the decade, several concise syntheses of racemic crispine A have been described, differing mainly in the strategies utilized to construct the pyrrolidine ring.[3] Interestingly, synthetic reports of this heterocycle can also be found in the literature prior to its identification as a natural product extract or its naming as crispine A.[4] A number of directed enantioselective syntheses of this alkaloid have also recently appeared in the literature,[5] along with asymmetric preparations of the (*S*) antipode[6] as well as crispine A analogues.[7] We nevertheless sought to contribute our own novel asymmetric approach based on a Pictet−Spengler bis-cyclization reaction between enantiopure methoxytyrosine derivatives and an acetal bearing a tethered terminal leaving group. This was envisioned to provide intermediate adducts that would undergo a concomitant second cyclization to provide the tricyclic pyrrolo[2,1-*a*]isoquinoline core of crispine A in one step. This communication summarizes our results toward this goal.

The first intermolecular condensation reaction between *β*-phenethylamine and an aldehyde surrogate in the presence of HCl to afford a tetrahydroisoquinoline was described in 1911 by Pictet and Spengler[8] and later applied to the preparation of tetrahydro-*β*-carbolines from tryptamines by Tatsui.[9] Since that time the Pictet−Spengler condensation reaction[10] has become one of the most widely used methods for the preparation of 1-substituted tetrahydroisoquinoline and tetrahydro-*β*-carboline natural products and related alkaloids with diverse biological activities.[11] When electron-rich α-substituted-*β*-phenethylamines are condensed with aldehydes or aldehyde surrogates, the chirality of the α-substituted center can influence the transition state conformation such that the thermodynamically more stable 1,3-*cis* stereochemistry is generally observed in the tetrahydroisoquinoline products.[12,13] Thus we envisioned the key step of our stereocontrolled construction of the crispine A core to provide a new chiral center through 1,3-transfer of chirality from an enantiopure methoxytyrosine precursor to preferentially provide a 1,3-*cis* adduct.

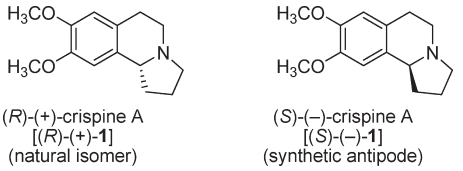


Figure 1. Natural product (+)-crispine A and its unnatural (−)-antipode.

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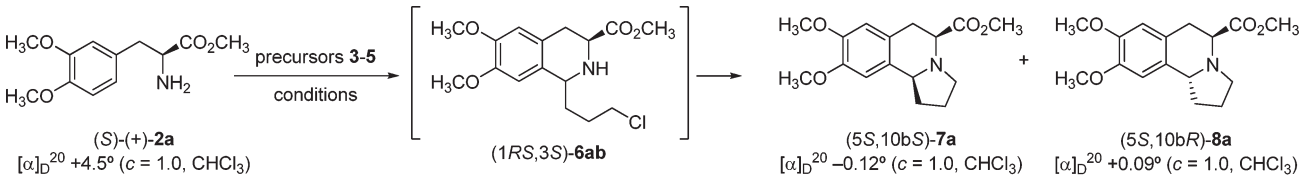
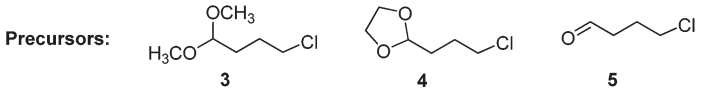
Table 1. Pictet−Spengler Condensation and Cyclization Conditions for (*S*)-(+)-2a





entry	precursor	conditions	ratio 7a:8a	result/yield
1	3	CH_2Cl_2/TFA (1:1), rt, 1 h	3:1	35%
2	3	CH_2Cl_2/TFA (4:1), rt, 4 h	4.5:1	38%
3	3	CH_2Cl_2/TFA (4:1), 4 Å mol. sieves, rt, 4 h	4.5:1	98%
4	4	CH_2Cl_2/TFA (4:1), 4 Å mol. sieves, rt, 4 h	4.5:1	55%[a]
5	5	CH_2Cl_2/TFA (4:1), 4 Å mol. sieves, rt, 4 h		no reaction
6	3	CH_3CN/TFA (4:1), 4 Å mol. sieves, rt, 4 h	2:1	95%
7	3	DME/TFA (4:1), 4 Å mol. sieves, rt, 4 h	2:1	91%
8	3	*i*PrOH/TFA (3:1), 4 Å mol. sieves, 50 °C, 3 h	3:1	95%
9	3	CH_2Cl_2, BF_3•OEt_2, rt, 15 h		no reaction
10	3	CH_2Cl_2, $TiCl_4$, rt, 15 h		decomposition
11	3	CH_2Cl_2, 1% TfOH, rt, 15 h		no reaction
12	3	NaOAc, HOAc, rt, 15 h		no reaction

[a] Longer reaction time (18 h) resulted in full conversion at 97% yield.

RESULTS AND DISCUSSION

To initiate our studies, we subjected commercially available (*S*)-(+)-methyl 2-amino-3-(3,4-dimethoxyphenyl)propanoate [(*S*)-(+)-**2a**][14] to Pictet−Spengler condensation conditions, first with 4-chloro-1,1-dimethoxybutane (**3**) as the coupling partner, and using trifluoroacetic acid as the catalyst (entries 1−3, Table 1). We found that the condensation reaction was very rapid, generating a mixture of tetrahydroisoquinoline isomers (1*RS*,3*S*)-**6ab** in a short time at room temperature (as determined by ^{1}H NMR and LC−MS analyses). Continued stirring led directly to a mixture of the 1,3-*cis* isomer (5*S*,10b*S*)-**7a** and 1,3-*trans* isomer (5*S*,10b*R*)-**8a** in ratios that were determined by ^{1}H NMR and LC−MS analyses. The crude reaction mixtures were then purified by column chromatography to isolate the stereoisomers, in every case favoring the 1,3-*cis* epimer as the major product. We found that the use of 4 Å molecular sieves in a 4:1 mixture of methylene chloride and trifluoroacetic acid at room temperature offered the best conditions to provide a 4.5:1 mixture of 1,3-*cis* isomer (5*S*,10b*S*)-**7a** and 1,3-*trans* isomer (5*S*,10b*R*)-**8a** after four hours (entry 3). Use of other solvents for the bis-cyclization transformation were less effective (entries 6−8), as were other acid catalysts (entries 9−12).

We also found that subjecting (*S*)-(+)-**2a** to the optimized two-component cyclization conditions with precursor 2-(3-chloropropyl)-1,3-dioxolane (**4**) in place of acetal **3** had no noticeable effect on the *cis*/*trans* product ratio, but the conversion to product was much slower, providing a comparatively lower isolated yield of the mixture over the same 4 h time course studied (entry 4, Table 1). When run for a longer time, however, the mixture fully converted to the **7a**/**8a** mixture in a 4.5:1 ratio in comparable yield. This longer reaction time can be attributed to the greater stability of the dioxolane acetal of **4** under acidic conditions when compared to the dimethoxy acetal of **3**. Interestingly, repeated attempts to use 4-chlorobutyraldehyde (**5**) failed to provide any of the Pictet−Spengler adduct or the bis-cyclized products (entry 5). Under these conditions **5** was observed to decompose rapidly, resulting in recovery of the unreacted precursor (*S*)-(+)-**2a**, consistent with our proposed acid-catalyzed mechanism (*vide infra*).

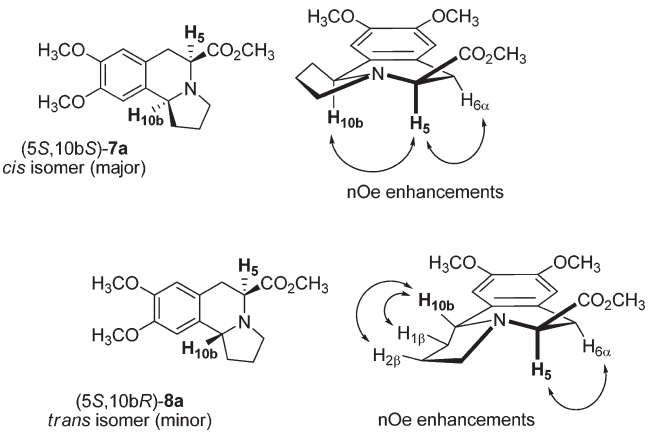


Figure 2. Stereochemical assignment of the 1,3-*cis* and 1,3-*trans* stereoisomers.

Proton and carbon NMR experiments were used to assign the structures of (5*S*,10b*S*)-**7a** and (5*S*,10b*R*)-**8a** as shown in Figure 2. The 1,3-*cis* relative stereochemistry for isomer (5*S*,10b*S*)-**7a** was confirmed through NOE difference experiments to measure the through-space interaction between the

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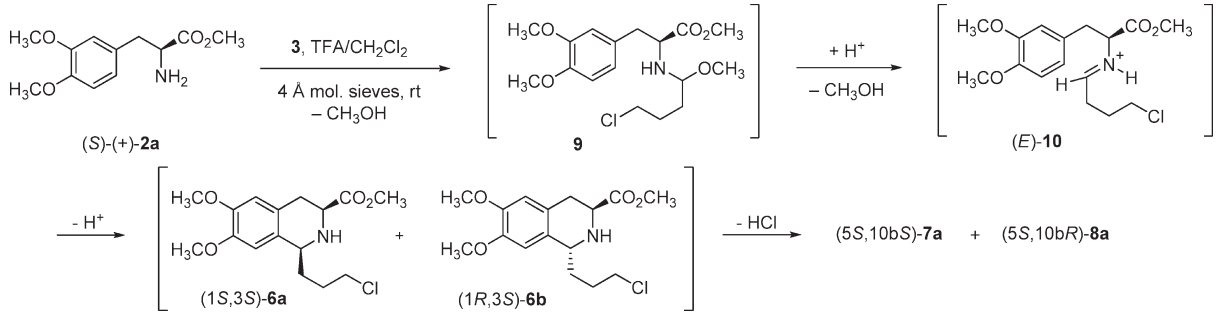
Scheme 1. Proposed Reaction Mechanism of the Pictet−Spengler bis-cyclization reaction



α-amino acid proton H-5 and the methine proton H-10b. It is well-known that 1,3-disubstituted dihydroisoquinolines prefer to adopt a framework resembling a half-chair conformation, where substituents can attain pseudoequatorial dispositions.[15] As a result, irradiation of the axial H-5 proton at 3.6 ppm resulted in an increased signal for the axial H-10b proton at 3.7 ppm, as well as for one of the two diastereotopic protons H-6 on the adjacent methylene at 2.5 ppm.

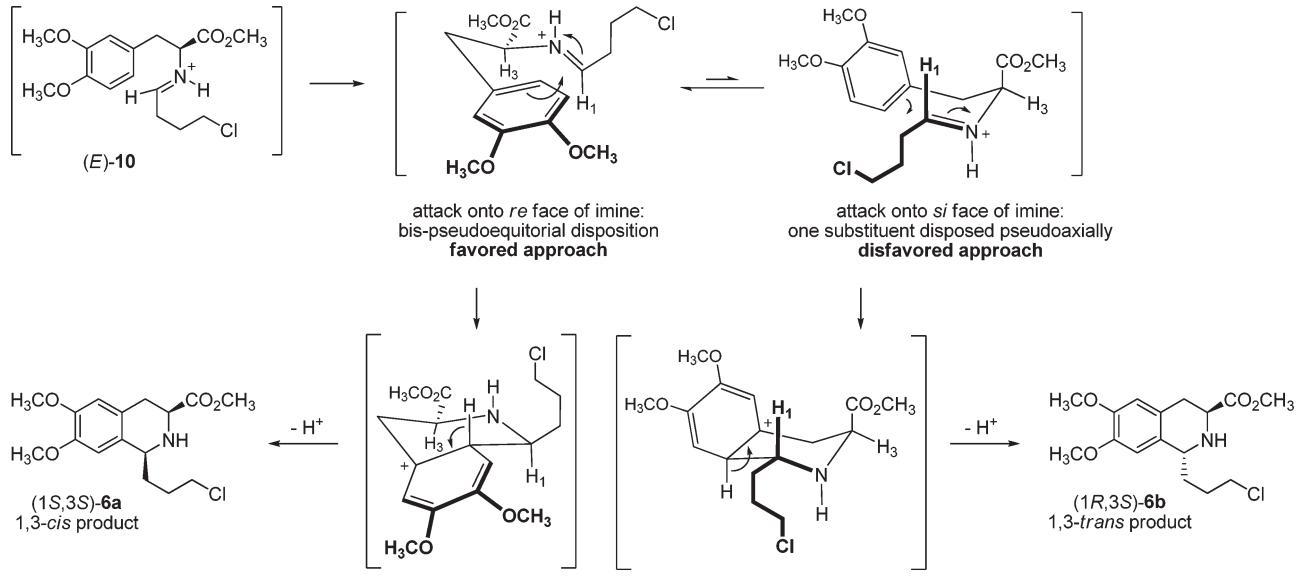
In contrast, 1,3-disubstitution on the 1,3-*trans* isomer (5*S*,10b*R*)-**8a** forces the H-10b proton to assume a pseudoequatorial configuration to accommodate the half-chair conformation (Figure 2). As a result, irradiation of the α-amino acid proton H-5 at 4.2 ppm does not result in a measurable NOE enhancement of the C-10b proton at 3.7 ppm and vice versa, leading to the designation of (5*S*,10b*R*)-**8a** as the minor 1,3-*trans* stereoisomer. As expected, irradiation of proton H-5 resulted in signal enhancements for one of the two diastereotopic protons H-6 on the adjacent methylene at 2.8 ppm, as well as for the pseudoaxial proton H-1 on the fused pyrrolidine ring at 2.4 ppm.

We propose a plausible mechanism for the transformation as depicted in Scheme 1. Several equivalents of trifluoroacetic acid play a role in inducing elimination of methanol, first in elimination from dimethyl acetal **3** to provide a reactive oxonium ion species that undergoes attack by the amino acid (*S*)-(+)-**2a**. The resulting hemiaminal **9** may then undergo acid-catalyzed expulsion of methanol to provide the thermodynamically favored (*E*)-iminium intermediate **10**. Electrophilic aromatic substitution then takes place to ultimately form the 1-(3-chloropropyl)tetrahydroisoquinoline adducts (1*S*,3*S*)-**6a** and (1*R*,3*S*)-**6b**. This is followed by the facile intramolecular displacement of the pendant alkyl chloride by the nitrogen to provide the tricyclic products (5*S*,10b*S*)-**7a** and (5*S*,10b*R*)-**8a**. From our examination of the reaction conditions, we surmise that the role of 4 Å molecular sieves is to largely sequester the two eliminated equivalents of methanol, driving the reaction to **10**.

A rationale to describe the observed 1,3-*cis* stereoselectivity of the ring closure step in the Pictet−Spengler cyclization is proposed in Scheme 2. Intramolecular approach of the pendant aromatic from the diastereotopic *re* face of the iminium species (*E*)-**10** forces the molecule to attain of a half-chair conformation[15] to facilitate molecular orbital overlap and allows both the α-ester and 3-chloropropyl substituents to adopt pseudoequatorial dispositions in the developing transition state configuration. Upon ring closure and rearomatization, this configuration leads to a 1,3-*cis* relationship between the substituents for the tetrahydroisoquinoline product (1*S*,3*S*)-**6a**.

In order for the pendant aromatic to approach from the *si* face of imine (*E*)-**10**, however, the alignment to a half-chair conformation forces the α-ester substituent into a pseudoaxial disposition, a less favorable energy state (Scheme 2). In addition, a developing

Scheme 2. Proposed Rationale for the Selective Generation of the *cis* Adduct (5*S*,10b*S*)-6a



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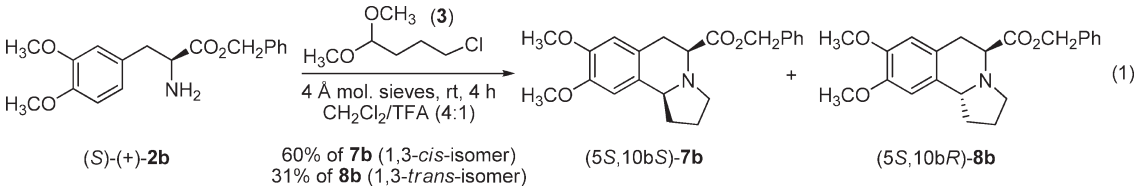
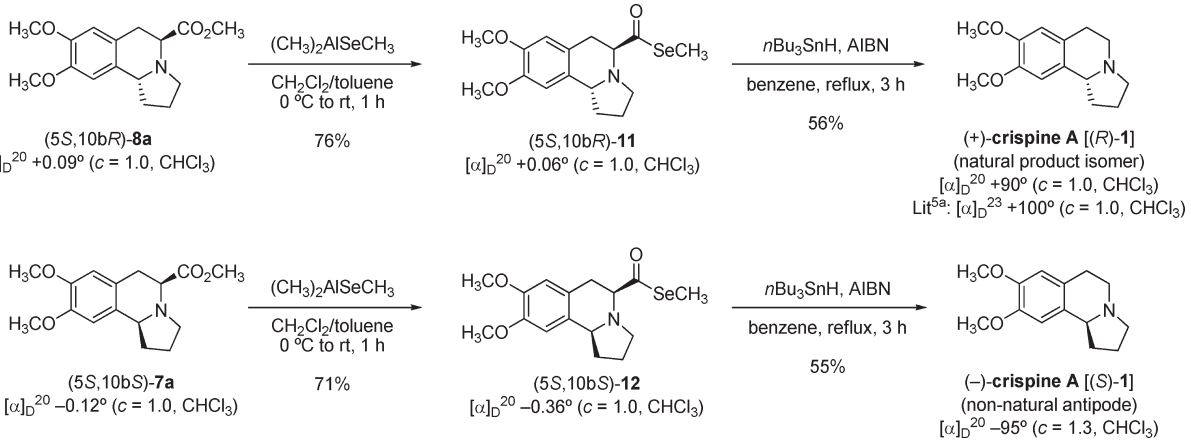


Scheme 3. Elaboration of L-DOPA-Derived Tricycles to (+)- and (−)-Crispine A



A[1,3] strain interaction between proton H_1 and the ester moiety in the developing transition state contributes to disfavor this arrangement. However, ring closure and rearomatization through this disfavored by accessible conformation leads to a 1,3-*trans* relationship between the substituents for the tetrahydroisoquinoline product (1*R*,3*S*)-**6b**. As one might predict on the basis of energy considerations, the bias to pass through the transition state conformation by attack onto the *re* face of iminium intermediate **10** is reflected in the observed ratio of products **6a**:**6b**, favoring the 1,3-*cis* diastereomer **6a**.

In order to probe the effects of the phenethylamine α-substituent on the facial selectivity of the two-step cyclization, we made a small effort to evaluate the consequences for selectivity utilizing the slightly larger benzyl ester (*S*)-(+)-**2b** (eq 1). Although it has been demonstrated that the size of the aldehyde (or surrogate) can affect the stereochemistry at the newly formed tetrahydroisoquinoline C-1 position,[10] we were not aware of many recent examples comparing the size of the phenethylamine α-substituent to the resulting stereoselectivity from 1,3-chiral transfer.[16] Although examples within one report suggested that the difference in size of phenethylamine α-esters would not significantly change the 1,3-*cis*/*trans* product ratio,[17] we were initially surprised to find that increasing the size of the α-methyl ester (*S*)-(+)-**2a** to the benzyl ester (*S*)-(+)-**2b**[18] diminished the preference for the 1,3-*cis* isomer (5*S*,10b*S*)-**7** from 4.5:1 to 2:1. Although we cannot at present propose considerations to account for this observation, these effects may be analogous to the loss of stereoselectivity noted in similar systems when the relative size of the aldehyde component is increased.[19]

The enantiopure tricyclic tetrahydroisoquinoline isomers were then individually elaborated to the natural product and antipode isomers of crispine A, as shown in Scheme 3. First, 1,3-*trans* isomer (5*S*,10b*R*)-**8a**, the minor adduct from the Pictet−Spengler cyclization, was converted to the methylselenyl ester (5*S*,10b*R*)-**11** by the use of dimethylaluminum methaneselenolate.[20] Subjection of (5*S*,10b*R*)-**11** to radical decarboxylation conditions[21,22] led to the natural product isomer of crispine A [(*R*)-(+)-**1**][1,5] in 42% isolated yield for the two-step process. The measured optical rotation $[\alpha]^{20}_{D}$ +90° (*c* 1.0, $CHCl_3$) for (*R*)-(+)-**1** was consistent with the two literature values reported in chloroform of $[\alpha]^{25}_{D}$ +97° (*c* 1.1)[5b] and $[\alpha]^{23}_{D}$ +100° (*c* 1.0)[5a] and was a single enantiomer by chiral HPLC analysis (see Supporting Information).

Similarly, the *cis* isomer (5*S*,10b*S*)-**7a**, the major adduct from the Pictet−Spengler cyclization, was converted to the methylselenyl ester (5*S*,10b*S*)-**12** as shown in Scheme 3. As with the regioisomer (5*S*,10b*R*)-**11**, the radical decarboxylation protocol transformed (5*S*,10b*S*)-**12** to the unnatural antipode of crispine A [(*S*)-(−)-**1**][1,6] in 39% isolated yield for the two-step process. The alkaloid enantiomer (*S*)-**1** was found to rotate polarized light in an equal but opposite manner to (*R*)-**1** and was also shown to be a single isomer by chiral HPLC analysis (see Supporting Information). This confirms the identity of both intermediates **7a** and **8a** as a diastereomeric pair and also demonstrates that no appreciable epimerization had occurred during the synthetic manipulations to (*S*)-(−)- and (*R*)-(+)-**1**.

The Pictet−Spengler bis-cyclization reaction was then applied to commercially available (but quite a bit more expensive) (*R*)-(−)-methyl 2-amino-3-(3,4-dimethoxyphenyl)propanoate [(*R*)-(−)-**2a**] as shown in Scheme 4. Thus, a slight excess of 4-chloro-1, 1-dimethoxybutane (**3**) was added to a stirring suspension of (*R*)-(−)-methyl 2-amino-3-(3,4-dimethoxyphenyl)propanoate [(*R*)-(−)-**2a**] and 4 Å molecular sieves in a 4:1 mixture of methylene chloride and trifluoroacetic acid at room temperature. After 4 h, the components had converted to a mixture of tetrahydroisoquinoline isomers from which the 1,3-*cis* isomer (5*R*,10b*R*)-**7a** was isolated by chromatography in 82% yield. This preferentially formed tricyclic adduct was then subjected to the selenyl esterification and radical decarboxylation two-step protocol to provide the enantiopure natural product (+)-**1** with an overall

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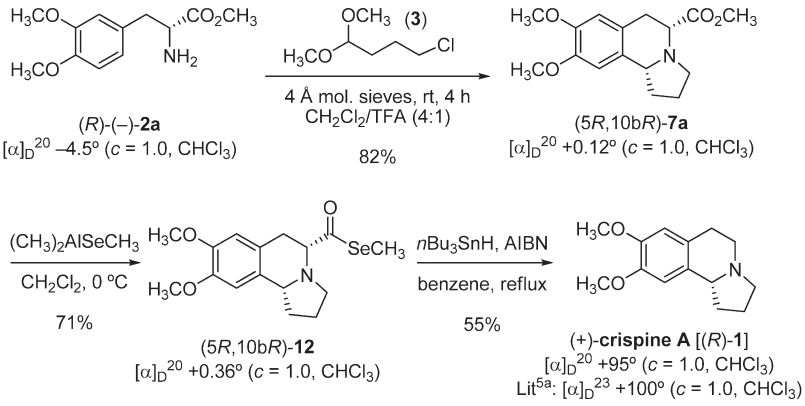
Scheme 4. Preparation of (+)-Crispine A from D-DOPA-Derived Precursor (*R*)-(−)-2a

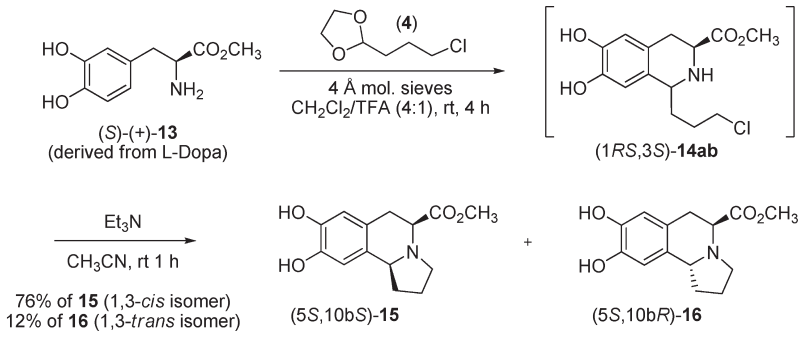


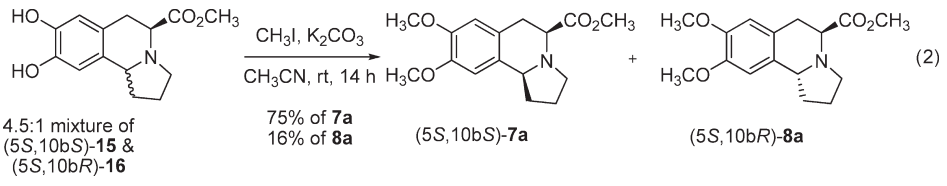
32% isolated yield from the amino acid. The optical rotation, chiral HPLC analysis and other spectral data were found to match the (*R*)-(+)-**1** isomer prepared through the route using (*S*)-(+)-**2a**, confirming the chiral integrity of this asymmetric approach.

During the time we were determining suitable conditions for the bis-condensation reaction with the bis-methoxy precursor (*S*)-(+)-**2a**, we also explored the feasibility for synthesis with the much less expensive (*S*)-(+)-methyl 2-amino-3-(3,4-dihydroxyphenyl)propanoate [(*S*)-(+)-**13**],[23] which is derived from L-DOPA (Scheme 5). Thus, (*S*)-(+)-**13** was subjected to the Pictet−Spengler condensation conditions with 2-(3-chloropropyl)-1,3-dioxolane (**4**) at room temperature, cleanly providing a 4:1 mixture of tetrahydroisoquinoline isomers (1*RS*,3*S*)-**14ab** in a 4.5:1 ratio (as determined by ^{1}H NMR and LC−MS analyses). However, even upon prolonged stirring at room temperature, the mixture of diastereomers did not cyclize to the tricyclic adducts, as was seen with the bis-methoxy precursors (*S*)-(+)-**2a**, although upon workup and purification of the crude reaction mixture, we found that the individual adducts spontaneously cyclized on exposure to silica gel, providing both the 1,3-*cis* isomer (5*S*,10b*S*)-**15** and 1,3-*trans* isomer (5*S*,10b*R*)-**16** as they were eluted from the chromatography column. Alternatively, when the conversion from (*S*)-(+)-**13** to the (1*RS*,3*S*)-**14ab** mixture under the Pictet−Spengler condensation conditions was judged to be complete, the solids were removed from the reaction mixture by filtration, the filtrate was concentrated, and the residue was dissolved in acetonitrile. Treatment of the resulting mixture with triethylamine allowed the second cyclization to take place at room temperature in 1 h, providing (5*S*,10b*S*)-**15** and (5*S*,10b*R*)-**16** in a 4.5:1 ratio of stereoisomers favoring the 1,3-*cis* epimer, and were separated by column chromatography to provide the individual isomers.

In a separate experiment, we subjected the 4.5:1 mixture of (5*S*,10b*S*)-**15** and (5*S*,10b*R*)-**16** diol isomers to alkylation conditions with excess iodomethane and potassium carbonate in acetonitrile at room temperature (eq 2). After separation of the components by chromatography, the dimethoxy products (−)-(5*S*,10b*S*)-**7a** and (+)-(5*S*,10b*R*)-**8a** were individually isolated in a ratio of yields reflecting the starting composition and were each found to match the spectral data for (5*S*,10b*S*)-**7a** and (+)-(5*S*,10b*R*)-**8a** prepared by the route from amino acid ester (*S*)-(+)-**2a** and dimethyl acetal precursor **3**.

Scheme 5. Pictet−Spengler Cyclization of (*S*)-(+)-13 with 2-(3-Chloropropyl)-1,3-dioxolane (4)





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In summary, we have demonstrated an asymmetric total synthesis of both the natural product (+)-crispine A and its unnatural (−) antipode employing a Pictet−Spengler bis-cyclization reaction between commercially available L- and D-DOPA-derived precursors and an aldehyde surrogate bearing a terminal leaving group. This procedure preferentially provides 1,3-*cis* tetrahydroisoquinoline adducts that undergo a concomitant second cyclization to generate the tricyclic pyrrolo[2,1-*a*]isoquinoline core of crispine A in one step. Decarboxylation by a convenient two-step protocol provides the enantiopure natural product in three steps from the amino acid. The opposite antipode may also be similarly prepared from the minor 1,3-*trans* adduct formed during the bis-cyclization. We have since this time applied our strategy to the asymmetric preparation of other natural product alkaloids, which will be reported in due course. We have also initiated investigations into computational analyses of transition state models, which we also hope to advance as warranted.

EXPERIMENTAL SECTION

General Experimental. All nonaqueous reactions were performed under an atmosphere of dry nitrogen unless otherwise specified. Commercial grade reagents and anhydrous solvents were used as received from vendors, and no attempts were made to purify or dry these components further. Removal of solvents under reduced pressure was accomplished with a rotary evaporator using a Teflon-lined KNF vacuum pump. Flash column chromatography was performed using an automated medium-pressure chromatography system using normal-phase disposable prepacked silica gel columns. Melting points are uncorrected. Data for proton NMR spectra were obtained 300 or 500 MHz and are reported in ppm δ values, using tetramethylsilane as an internal reference. Low-resolution mass spectroscopic analyses were performed on a single quadrupole mass spectrometer utilizing electrospray ionization (ESI). High-resolution mass spectroscopic analyses were performed on a time-of-flight mass spectrometer utilizing electrospray ionization (ESI).

(5*S*,10b*S*)-Methyl 8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboxylate [(5*S*,10b*S*)-7a] and (5*S*,10b*R*)-Methyl 8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboxylate [(5*S*,10b*R*)-8a] from (*S*)-(+)-Methyl 2-Amino-3-(3,4-dimethoxyphenyl)propanoate [(*S*)-(+)-2a]. 4-Chloro-1,1-dimethoxybutane (**3**, 0.90 mL, 6.0 mmol) was added to a stirring suspension of commercially available (*S*)-(+)-methyl 2-amino-3-(3,4-dimethoxyphenyl)propanoate [(*S*)-(+)-**2a**, 1.3 g, 5 mmol] and 4 Å molecular sieves (1 g) in a mixture of anhydrous methylene chloride (20 mL) and trifluoroacetic acid (5 mL) at room temperature under nitrogen. The mixture was stirred for 4 h, at which time the conversion to the intermediate (1*RS*,3*S*)-methyl 1-(3-chloropropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate [(1*RS*,3*S*)-**6ab**] was judged to be complete (>99% conversion of the intermediate by LC−MS analysis). The solids were removed by filtration, and the solvents were removed from the organic filtrate under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with THF/methylene chloride (1:4), to first afford the less polar isomer (5*S*,10b*S*)-**7a** (1.1 g, 80%) as a light orange solid: $[\alpha]^{20}_{D}$ −0.12° (*c* 1.0, $CHCl_3$); mp 91−94 °C; ^{1}H NMR (500 MHz, CDCl3) δ 6.58 (s, 1H), 6.57 (s, 1H), 3.85 (s, 6H), 3.80 (s, 3H), 3.70 (t, *J* = 7.3 Hz, 1H), 3.59 (dd, *J* = 5.2, 6.8 Hz, 1H), 3.17 (dd, *J* = 11.5, 3.5 Hz, 1H), 3.08 (dd, *J* = 8.5, 6.0 Hz, 1H), 2.90 (dd, *J* = 4.5, 11.5 Hz, 1H), 2.49 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.41−2.32 (m, 1H), 1.92−1.80 (m, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 172.9, 147.6, 147.6, 130.2, 124.7, 111.0, 108.5, 63.1, 61.6, 56.0, 55.9, 52.1, 48.8, 30.0, 29.3, 22.0; ESI MS *m*/*z* 292.1 $[M + H]^+$; HRMS (ESI) *m*/*z* 292.1555 $[M + H]^+$ (292.1549 calculated for $C_{16}H_{21}NO_4 + H$). The relative 1,3-stereochemistry was determined as *cis* based on an ^{1}H NOE NMR experiment (500 MHz, $CDCl_3$): irradiation of the H5 proton (3.59 ppm) resulted in a 4% enhancement of the H10b proton signal (3.70 ppm) as well as 3% for H3α (2.90 ppm) and 2% for H6α (2.49 ppm). Further elution afforded the more polar isomer (5*S*,10b*R*)-**8a** (0.25 g, 18%) as an amorphous colorless solid: $[\alpha]^{20}_{D}$ +0.09° (*c* 1.0, $CHCl_3$); mp 91−95 °C; ^{1}H NMR (500 MHz, CDCl3) δ 6.59 (s, 1H), 6.57 (s, 1H), 4.25 (t, *J* = 7.5 Hz, 1H), 3.84 (s, 6H), 3.76 (t, *J* = 5.5 Hz, 1H), 3.70 (s, 3H), 3.19−3.14 (m, 1H), 3.07 (dd, *J* = 5.5, 15.8 Hz, 1H), 2.97 (dd, *J* = 5.5, 15.8 Hz, 1H), 2.82 (q, *J* = 7.4 Hz, 1H), 2.43−2.36 (m, 1H), 1.96−1.84 (m, 2H), 1.73−1.66 (m, 1H); ^{13}C NMR (125 MHz, CDCl3) δ 173.3, 147.7, 147.3, 130.7, 124.2, 110.0, 109.0, 58.9, 57.9, 55.9, 55.9, 52.1, 51.9, 32.8, 29.5, 23.3; ESI MS *m*/*z* 292.1 $[M + H]^+$; HRMS (ESI) *m*/*z* 292.1555 $[M + H]^+$ (292.1549 calculated for $C_{16}H_{21}NO_4 + H$). The relative 1,3-stereochemistry was determined as *trans* based on a ^{1}H NOE NMR experiments (500 MHz, $CDCl_3$): irradiation of the H5 proton (4.25 ppm) resulted in no enhancement of the H10b proton signal (3.76 ppm) but did result in 3% enhancement for H6α (2.97 ppm) and 2% for H7 (6.57 ppm); irradiation of the H10b proton (3.76 ppm) resulted in no enhancement of the H5 proton signal (4.25 ppm), but did result in 3% enhancement for H1β (1.73−1.66 ppm) and 1% for H2β (1.96−1.84 ppm).

Preparation of (5*S*,10b*S*)-Methyl 8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboxylate [(5*S*,10b*S*)-7a] and (5*S*,10b*R*)-Methyl 8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboxylate [(5*S*,10b*R*)-8a] by Pictet−Spengler Bis-cyclization Reaction with 2-(3-Chloropropyl)-1,3-dioxolane (4). Using the procedure described for the preparation of (5*S*,10b*S*)-**7a** and (5*S*,10b*R*)-**8a** from (*S*)-(+)-**2a**, but instead utilizing 2-(3-chloropropyl)-1,3-dioxolane (**4**, 1.8 mL, 12.0 mmol), flash column chromatography on silica gel afforded the mixture of isomers (5*S*,10b*S*)-**7a** and (5*S*,10b*R*)-**8a** (2.10 g, 75%) as an off-white solid. The mixture was determined to be a 4.5:1 mixture of isomers by ^{1}H NMR and HPLC analyses, but was not further purified to isolate the diastereomers.

(5*S*,10b*S*)-Benzyl 8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboxylate [(5*S*,10b*S*)-7b] and (5*S*,10b*R*)-Benzyl 8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboxylate [(5*S*,10b*R*)-8b] from (*S*)-Benzyl 2-Amino-3-(3,4-dimethoxyphenyl)propanoate [(*S*)-2b]. Using the procedure described for the preparation of (5*S*,10b*S*)-**7a** and (5*S*,10b*R*)-**8a** from (*S*)-(+)-**2a**, but instead utilizing the free base derived from (*S*)-benzyl 2-amino-3-(3,4-dimethoxyphenyl)propanoate *p*-toluenesulfonate [(*S*)-**2b**·*p*TsOH,[18] 0.40 g, 1.2 mmol), flash column chromatography on silica gel first afforded the less polar isomer (5*S*,10b*S*)-**7b** (0.27 g, 60%) as a brown gum: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.32 (m, 5H), 6.57 (s, 1H), 6.56 (s, 1H), 5.23 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.69−3.59 (m, 2H), 3.21−3.07 (m, 2H), 2.91 (dd, *J* = 4.6, 16.3 Hz, 1H), 2.50−2.44 (m, 1H), 2.37−2.35 (m, 1H), 1.89−1.81 (m, 3H); ESI MS *m*/*z* 368.1 $[M + H]^+$. Further elution afforded the more polar isomer (5*S*,10b*R*)-**8b** (0.13 g, 31%) as an orange gum: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31−7.27 (m, 3H), 7.22−7.18 (m, 2H), 6.56 (s, 1H), 6.54 (s, 1H), 5.13 (s, 2H), 4.28 (t, *J* = 7.9 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 4H) 3.20−3.16 (m, 1H), 3.16−2.93 (m, 2H), 2.83 (q, *J* = 7.1 Hz, 1H), 2.40−2.35 (m, 1H), 1.91−1.86 (m, 2H), 1.97−1.60 (m, 1H); ESI MS *m*/*z* 368.1 $[M + H]^+$.

(5*S*,10b*R*)-*Se*-Methyl 8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboselenoate [(5*S*,10b*R*)-11]. A solution of dimethylaluminum methaneselenolate (0.60 mL, 1.2 mmol, ca. 2 M in toluene) was added dropwise to a degassed stirring solution of (5*S*,10b*R*)-methyl 8,9-dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboxylate [(5*S*,10b*R*)-**8a**, 290 mg, 1.0 mmol] in anhydrous methylene chloride (5 mL) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 30 min and then warmed to room temperature, stirring for a total of 1 h. The mixture was treated with wet sodium sulfate and extracted with diethyl ether (2 × 25 mL). The combined organic extracts were dried with anhydrous magnesium sulfate and filtered, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on

silica gel, eluting with hexanes/ethyl acetate (9:1), to provide (5*S*,10b*R*)-*Se*-methyl 8,9-dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboselenoate [(5*S*,10b*R*)-**11**, 270 mg, 76%] as a light orange solid (this material was stored in the dark and used immediately in the next step): $[\alpha]^{20}_{D}$ +0.06° (*c* 1.0, $CHCl_3$); mp 95−97 °C; ^{1}H NMR (500 MHz, CDCl3) δ 6.63 (s, 1H), 6.58 (s, 1H), 4.40 (t, *J* = 7.5 Hz, 1H), 3.84 (s, 6H), 3.34 (t, *J* = 6.5 Hz, 1H), 3.32 (t, *J* = 2.5 Hz, 1H), 2.92 (d, *J* = 5.5 Hz, 2H), 2.78−2.75 (m, 1H), 2.40−2.38 (m, 1H), 2.06 (s, 3H), 1.98−1.84 (m, 2H), 1.79−1.76 (m, 1H); ^{13}C NMR (125, MHz CDCl3) δ 209.9. 147.8, 147.7, 131.2, 124.6, 111.1, 109.0, 69.6, 57.5, 56.0, 55.9, 54.2, 33.9, 29.7, 25.3, 3.8; ESI MS *m*/*z* 356.0 $[M + H]^+$; HRMS (ESI) *m*/*z* 356.0765 $[M + H]^+$ (356.0765 calculated for $C_{16}H_{21}NO_3Se + H$).

(*R*)-8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline [(+)-Crispine A, (*R*)-1][1,5] from Selenyl Ester (5*S*,10b*R*)-11. Tri-*n*-butyltin hydride (300 mg 1.0 mmol) was added to a stirring mixture of (5*S*,10b*R*)-*Se*-methyl 8,9-dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboselenoate [(5*S*,10b*R*)-**11**, 180 mg, 0.50 mmol) and AIBN (14 mg, 0.080 mmol) in anhydrous benzene (85 mL) at room temperature under nitrogen, after which the mixture was heated to reflux and stirred for 3 h. The cooled mixture was treated with saturated aqueous sodium fluoride (15 mL), and the biphasic mixture was stirred at room temperature for 15 min. The mixture was extracted with methylene chloride (3 × 20 mL), and the combined organic extracts were dried with magnesium sulfate and filtered, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with methylene chloride/methanol (49:1), to provide (+)-crispine A [(*R*)-**1**, 64 mg, 55%] as a colorless solid: $[\alpha]^{20}_{D}$ +90° (*c* 1.0, $CHCl_3$) {lit. $[\alpha]^{23}_{D}$ +100.4° (*c* 1.0, $CHCl_3$),[5a] $[\alpha]^{25}_{D}$ +96.9° (*c* 1.1, $CHCl_3$)[5b]}; mp 86−88 °C (lit. mp1 87−89 °C); ^{1}H NMR (500 MHz, CDCl3) δ 6.61 (s, 1H), 6.57 (s, 1H), 3.84 (s, 6H), 3.41 (t, *J* = 9.7 Hz, 1H), 3.18 (dd, *J* = 2.8, 4.6 Hz, 1H), 3.09−2.86 (m, 2H), 2.73 (dt, *J* = 16.8, 3.8 Hz, 1H), 2.66−2.60 (m, 1H), 2.55 (dd, *J* = 11.0, 9.5 Hz, 1H), 2.36−2.28 (m, 1H), 1.98−1.88 (m, 1H), 1.88−1.82 (m, 1H), 1.77−1.67 (m, 1H); ^{13}C NMR (125 MHz, CDCl3) δ 147.4, 147.3, 130.8, 126.2, 111.4, 108.9, 62.9, 56.0, 55.9, 53.1, 48.3, 30.5, 28.0, 23.3; ESI MS *m*/*z* 234.1 $[M + H]^+$; HRMS (ESI) *m*/*z* 234.1495 $[M + H]^+$ (234.1494 calculated for $C_{14}H_{19}NO_2 + H$). The enantiomeric purity was determined by HPLC (Chiralcel, OJ, heptane/ethanol = 95:5, 1.0 mL/min, 240 nm, t_R (minor) = 9.6 min, t_R (major) = 10.6 min): 97.8% ee.

(5*S*,10b*S*)-*Se*-Methyl 8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboselenoate [(5*S*,10b*S*)-12]. Using the procedure described for compound (5*S*,10b*R*)-**8a**, but instead utilizing (5*S*,10b*S*)-**7a**, (5*S*,10b*S*)-**12** (250 mg, 71%) was isolated as a light orange solid (this material was stored in the dark and used immediately in the next step): $[\alpha]^{20}_{D}$ −0.36° (*c* 1.0, $CHCl_3$); mp 95−98 °C; ^{1}H NMR (500 MHz, CDCl3) δ 6.63 (s, 1H), 6.61 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.79−3.78 (m, 1H), 3.66 (t, *J* = 7 Hz, 1H), 3.13−3.11 (m, 1H), 3.04−2.92 (m, 2H), 2.68−2.63 (m, 1H), 2.36−2.32 (m, 1H), 2.07 (s, 3H), 1.99−1.86 (m, 3H); ^{13}C NMR (125, MHz CDCl3) δ 210.6, 147.8, 147.4, 131.3, 125.0, 111.1, 109.0, 69.6, 59.5, 57.4, 56.5, 55.3, 33.9, 28.2, 22.4, 3.8; ESI MS *m*/*z* 356.0 $[M + H]^+$; HRMS (ESI) *m*/*z* 356.0765 $[M + H]^+$ (356.0765 calculated for $C_{16}H_{21}NO_3Se + H$).

(*S*)-8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline [(−)-Crispine A, (*S*)-1][1,5,6] from Selenyl Ester (5*S*,10b*S*)-12. Using the procedure described for compound (*R*)-**1**, but instead utilizing (5*S*,10b*S*)-**12**, (−)-crispine A [(*S*)-**1**, 65 mg, 56%) was isolated as a colorless solid: $[\alpha]^{20}_{D}$ −95° (*c* 1.3, $CHCl_3$) {lit. for antipode $[\alpha]^{23}_{D}$ +100.4° (*c* 1.0, $CHCl_3$),[5a] $[\alpha]^{25}_{D}$ +96.9° (*c* 1.1, $CHCl_3$)[5b]}; mp 86−88 °C (lit. mp for antipode[1] 87−89 °C). The spectral data were matched with the data from the corresponding antipode (*R*)-**1**. The compound was shown to be a single enantiomer by chiral HPLC analysis (see Supporting Information). The enantiomeric purity was determined by HPLC (Chiralcel, OJ, heptane/ethanol = 95:5, 1.0 mL/min, 240 nm, t_R (major) = 9.6 min, t_R (minor) = 10.8 min): 96.6% ee.

(5*R*,10b*R*)-Methyl 8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboxylate [(5*R*,10b*R*)-7a] from (*R*)-(−)-Methyl 2-Amino-3-(3,4-dimethoxyphenyl)propanoate [(*R*)-(−)-2a]. Using the procedure described for the preparation of (5*S*,10b*S*)-**7a** from (*S*)-(+)-**2a**, but instead utilizing commercially available (*R*)-(−)-methyl 2-amino-3-(3,4-dimethoxyphenyl)propanoate [(*R*)-(−)-**2a**, 0.24 g, 1.0 mmol], flash column chromatography on silica gel afforded the less polar isomer (5*R*,10b*R*)-**7a** (0.23 g, 82%) as a viscous orange oil. The spectral data were matched with the data from the corresponding antipode (5*S*,10b*S*)-**7a**.

(5*R*,10b*R*)-*Se*-Methyl 8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboselenoate [(5*R*,10b*R*)-12]. Using the procedure described for compound (5*S*,10b*R*)-**12**, but instead utilizing (5*R*,10b*R*)-**7a** (0.20 g, 0.60 mmol), (5*R*,10b*R*)-**12** (0.17 g, 71%) was isolated as a light orange solid, which was stored in the dark and used immediately in the next step: $[\alpha]^{20}_{D}$ +0.36° (*c* 1.0, $CHCl_3$); mp 95−97 °C. The spectral data were matched with the data from the corresponding antipode (5*S*,10b*S*)-**12**.

(*R*)-8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline [(+)-Crispine A, (*R*)-1][1,5] from Selenyl Ester (5*R*,10b*R*)-12. Using the procedure described for compound (*R*)-**1** from selenyl ester (5*S*,10b*R*)-**11**, but instead utilizing (5*R*,10b*R*)-**12** (0.10 g, 0.30 mmol), (+)-crispine A [(*R*)-**1**, 0.030 g, 55%] was isolated as a colorless solid: $[\alpha]^{20}_{D}$ +95° (*c* 1.0, $CHCl_3$) {lit. $[\alpha]^{23}_{D}$ +100.4° (*c* 1.0, $CHCl_3$),[5a] $[\alpha]^{25}_{D}$ +96.9° (*c* 1.1, $CHCl_3$)[5b]}; mp 86−88 °C (lit. mp 87−89 °C). The spectral data were matched with the data from the corresponding compound (*R*)-**1** prepared from the selenyl ester (5*S*,10b*R*)-**11**. The enantiomeric purity was determined by HPLC (Chiralcel, OJ, heptane/ethanol = 95:5, 1.0 mL/min, 240 nm, t_R (minor) = 9.6 min, t_R (major) = 10.6 min): 97.8% ee.

(5*S*,10b*S*)-Methyl 8,9-Dihydroxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboxylate [(5*S*,10b*S*)-15] and (5*S*,10b*R*)-Methyl 8,9-Dihydroxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboxylate [(5*S*,10b*R*)-16] from (*S*)-(+)-Methyl 2-Amino-3-(3,4-dihydroxyphenyl)propanoate [(*S*)-(+)-13]. 2-(3-Chloropropyl)-1,3-dioxolane (4, 0.90 mL, 6.0 mmol) was added to a stirring suspension of commercially available (*S*)-(+)-methyl 2-amino-3-(3,4-dihydroxyphenyl)propanoate [(*S*)-(+)-**13**, 1.2 g, 5.0 mmol] and 4 Å molecular sieves (1 g) in a mixture of anhydrous methylene chloride (20 mL) and trifluoroacetic acid (5 mL) at room temperature under nitrogen. The mixture was stirred at room temperature for 4 h, at which time the conversion to the intermediate (1*RS*,3*S*)-methyl 1-(3-chloropropyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate [(1*RS*,3*S*)-**14ab**] was judged to be complete (>99% by LC−MS analysis). The solids were removed by filtration, and the solvents were removed from the organic filtrate under reduced pressure. The residue was dissolved in anhydrous acetonitrile (50 mL), triethylamine (0.45 mL, 16 mmol) was added, and the mixture was stirred at room temperature under nitrogen for 1 h. The solvent was removed under reduced pressure to provide a crude residue that was judged to be a mixture of tricyclic compounds (5*S*,10b*S*)-**15** and (5*S*,10b*R*)-**16** in a 4.5:1 ratio (HPLC and ^{1}H NMR analyses). The residue was purified by flash column chromatography on silica gel, eluting with THF/methylene chloride (1:4), to first afford the less polar isomer (5*S*,10b*S*)-methyl 8,9-dihydroxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboxylate [(5*S*,10b*S*)-**15**, 0.91 g, 76%] as a light yellow solid: $[\alpha]^{20}_{D}$ −0.36° (*c* 1.3, CH_3OH); mp 95−99 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ 6.51 (s, 1H), 6.50 (s, 1H), 3.75 (s, 3H), 3.43−3.37 (m, 2H), 3.19−3.15 (m, 1H), 3.00 (dd, *J* = 4.9, 13.1 Hz, 1H), 2.88 (dd, *J* = 5.0, 13.0 Hz, 1H), 2.37−2.27 (m, 2H), 1.89−1.82 (m, 2H), 1.76−1.74 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.1, 145.3, 145.0, 129.8, 124.7, 115.6, 113.1 65.0, 63.8, 52.5, 50.8, 31.6, 30.1, 22.5; ESI MS *m*/*z* 264.1 $[M + H]^+$; HRMS (ESI)

m/*z* 264.1233 $[M + H]^+$ (264.1236 calculated for $C_{14}H_{17}NO_4 + H$). Further elution afforded the more polar isomer (5*S*,10b*R*)-methyl 8,9-dihydroxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboxylate [(5*S*,10b*R*)-**16**, 0.22 g, 12%] as an amorphous colorless solid: $[\alpha]^{20}_D$ +0.14° (*c* 1.0, CH_3OH); ^1H NMR (CD_3OD, 500 MHz) δ 6.52 (s, 1H), 6.51 (s, 1H), 4.10 (t, *J* = 8.5 Hz, 1H), 3.67 (s, 3H), 3.36 (dd, *J* = 7.0, 2.0 Hz, 1H), 3.10−3.06 (m, 1H), 2.94−2.89 (m, 1H), 2.85−2.76 (m, 2H), 2.34−2.27 (m, 1H), 1.88−1.82 (m, 2H), 1.67−1.59 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.6, 145.3, 145.0, 130.2, 124.1, 115.5, 113.9, 60.2, 60.1, 53.5, 52.4, 35.9, 30.8, 24.0; ESI MS *m*/*z* 264.1 $[M + H]^+$.

(5*S*,10b*S*)-Methyl 8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboxylate [(5*S*,10b*S*)-7a] and (5*S*,10b*R*)-Methyl 8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboxylate [(5*S*,10b*R*)-8a]. Iodomethane (0.12 mL, 11 mmol) and potassium carbonate (0.41 g, 3.0 mmol) were added to a solution of crude isomers (5*S*,10b*S*)-**15** and (5*S*,10b*R*)-**16** (0.26 g, 1.0 mmol, 4.5:1 ratio) in anhydrous acetonitrile (10 mL) at room temperature under nitrogen. The mixture was stirred for 14 h, after which the solvents were removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel, eluting with THF/methylene chloride (1:4), to first afford the less polar isomer (5*S*,10b*S*)-methyl 8,9-dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboxylate [(5*S*,10b*S*)-**7a**, 0.22 g, 75%] as a light orange solid. Further elution afforded the more polar isomer (5*S*,10b*R*)-methyl 8,9-dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboxylate [(5*S*,10b*R*)-**8a**, 0.050 g, 16%] as a colorless solid. The spectral data for both compounds matched with the data from the corresponding compounds as prepared from the dimethoxyphenyl precursor (*S*)-(+)-**2a**.

■ ASSOCIATED CONTENT

Supporting Information. Proton and carbon NMR spectra for all compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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