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Electrochemical Synthesis and Chemistry of Chiral 1-Cyanotetrahydroisoquinolines. An Approach to the Asymmetric Syntheses of the Alkaloid (−)-Crispine A and Its Natural (+)-Antipode

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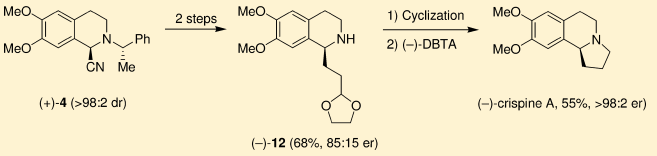
Supporting Information

ABSTRACT: The stereoselective convergent total syntheses of both enantiomers of the tetrahydroisoquinoline (THIQ) alkaloid crispine A are described. The THIQ precursors (−)-**6** (90:10 dr) and (−)-**11** (85:15 dr) were prepared from the alkylation−reduction sequence of a common α-amino nitrile (+)-**4** derivative that has been conveniently prepared by anodic cyanation. Elaboration of the pyrrolidine ring of the title compound was cleanly achieved by two efficient ring closures methods involving (a) the displacement of a halogen atom and (b) the formation of a cyclic iminium cation to afford (−)-crispine A in 90% and 85% yields, respectively. A crystallization of enantioenriched (−)-crispine A (90:10 er) with 1 equiv of (−)-DBTA afforded the tartrate salt (−)-**14** (≥98:2 dr) in 81% yield. The absolute *S* configuration of (−)-crispine A was simply deduced from examination of the X-ray data of tartrate salt (−)-**14**. Likewise, the natural (+)-crispine A was prepared in seven workup steps in an overall 30% yield, and reciprocal crystallization with (+)-DBTA afforded the enantiomeric tartrate salt (+)-**14** in a ≥98:2 dr. Both enantiomers of crispine A were liberated from their respective DBTA salts in ≥98:2 er's which were determined by proton and carbon NMR spectroscopy, utilizing (*R*)-(+)-*tert*-butylphenylphosphinothioic acid (+)-**15** as chiral solvating agent.



INTRODUCTION

The pyrroloisoquinoline alkaloid (+)-crispine A was first isolated by Zhao and co-workers from the Mongolian thistle *Carduus crispus*.[1] An extract of this plant showed significant cytotoxic activities, providing an impetus to an already fertile area of research.[2] It is worthy of note that racemic crispine A was made long before its naming, isolation, and characterization.[3] In the past decade, stereoselective syntheses of (+)-crispine A or its unnatural (−)-antipode have also been achieved by the application of various methodologies, including asymmetric Strecker condensations,[4] asymmetric hydrogen transfer,[5,6] asymmetric allylation of cyclic imines,[7] diastereoselective *N*-acyliminium cyclization,[8] chemo-enzymatic deracemization,[9] α-amidoalkylation of tricyclic lactams,[10] or more recently by application of a Pictet−Spengler stereodirected cyclization.[11] In this paper, we report our own strategy which is based on the electrochemical syntheses of stable THIQ α-amino nitrile derivatives and their use in the asymmetric syntheses of (−)-crispine A and its natural (+)-antipode (Figure 1).

For the present work, it was necessary to design a new system allowing a 1−3 stereoinduction between a chiral auxiliary linked to the nitrogen atom and the C-1 atom of the THIQ nucleus. α-Phenylethylamine (α-PEA), available in both enantiomers and accessible at low price, proved to be a valuable source of nitrogen and chirality.[12]

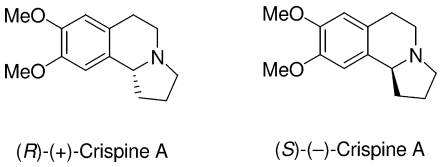


Figure 1. Natural (*R*)-(+)-crispine A and its synthetic optical antipode.

The retrosynthetic analysis is delineated in Scheme 1 and is centered on the first incorporation of a three carbon chain at C-1 through the alkylation of α-amino nitrile (+)-**4**, while in the second step, an asymmetric reductive decyanation procedure would control the absolute configuration of the future C-10b stereogenic center. Finally, an appropriate cyclization method involving the future N-4 and the future C-3 atoms would construct the pyrrolidine ring of crispine A. With these purposes in mind, we report here the electrochemical syntheses of α-amino nitrile (+)-**4** and its antipode and their use as efficient building blocks for the stereoselective synthesis of the tricyclic system of crispine A.[13]

RESULTS AND DISCUSSION

Synthesis of Amine (+)-3. As outlined in Scheme 2, our synthesis began by the *N*-acylation of (−)-α-PEA with the acid

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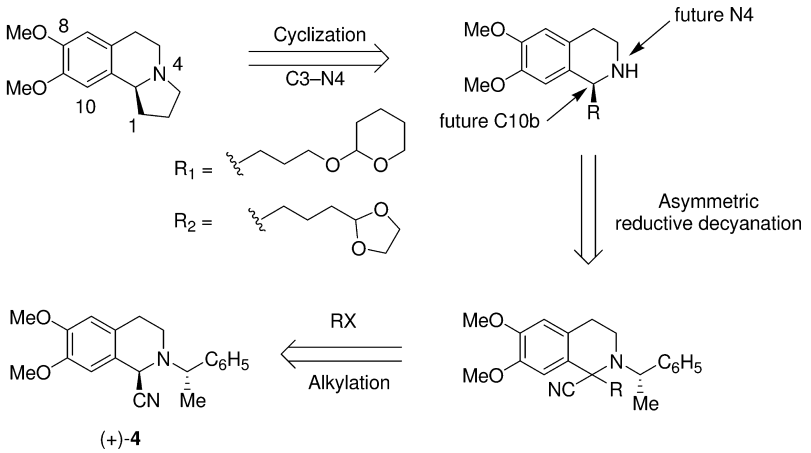
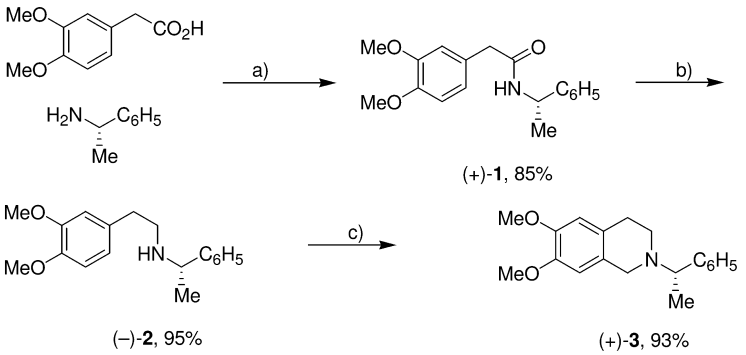
Scheme 1. Retrosynthetic Analysis of (−)-Crispine A from α-Amino Nitrile (+)-4



Scheme 2. Synthesis of THIQ (+)-3[a]

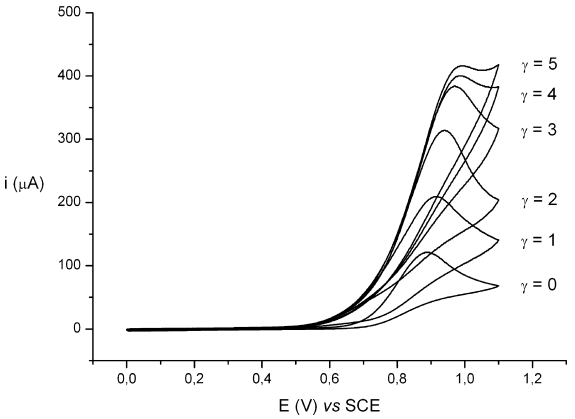


[a]Reagents and conditions: (a) $(COCl)_2$, CH_2Cl_2, rt, 12 h, then (−)-α-PEA, NEt_3, CH_2Cl_2, rt, 12 h; (b) $BF_3{\cdot}Et_2O$, $BH_3{\cdot}THF$, THF, reflux, 2 h; (c) HCO_2H, $(CH_2O)_n$, 50 °C, 12 h.

chloride derived from 3,4-dimethoxyphenylacetic acid upon its treatment with oxalyl chloride.[14] Amide (+)-**1** was obtained as a white powder in an overall 85% yield and we unsuccessfully attempted its reduction by refluxing it in THF in the presence of 4 equiv of $LiAlH_4$. To reduce the amide function selectively, we found it convenient to use the protocol first described by Polniaszek.[15] Accordingly, amide (+)-**1** was lightly refluxed for 2 h in THF in the presence of 2.0 equiv of $BF_3{\cdot}Et_2O$ followed by the addition of 2.5 equiv of $BH_3{\cdot}THF$. The amine was displaced from its borane complex by stirring it with a 6 M HCl solution for 2 h, and after basification, the oily residue was purified by column chromatography to afford amine (−)-**2** in 95% yield as a viscous oil. The Pictet–Splengler cyclization of (−)-**2** was carried out using the protocol described by Fukuyama in which the amine was refluxed in formic acid at 50 °C in the presence of 1 equiv of paraformaldehyde.[16] Under these reaction conditions, THIQ (+)-**3** could be obtained on a 10 g scale and its proton NMR spectrum recorded in $CDCl_3$ revealed two characteristic singlets at δ 6.49 and 6.57 which were easily attributed to the aromatic protons H-5 and H-8.

Analytical Study and Anodic Cyanation of THIQ (+)-3. To achieve electrosynthesis, we first established the redox properties of sodium cyanide, THIQ (+)-**3**, and α-amino nitrile (+)-**4**. The voltammograms were recorded at a glassy carbon electrode in methanol containing $LiClO_4$ as the supporting electrolyte, and the peak potentials were expressed versus a saturated calomel electrode. As shown in the Supporting Information, cyanide anions are slowly oxidized at the electrode surface to produce an ill-defined irreversible oxidation peak at E_p = +1.4 V. On the other hand, the voltammogram of a 15 mM solution of THIQ (+)-**3** (Table 1, γ = 0) displayed an

Table 1. Cyclic Voltammograms of THIQ (+)-3 in the Absence (γ = 0) and in the Presence (γ = 1–5) of Sodium Cyanide[a]



γ = 1 (i_p/i_p^0)	γ = 2 (i_p/i_p^0)	γ = 3 (i_p/i_p^0)	γ = 4 (i_p/i_p^0)	γ = 5 (i_p/i_p^0)
1.72	2.59	3.17	3.30	3.35

[a]MeOH/$LiClO_4{\cdot}3H_2O$ (0.1 M), glassy carbon electrode, v = 0.05 V s^{-1}. γ = 0: THIQ (+)-**3**, (15 mM) alone, γ = 1 plus NaCN (15 mM), γ = 2: plus NaCN (30 mM), γ = 3: plus NaCN (45 mM), γ = 4: plus NaCN (60 mM), γ = 5: plus NaCN (75 mM).

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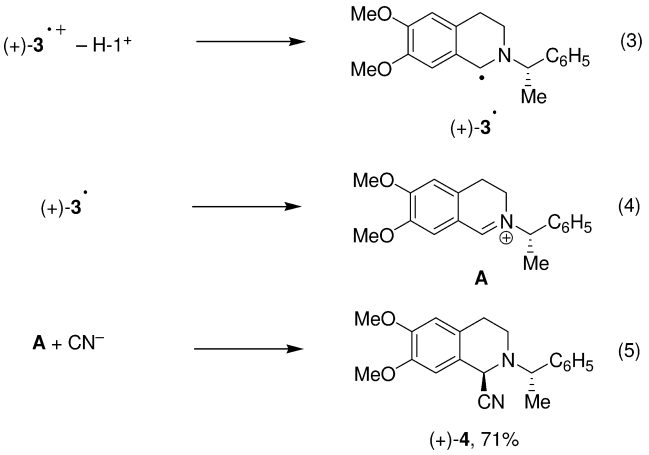
irreversible bielectronic system at E_p = +0.90 V. Thus, the potential required for the anodic oxidation of the substrate is 0.5 V less anodic than that required for the oxidation of the cyanide anions. A new curve (Table 1, γ = 1) was registered after the addition of 1 molar equiv of sodium cyanide to the previous solution. Surprisingly, this causes an increase of the anodic current of THIQ (+)-**3** whose height was twice than that recorded in the absence of sodium cyanide. A similar phenomenon was observed upon the incremental addition (γ = 2, i_p/i_p^0 = 2.59; γ = 3, i_p/i_p^0 = 3.17) of sodium cyanide in the electrolysis medium. This increase in height of the anodic current is typical of the return of aminium cation radical (+)-**3**$^{\bullet+}$ to its neutral form (+)-**3**, as illustrated in equations in Scheme 3. The value of the i_p/i_p^0 ratio (where i_p and i_p^0 are the anodic currents of (+)-**3** with and without sodium cyanide, respectively) is useful to describe the quantitative features of the present homogeneous redox catalysis . In such cases, oxidation of the cyanide anion occurred through a homogeneous redox transfer and took place at a potential lower than that required for its direct oxidation at the electrode surface.[17] It then appeared that the aminium radical cation is able to oxidize the cyanide anions and this unwanted side-reaction could constitute a major limitation of our synthetic plan. It was also felt that a follow-up reaction is required to displace the equilibrium to the expected α-amino nitrile (+)-**4**. Obviously, proton abstraction from aminium radical cation (+)-**3** to afford the aminyl radical (+)-**3**$^{\bullet}$ (Scheme 4) could fulfill this need.

When the concentrations of sodium cyanide ranged from 60 (γ = 4) to 75 mM (γ = 5), the i_p/i_p^0 ratios turned to be 3.30 and 3.35, respectively. Therefore, the i_p/i_p^0 ratio is limited at high concentrations of cyanide anions and indicates that they could also act as a base, thereby reducing the lifetime of the aminium cation radical (+)-**3**$^{\bullet+}$ through the abstraction of H-1$^+$ (Scheme 4, eq 3). This favorable follow-up proton transfer would drive the unfavorable equilibrium in eq 2 toward the formation of the neutral aminyl radical (+)-**3**$^{\bullet}$.

These results clearly indicate that redox properties of (+)-**3**$^{\bullet+}$ ought to dominate at low concentrations of sodium cyanide and in the absence of an electrogenerated base, whereas the acidic properties of (+)-**3**$^{\bullet+}$ ought to dominate at concentrations of sodium cyanide higher than 30 mM, accounting for the formation of iminium cation **A** through the stepwise removal of one proton and one electron from (+)-**3**$^{\bullet+}$ (Scheme 4, eqs 3 and 4).

Given the homogeneous catalysis that exists between (+)-**3**$^{\bullet+}$ and the cyanide anions, we found it convenient to carry out the anodic cyanation of (+)-**3** at concentrations of substrate ranging from 15 to 25 mM in an *undivided cell* fitted with a glassy carbon anode at a controlled potential of +0.95 V in the presence of 2.5 equiv of sodium cyanide.[18] Under these optimized reaction conditions and after the consumption of 2.1 F per mole of substrate, the completion of the electrolysis

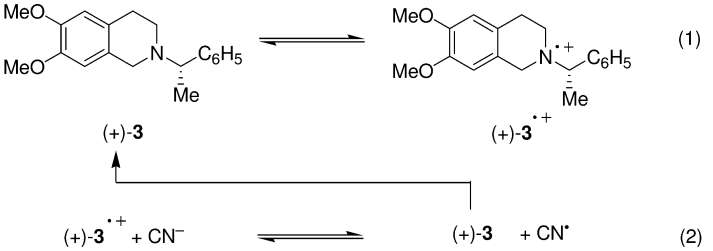
Scheme 4. Proton transfer option for aminium cation radical (+)-3$^{\bullet+}$ and synthesis of α-amino nitrile (+)-4



was attested by the disappearance of the first oxidation peak and α-amino nitrile (+)-**4** was obtained as a colorless powder in 71% yield after crystallization in hot ethanol.[19]

It should be pointed out that when the electrolyses were carried out at higher sodium cyanide concentration values (100 mM), we observed the formation of the alternate regioisomer cyanated at C-3 in 10% yield. This product distribution provided a direct indication of the site of the α-CH deprotonation step. The presence of this unwanted regioisomer indicates that a competitive kinetic deprotonation took place at C-3 in the presence of an excess of NaCN. Moreover, the selective α-CH-1 deprotonation step (in comparison to its exocyclic α-CH-1′ counterpart) could be explained by a favorable overlap of the half filled nitrogen p orbital with the developing carbon p radical. As suggested previously by Lewis and co-workers, it is possible that a small stereoelectronic effect counterbalance the greater product stability of the more branched free radical.[20] This feature should be taken into account to explain some "abnormal" regioselectivities which could be encountered during oxidation of tertiary amine by electrochemical,[13] photochemical,[21] or chemical SET processes.[22] The proton NMR spectrum of (+)-**4** was recorded within 5 min in THF-d_8 attesting for the presence of a single diastereomer. We could also observe that a slow epimerization of the C-1 carbon took place in this solvent (see details in the Supporting Information). Indeed, an additional resonance signal at δ 4.50 attributed to the alternate diastereomeric H-1 progressively appeared and equilibrium (60:40 dr) is reached after a 2 days standing in THF-d_8.[23] The obtention of α-amino nitrile (+)-**4** as a single stereoisomer is worthy of an additional comment. As shown previously, the equilibrium between an α-amino nitrile and its iminium counterpart is well established. Since formation of the new C1−CN bond can lead to either

Scheme 3. Homogeneous Redox Catalysis Option for the Radical Cation (+)-3$^{\bullet+}$



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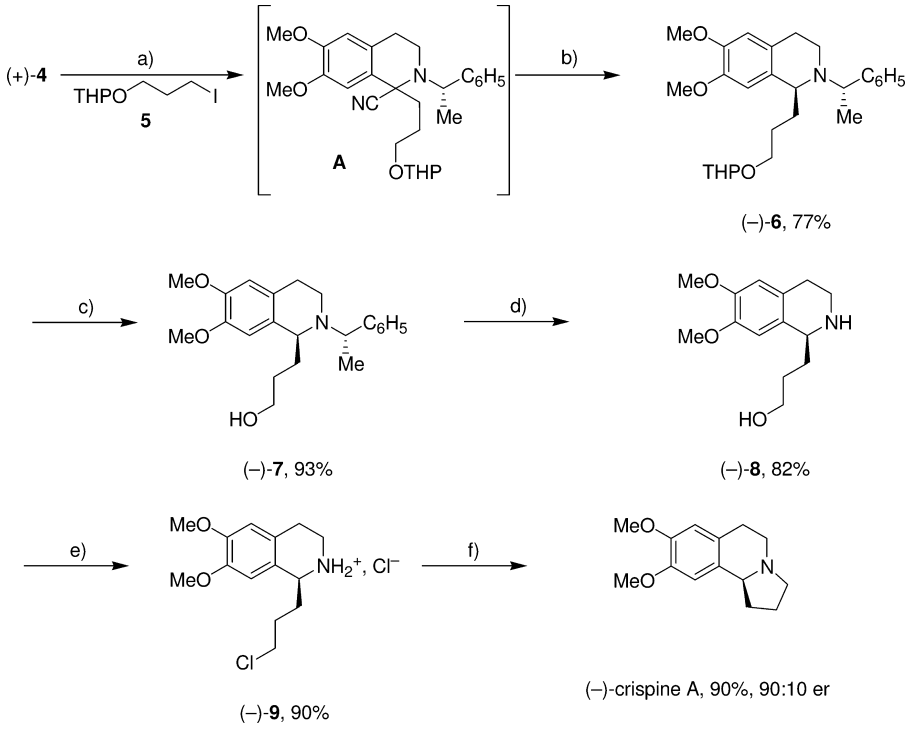
Scheme 5. Synthesis (−)-Crispine A from Nucleophilic Substitution[a]



[a]Reagents and conditions: (a) LDA, THF, −80 to −20 °C, 2 h, then, 5, −80 °C to rt; (b) $NaBH_4$, EtOH, −20 to 20 °C, 12 h; (c) 1.5 M H_2SO_4/THF, 80 °C, 6 h; (d) 10% Pd/C, H_2 (5 bar), 10% HCl/EtOH, 20 °C, 48 h; (e) $SOCl_2$, CH_2Cl_2, 40 °C, 3 h; (f) 2 M NaOH/Et_2O, 20 °C, 5 h.

stereoisomer, the diastereomers are in equilibrium in solution. However, in the solid state, this equilibrium is shifted toward the less soluble *R,S* stereoisomer. Conversely, the electrolysis of *rac*-**3** yielded the less soluble *R*,R** stereoisomer whose relative configuration was determined by X-ray diffraction.[24] These observations point out that chiral compounds exhibit significant different solubilities for the racemate and the corresponding pure enantiomer. With the required α-amino nitrile (+)-**4** in hand, we turned our attention to the synthesis of (−)-crispine A.

Synthesis of (−)-Crispine A (90:10 er) from Nucleophilic Substitution. In order to introduce the three-carbon chain tethered by a potential terminal leaving group, lithiation of a THF solution of α-amino nitrile (+)-**4** was carried out by the rapid addition of an LDA solution at −80 °C (Scheme 5).[25] The characteristic red anion solution was then warmed at −20 °C for a 2-h period and then cooled to a temperature of −80 °C. The addition of iodide **5** (see the synthesis in the Supporting Information) containing a terminal tetrahydropyranyl ether as protecting group afforded the corresponding unstable quaternary α-amino nitrile **A** which could not be purified by silica gel chromatography. After removal of the solvent, α-amino nitrile **A** was dissolved in ethanol and treated with 4 equiv of $NaBH_4$ at −20 °C to afford THIQ (−)-**6** as a mixture of stereoisomers which could not be separated by column chromatography. In the proton NMR spectrum, the H-8 proton of the major *S,S* diastereomer resonated as a singlet at δ 6.32, whereas in the minor *R,S* diastereomer this proton displayed a singlet at δ 6.60. Integration of these signals indicated that the reductive decyanation of parent α-amino nitrile **A** proceeded stereoselectively to afford (−)-**6** in a 90:10 dr. Hydrolysis of the tetrahydropyranyl group was carried out without events by refluxing it in a mixture (1:10) of THF/1.5 M H_2SO_4 to afford (−)-**7** in 93% yield.[26] The penultimate step consisted in the removal of the chiral appendage by stirring (−)-**7** in acidic ethanol in the presence of Pd/C under a hydrogen pressure of 5 bar. After basification, the crude reaction mixture was filtered over a small pad of silica to afford (−)-**8** in 82% yield. The last step was devoted to the elaboration of the pyrrolidine ring through the halogenation of the pendant alcohol function. In our first experiments, we used the Appel reaction to produce an intermediary alkyl bromide.[27] Therefore, THIQ (−)-**8** was stirred at room temperature in dichloromethane in the presence of CBr_4 and PPh_3.

The reaction proceeded well, and the conversion yield was high but our sample of (−)-crispine A was contaminated with large amount of phosphorus derivatives that were difficult to remove. Nevertheless, after several purifications, (−)-crispine A was obtained in a low 10% yield. To overcome this drawback, an alternate cyclization procedure based on the slow inverse addition of (−)-**8** onto $SOCl_2$ was explored.[2g] Under these reaction conditions, the product became protonated upon contact with adventitious hydrochloric acid generated during the *O*-sulfonylation. Accordingly, the addition of (−)-**8** onto a dichloromethane solution containing 1.4 equiv of $SOCl_2$ produced the hydrochloride (−)-**9**, which could be isolated and characterized spectroscopically. For example, magnetically non equivalent ammonium protons were registered at δ 9.30 and 10.30. The intramolecular displacement of the terminal chlorine atom was readily achieved by stirring the hydrochloride (−)-**9** in a 2 M NaOH/diethyl ether biphasic system. Workup followed by a subsequent purification of the crude reaction mixture over a silica column afforded (−)-crispine A in 90% yield. The sign of the optical rotation $[\alpha]^{22}_D$ −73 (*c* 1, $CHCl_3$) indicated that the absolute configuration of the C-10b

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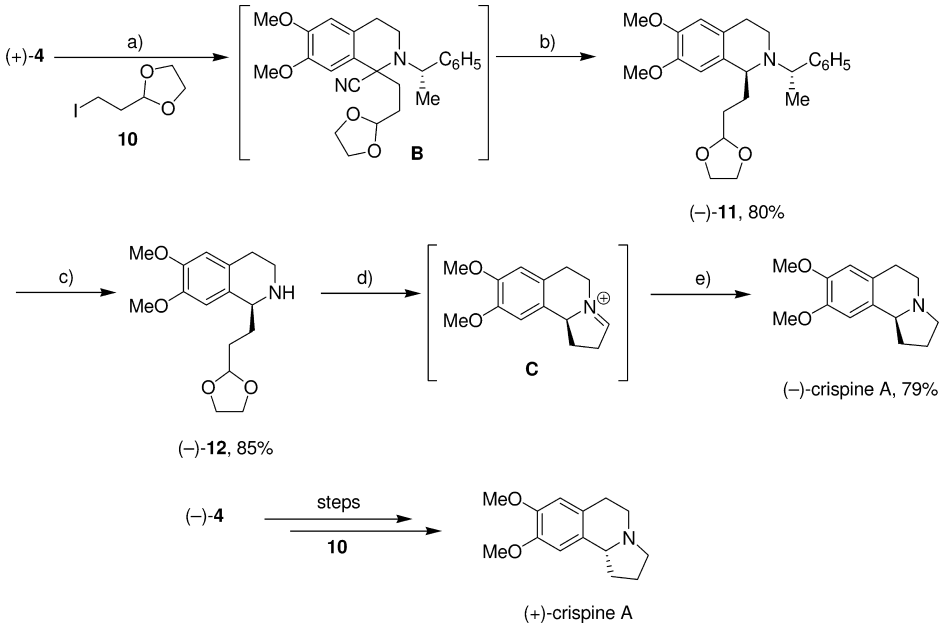
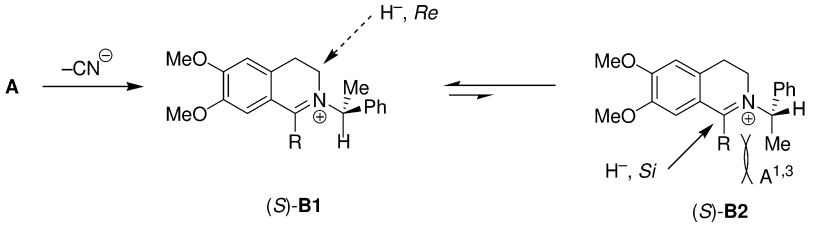
Scheme 6. Synthesis (−)-Crispine A from Iminium Ion Cyclization[a]



[a]Reagents and conditions: (a) LDA, THF, −80 to −20 °C, 2 h, then, **10**, −80 to +20 °C; (b) $NaBH_4$, EtOH, −20 to +20 °C, 12 h; (c) 20% $Pd(OH)_2$, H_2 (5 bar), MeOH, 20 °C, 48 h; (d) 10% HCl/THF, 24 h, 20 °C; then AcONa, pH = 4.5; (e) $NaBH_3CN$, 20 °C, 3 h.

Scheme 7. Proposed Rationale for the Observed Stereoselectivities



atom was *S* and its magnitude is in keeping with a 90:10 er. This also confirms that neither epimerization nor racemization had occurred during the synthetic manipulations and that (−)-**6** had an absolute *S,S* configuration.

Synthesis of (−)-Crispine A (85:15 er) and Its (+)-Antipode from Iminium Ion Cyclization. These encouraging results prompted us to investigate an alternate method for the preparation of (−)-crispine A involving iodide **10** tethered by a pendant carbonyl group protected as its 1,3-dioxolane derivative. This route is depicted in Scheme 6 and was expected to be more direct and would involve only four purification steps from α-amino nitrile (+)-**4**. The alkylation−reduction sequence involving α-amino nitrile (+)-**4** and iodide **10** (see the synthesis in the Supporting Information) was carried out as described above to provide THIQ (−)-**11** in an overall 80% yield. The reaction sequence provided two diastereomers which could be differentiated by distinct resonance signals of the CH protons of the *O,O*-acetal groups. In the major *S,S* diastereomer this signal resonated as a triplet (^3J = 4.60 Hz) at δ 4.75.

Comparison of the relative integrations of these diagnostic protons established that reductive decyanation of the intermediary quaternary α-amino nitrile **B** took place in a 85:15 dr. Having secured the absolute configuration of the future C-10b atom, catalytic hydrogenolysis was carried out in methanol in the presence of Pearlman's catalyst under a hydrogen pressure of 5 bar to afford (−)-**12** in 85% yield.[28] Hydrolysis of the acetal function was carried out in a degassed mixture of THF and 10% HCl at 20 °C over a 24 h period. When the reaction was judged to be complete, the excess of THF was evaporated under an argon atmosphere to afford an emerald green clear aqueous solution whose pH was raised to 4.5 by the addition of an excess of sodium acetate. The subsequent addition of four equivalents of $NaBH_3CN$ caused the reduction of the intermediary iminium cation **C** and the precipitation of (−)-crispine A in 79% yield.[29] The magnitude of this optical rotation of $[\alpha]^{22}_D$ −69 (*c* 1.0, $CHCl_3$, 85:15 er) was found to match that recorded for the previous sample of (−)-crispine A, confirming the chiral conservation in both asymmetric approaches. Finally, as shown in Scheme 6, the synthesis of the natural (+)-crispine A alkaloid was also considered involving enantiomeric α-amino nitrile (−)-**4** and iodide **10**. In this way, (+)-crispine A was obtained in four steps in an overall 58% yield.

The proposed mechanism accounting for the observed 1−3 stereoselectivities is reported in Scheme 7. This process first involved the formation of an intimate ion pair between the iminium cation (*S*)-**B** and the borohydride anion. This iminium cation possesses a positively charged carbon−nitrogen double bond embedded in a rigid six-membered ring system and rotation about the C−N single bond linking the nitrogen atom to the stereogenic center yielded the conformation (*S*)-**B1** in

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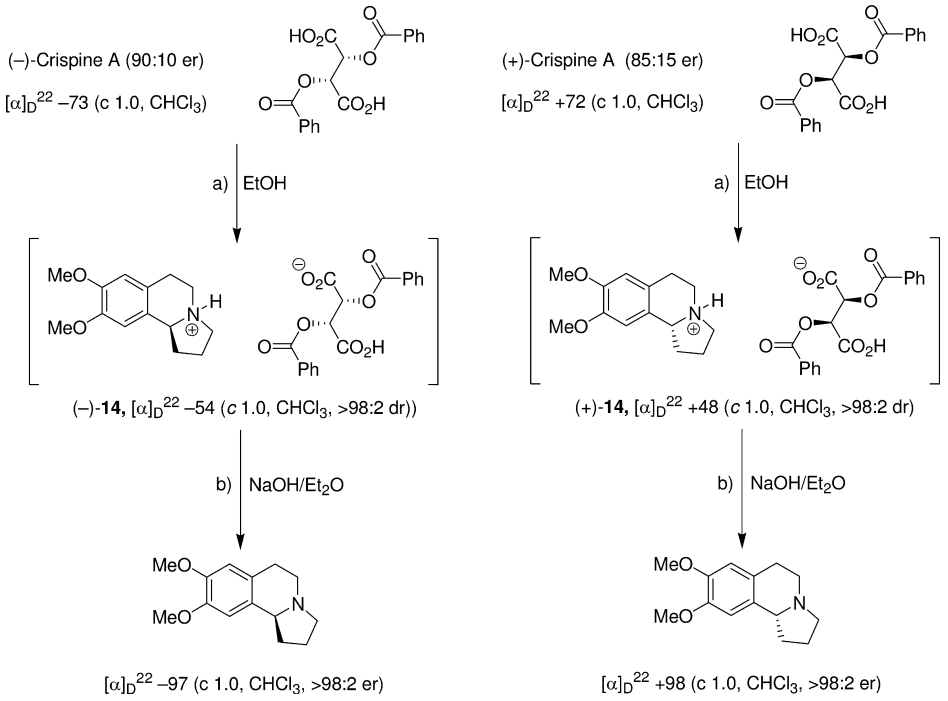
Scheme 8. Synthesis of Tartrate (−)-14 and Its (+)-Antipode



which the allylic 1,3-strain is minimal.[30] The incorporation of the hydride anion occurred on the least hindered *Re* face of this preferred conformer and tended to produce the *S,S* absolute configuration, while addition of the hydride anion on the least hindered *Si* face of alternate disfavored conformer (*S*)-**B2** would produce the *R,S* absolute configuration in the final compound. As expected and observed, the structural differences in the R alkyl chains would not significantly modify the diastereoisomeric ratio.

Resolution of Enantioenriched (−)-Crispine A and Its (+)-Antipode from DBTA. It should be pointed out that neither alteration of the reaction conditions (solvent, temperature) nor variation of the hydride source significantly modified the stereochemical outcome of the reductive decyanations of α-amino nitriles **A** and **B**. Therefore, to obtain enantiopure (−)-crispine A, a screening of chiral carboxylic acids that were hoped to form diastereomeric salts with our synthetic (−)-crispine A was undertaken. For this purpose, we explored the use of mandelic acid, amino acids such as *N*-acetylleucine, and tartaric acid. These experiments afforded unsatisfactorily results, and it was felt that resolution of an enantiomerically enriched sample of (−)-crispine A could be best achieved with (−)-*O,O*′-dibenzoyl-L-tartaric acid [(−)-(DBTA)] as the resolving agent.[31] Indeed, the addition of one equivalent of (−)-DBTA onto a partially resolved mixture (90:10 er) of (−)-crispine A led to the formation of tartaric salt (−)-**14** (≥98:2 dr), which was obtained as a colorless powder in 81% yield (Scheme 8).

From the examination of the proton NMR spectrum of tartrate (−)-**14** it can be seen that our salt had a 1:1 stoichiometry and that one molecule of ethanol was present in the crystal structure. A slow crystallization of tartrate (−)-**14** furnished single crystals whose ORTEP view (Figure S74, Supporting Information) confirmed the stoichiometry of the salt and the presence of one molecule of ethanol in the asymmetric unit. As the absolute configuration of (−)-DBTA is known, the *S* configuration of our synthetic (−)-crispine A was simply deduced from the X-ray structure.

Finally, the enantiopure (−)-crispine A was liberated from its DBTA salt (−)-**14** by the addition of a 10% aqueous NaOH and extraction with diethyl ether (Scheme 8, left). The measured optical rotation $[\alpha]^{22}_{D}$ −97 (*c* 1.02, $CHCl_3$) for (−)-crispine A was consistent with the literature value $[\alpha]^{22}_{D}$ −100 (*c* 0.32, $CHCl_3$).[10] Reciprocal diastereomer-mediated resolution of partially resolved (+)-crispine A (85:15 er) was cleanly achieved with (+)-DBTA (Scheme 8, right) affording the tartaric salt (+)-**14** (≥98:2 dr) in 78% yield. When this complex was subjected to the basic treatment depicted above, (+)-crispine A was obtained in 98% yield. The specific optical rotation of a sample of (+)-crispine A proved to be $[\alpha]^{22}_{D}$ +98 (*c* 1.0, $CHCl_3$), which is in close agreement with the literature values $[\alpha]_{D}^{22}$ +90 (*c* 1.0, $CHCl_3$).[11] The enantiomeric ratios of both enantiomers of crispine A were determined by proton and carbon NMR spectroscopic methods using (*R*)-(+)-*tert*-butylphenylphosphinothioic acid which proved to be the chiral solvating agent of choice for the analysis of THIQ derivatives.[32] The full details of this enantiomer analysis are provided in the Supporting Information, and from examination of these spectra, it can be assumed that our products have ≥98:2 er's.

■ CONCLUSION

In summary, an efficient stereocontrolled synthesis of both enantiomers of crispine A, adaptable to the synthesis of an interesting set of isoquinoline alkaloids, has been developed. Apart from the high yields in each individual step, the most prominent feature of the synthesis are (a) the usefulness of anodic cyanation as an efficient tool to activate the C-1 position of the THIQ nucleus, (b) the efficiency of metalated α-amino nitrile chemistry for the formation of new C-1−C-α bond, (c) the utilization of the α-PEA group as an inexpensive chiral auxiliary, and (d) the efficacy of solvating agent (+)-**15** for the direct in situ determination of enantiomeric purity in both

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proton and carbon NMR. Application of this strategy to the stereoselective synthesis of other THIQ alkaloids has been achieved and will be published in due course.

EXPERIMENTAL SECTION

General Techniques. Purification by column chromatography was performed with 70−230 mesh silica gel. TLC analyses were carried out on alumina sheets precoated with silica gel 60 F254 and visualized with UV light; R_f values are given for guidance. The ^{1}H NMR spectra were recorded with a 500, 400, or 300 MHz spectrometer. The ^{13}C NMR spectra were recorded with a 125, 100, or 75 MHz spectrometer. Chemical shifts are expressed in ppm downfield from TMS. Data are reported as follows: chemical shift [multiplicity (s: singlet, d: doublet, dd: double doublet, ddd: double double doublet, dm: double multiplet, dt: double triplet, t: triplet, td triple doublet, tm, triple multiplet, tt: triple triplet, q: quartet, quint: quintuplet, m: multiplet, br: broad), coupling constants (J) in hertz, integration]. Number of attached proton(s) in the ^{13}C NMR spectra was elucidated using DEPT and are described as: (p) primary, RCH_3; (s) secondary, R_2CH_2; (t) tertiary, R_3CH; (q) quaternary, R_4C. Molecular ions of mass spectra run in the EI mode are reported as M^+, while those run in chemical ionization or FAB mode are reported as MH^+. Elemental analyses are expressed as percentage values. Melting points were measured on a Kofler apparatus, with values reported in °C, and were uncorrected. For air-sensitive reactions, all glassware was oven-dried (120 °C) over a 24 h period and cooled under a stream of argon. All commercially available reagents were used as supplied. THF was distilled over sodium benzophenone ketyl and stored under an atmosphere of argon. Diisopropylamine was distilled from potassium hydroxide. Air-sensitive reagents were transferred by syringe or with a double-ended needle. Yields refer to chromatographically and spectroscopically (^{1}H, ^{13}C) homogeneous material. Optical rotations were recorded at 20 °C in a 1 dm cell. Enantiomer ratios (er's) were determined using (*R*)-(+)-**15** as a chiral solvating agent (CSA), all the spectra were recorded in C_6D_6.

Electrochemical Procedure and Equipment. Cyclic voltammetry curves were carried out on a potentiostat using a three-electrode arrangement with a glassy carbon electrode (GCE, diameter = 2 mm) as the working electrode, an SCE (saturated calomel electrode) as the reference electrode, and a platinum wire as the counter electrode. Cyclic voltammetry experiments were carried out in methanol solutions containing $LiClO_4{\cdot}3H_2O$ (0.10 mol L^{-1}) as supporting electrolyte. Experiments were carried out at ambient temperature. All potential values are referred vs SCE. Electrolyses were carried out in a homemade undivided electrolysis cell (see the schematic diagram in the Supporting Information).

*(S)-(+)-2-(3,4-Dimethoxyphenyl)-N-(1-phenylethyl)acetamide, (+)-**1**.* In a 200-mL, three-necked Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube and a bubbler, was placed 4.0 g (20.40 mmol) of 3,4-dimethoxyphenylacetic acid. The flask was flushed with argon followed by the addition of 40 mL of degassed dichloromethane. The solution was cooled to 0 °C, 1.90 mL (2.85 g, 22.45 mmol) of oxalyl chloride was added by means of syringe, and the solution was stirred at 20 °C for a period of 12 h. To this was added, dropwise at 0 °C, a solution of 2.60 mL (2.47 g, 20.40 mmol) of (*S*)-(−)-1-phenylethylamine and 3.96 mL of triethylamine (2.88 g, 28.49 mmol) in 25 mL of dichloromethane. The reaction mixture was stirred at 20 °C for 12 h, and the solvent was removed with a rotary evaporator. The residue was treated with 20 mL of a 2% HCl aqueous solution, and the mixture was extracted with two 50-mL portions of dichloromethane. The combined organic extracts were washed with 10 mL of a 5% aqueous sodium carbonate solution, dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The resulting residue was vigorously stirred in 100 mL of diethyl ether for 3 h to afford a 5.50 g of a white precipitate which was separated over a sintered-glass funnel. This crude solid was diluted with 10 mL of dichloromethane and poured into a chromatographic column (30 × 3.5 cm), prepared with 100 g of silica and 90:10 dichloromethane−diethyl ether. The combined fractions were evaporated, and the pale-yellow oily residue solidified readily on standing to afford 5.23 g (85%) of amide (+)-**1** as a white powder: mp 110−111 °C (lit.[33] mp =107−109 °C); R_f = 0.40 (dichloromethane−diethyl ether, 90:10); $[\alpha]^{22}_D$ +12.5 (*c* 1, $CHCl_3$) [lit.[34] $[\alpha]^{22}_D$−17.4 (*c* 0.29, $CHCl_3$, this value is referred to the *R* enantiomer)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.37 (d, J = 7.0 Hz, 3 H), 3.45 (s, 2 H), 3.78 (s, 3 H), 3.83 (s, 3 H), 5.09 (quint, J = 7.0 Hz, 1 H), 6.22 (d, br, J = 7.0 Hz, 1 H), 6.74−6.80 (m, 3 H), 7.18−7.21 (m, 3 H), 7.25−7.27 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 21.8 (p), 43.2 (s), 48.6 (t), 55.7 (p), 55.8 (p), 111.4 (t), 112.3 (t), 121.5 (t), 125.96 (t), 127.2 (t), 127.6 (q), 128.5 (t), 143.3 (q), 148.1 (q), 149.1 (q), 170.4 (q); HRMS ($C_{18}H_{21}NO_3$, $[M^+]$) calcd for 299.1521, found 299.1526. Anal. Calcd for $C_{18}H_{21}NO_3$ (299.36): C, 72.22; H, 7.07; N, 4.68. Found: C, 72.07; H, 7.00; N, 4.64.

*(R)-(−)-2-(3,4-Dimethoxy-phenyl)-N-(1-phenylethyl)acetamide, (−)-**1**.* The synthesis was as reported for (+)-**1** but with (*R*)-(+)-1-phenylethylamine to afford (−)-**1** as a white powder: mp 110−112 °C (lit.[35] mp =108−110 °C); $[\alpha]^{22}_D$ −16.5 (*c* 1, $CHCl_3$) [lit.[2] $[\alpha]^{22}_D$−17.4 (*c* 0.29, $CHCl_3$)].

*(S)-(−)-[2-(3,4-Dimethoxyphenyl)ethyl](1-phenylethyl)amine, (−)-**2**.* A 200-mL, three-necked Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube and a water condenser, was charged with 40 mL of anhydrous tetrahydrofuran, 2.0 g of (+)-**1** (6.68 mmol), and 1.7 mL of $BF_3{\cdot}Et_2O$ (1.95 g, 13.77 mmol). The resulting solution was heated to reflux, and 16.7 mL of $BH_3{\cdot}$THF (1.0 M in THF, 16.7 mmol) was added dropwise at that temperature. The solution was heated to reflux for an additional 2 h period and was cooled to 0 °C. The reaction mixture was quenched by the slow addition of 30 mL of a 6 M aqueous hydrochloric acid solution, and the resulting mixture was stirred for 12 h at 0 °C. *In our hands, the reaction produced a mixture of diastereomeric amine−borane complexes which could only be decomposed by quenching the reaction mixture with a 6 N hydrochloric acid solution.* The solution was basified with solid KOH until the complete precipitation of the amine as an oily residue. The solvent was removed by a rotary evaporator, and the aqueous phase was extracted twice with 50 mL of dichloromethane. The combined organic extracts were washed with water until the aqueous layer remained neutral to litmus paper, dried over anhydrous magnesium sulfate, and concentrated to afford 1.90 g of a colorless oil. This crude oil was diluted with 5 mL of dichloromethane and poured into a chromatographic column (30 × 3.5 cm), prepared with 50 g of silica and 90:10 dichloromethane/methanol. The combined fractions were evaporated to yield 1.83 g (95%) of (−)-**2** as a colorless viscous oil: R_f = 0.5 (dichloromethane/methanol, 95:5); $[\alpha]^{22}_D$ −43 (*c* 1.15, $CHCl_3$) [lit.[31] $[\alpha]^{22}_D$ −38.9 (*c* 1.7, CH_2Cl_2)]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.31 (d, J = 7.0 Hz, 3 H), 1.70−1.90 (br, 1 H), 2.65−2.75 (m, 4 H), 3.74 (q, J = 7.0 Hz, 1 H), 3.78 (s, 3 H), 3.79 (s, 3 H), 6.65−6.70 (m, 2 H), 6.74 (d, J_{AB} = 8.0 Hz, 1 H), 7.15−7.29 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 24.2 (p), 35.8 (s), 48.8 (s), 55.7 (p), 55.8 (p), 58.2 (t), 111.3 (t), 111.8 (t), 120.6 (t), 126.5 (t), 126.8 (t), 128.3 (t), 132.5 (q), 145.4 (q), 147.4 (q), 148.8 (q); HRMS ($C_{18}H_{24}NO_2$, $[M + H]^+$) calcd for 286.1807, found 286.1802. Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 74.76; H, 8.14; N, 4.76.

*(R)-(+)-[2-(3,4-Dimethoxyphenyl)ethyl](1-phenylethyl)amine, (+)-**2**.* The synthesis was as reported for (−)-**2** but with (−)-**1** to afford (+)-**2** as a colorless oil: $[\alpha]^{22}_D$ +35.5 (*c* 1.0, $CHCl_3$).

*(S)-(+)-6,7-Dimethoxy-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline, (+)-**3**.* A 50-mL, two-necked Schlenk tube, fitted with a magnetic stirring bar, connected to a water condenser, was charged with 3.22 mL of formic acid (3.92 g, 85.36 mmol), 1.83 g of (−)-**2** (6.41 mmol), and 0.2 g (6.66 mmol) of paraformaldehyde. The solution was heated at 50 °C for 12 h, and the resulting mixture was poured onto 50 mL of water. The solution was made basic by the addition of solid NaOH until the amine precipitated completely. The aqueous phase was extracted twice with 50 mL of dichloromethane, and the combined organic layers were dried over anhydrous magnesium sulfate and concentrated to afford 1.90 g of a crude oil. This crude oil was diluted with 10 mL of dichloromethane and poured into a chromatographic column (30 × 3.5 cm), prepared with 30 g of silica and 70:30 diethyl ether/petroleum ether. The combined

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fractions are evaporated to yield 1.77 g (93%) of (+)-**3** as a colorless viscous oil: R_f 0.40 (diethyl ether/petroleum ether, 70:30); $[\alpha]^{22}_D$ + 7.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.46 (d, *J* = 6.70 Hz, 3 H), 2.59−2.64 (m, 1 H), 2.69−2.81 (m, 3 H); 3.48 (d, J_{AB} = 14.4 Hz, 1 H), 3.53 (q, *J* = 6.7 Hz, 1 H), 3.72 (d, J_{AB} = 14.4 Hz, 1 H), 3.80 (s, 3 H), 3.82 (s, 3 H), 6.49 (s, 1 H), 6.57 (s, 1 H), 7.23−7.27 (m, 1 H), 7.30−7.34 (m, 2 H), 7.36−7.39 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 20.2 (p), 28.9 (s), 48.1 (s), 53.3 (s), 55.9 (p, 2 C), 64.4 (t), 109.7 (t), 111.4 (t), 126.5 (q), 126.9 (t), 127.0 (q), 127.6 (t), 128.3 (t), 144.4 (q), 147.2 (q), 147.4 (q); HRMS ($C_{19}H_{23}NO_2$, [M$^+$]) calcd for 297.1729, found 297.1721. $C_{19}H_{23}NO_2$ (297.39): calcd. C, 76.73; H, 7.80; N, 4.71, found C, 76.65; H, 7.82; N, 4.70.

*(R)-(−)-6,7-Dimethoxy-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (−)-**3**.* The synthesis is as reported for (+)-**3** but with (+)-**2** to afford (−)-**3** as a colorless viscous oil: $[\alpha]^{22}_D$ −5.6 (*c* 1.0, $CHCl_3$).

*(1R,1′S)-(+)-6,7-Dimethoxy-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile, (+)-**4**.* A 500 mL undivided electrolysis cell fitted with a vitreous carbon anode (diameter = 100 mm) and a magnetic stirrer was successively charged with 300 mL of methanol, 3.0 g of $LiClO_4$, 0.82 g (16.73 mmol) of NaCN, 0.26 mL (0.28 g, 4.70 mmol) of acetic acid, and 2.0 g (6.72 mmol) of (+)-**3**. The working potential was adjusted to +0.95 V/SCE, and after the consumption of 1370 C, (2.1 F/mol) 100 mL of water was added to the electrolysis solution (**Caution**: *$LiClO_4$ may lead to severe explosions when the material is evaporated to dryness*). Methanol was carefully evaporated under reduced pressure at +50 °C, and the aqueous phase was extracted twice with 50 mL of dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated. The crude material was taken up in diethyl ether to afford a white powder which was crystallized in a minimum of ethanol to afford 1.53 g (71%) of (+)-**4**: white flakes; mp = 162−164 °C (ethanol); R_f (diethyl ether/petroleum ether, 70:30) = 0.3, compound (+)-**4** decomposed readily on silica plates, R_f value is given for guidance; $[\alpha]^{22}_D$ + 40.0 [*c* 1.0, C_6D_6, dr ≥ 98 (*R*,*S*):2 (*S*,*S*)], $[\alpha]^{22}_D$ −24.0 [*c* 1.0, C_6D_6, dr = 55 (*R*,*S*):45 (*S*,*S*)]. *Because of a slow epimerization of C1(R), the optical rotation should be recorded within a 5 min period*. ^{1}H NMR (C_6D_6, 400 MHz) δ = 1.29 (d, *J* = 6.7 Hz, 3 H), 2.01−2.10 (m, 1 H), 2.52−2.62 (m, 2 H), 2.71−2.80 (m, 1 H), 3.34 (s, 6 H), 3.74 (q, *J* = 6.7 Hz, 1 H), 4.89 (s, 1 H), 6.24 (s, 1 H), 6.46 (s, 1 H), 7.09 (tt, *J* = 6.3, 1.5 Hz, 1 H), 7.16 (tm, *J* = 6.3 Hz, 2 H), 7.26 (d, *J* = 6.3 Hz, 2 H); ^{13}C NMR (C_6D_6, 100 MHz) δ = 21.6 (p), 27.9 (s), 45.2 (s), 52.3 (t), 55.2 (p), 55.4 (p), 62.5 (t), 110.5 (t), 112.1 (t), 116.8 (q), 121.8 (q), 126.9 (q), 127.1 (t), 127.3 (t), 128.7 (t), 145.0 (q), 148.7 (q), 150.0 (q); HRMS ($C_{20}H_{22}N_2O_2$), [M$^+$]) calcd for 322.1681, found 322.1680; ^{1}H NMR (THF-d_8, 500 MHz) δ = 1.47 (d, *J* = 6.6 Hz, 3 H), 2.47−2.57 (m, 2 H), 2.75−2.81 (m, 1 H), 2.85−2.88 (m, 1 H), 3.70 (q, *J* = 6.6 Hz, 1 H), 3.78 (s, 3 H), 3.81 (s, 3 H), 5.25 (s, 1 H), 6.69 (s, 1 H), 6.90 (s, 1 H), 7.26 (t, *J* = 7.4 Hz, 1 H), 7.34 (t, *J* = 7.4 Hz, 2 H), 7.43 (d, *J* = 7.4 Hz, 2 H); ^{13}C NMR (THF-d_8, 125 MHz) δ = 21.2 (p), 27.9 (s), 45.1 (s), 51.9 (t), 55.2 (p), 55.3 (p), 62.5 (t), 110.7 (t), 112.0 (t), 116.4 (q), 122.2 (q), 126.8 (q), 127.0 (t), 127.1 (t), 128.5 (t), 145.1 (q), 148.5 (q), 149.9 (q). Anal. Calcd for $C_{20}H_{22}N_2O_2$ (322.40): C, 74.51; H, 6.88; N, 8.69. Found: C, 74.30; H, 6.82; N, 8.59.

*(1S,1′R)-(−)-6,7-Dimethoxy-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile, (−)-**4**.* The synthesis was as reported for (+)-**4** but with (−)-**3** to afford (−)-**4** as a white solid: $[\alpha]^{22}_D$ −38.0 (*c* 1.0, C_6D_6).

*2 (3-Iodopropoxy)tetrahydropyran, **5**.* A 200-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube and a water condenser, was charged with 25 mL of dichloromethane, 2.60 mL (4.0 g, 28.75 mmol) of 3-bromo-1-propanol, 2.62 mL (2.41 g, 28.71 mmol) of 3,4-dihydro-2*H*-pyran, and 0.4 g (2.10 mmol, 10% in mass) of *p*-toluenesulfonic acid. The mixture was refluxed under argon under a vigorous agitation overnight. Dichloromethane was removed under reduced pressure, and the crude material was poured into a chromatographic column (30 × 3.5 cm), prepared with 50 g of silica and 50:50 diethyl ether/petroleum ether. The combined fractions were evaporated to yield 5.64 g (88%) of 2-(3-bromopropoxy)tetrahydropyran as an orange oil: R_f = 0.90 (diethyl ether/petroleum ether, 50:50); GC t_R = 2.43 min (isotherm 200 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.50−1.90 (m, 6 H), 2.13 (quint, *J* = 6.10 Hz, 2 H), 3.46−3.57 (m, 4 H), 3.81−3.92 (m, 2 H), 4.60 (t, *J* = 3.0 Hz, 1H). A 200-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube and a water condenser, was charged with 25 mL of acetone, 5.64 g (25.28 mmol) of 2-(3-bromopropoxy)tetrahydropyran, and 7.58 g (50.57 mmol) of NaI. The suspension was refluxed under argon overnight, and GC indicated the consumption of starting material. The reaction mixture was filtered over a sintered glass funnel, and the solvent was evaporated under reduced pressure. The resulting paste was diluted with 50 mL of dichloromethane, and the solution was washed with a 0.1 M $Na_2S_2O_3$ aqueous solution. The organic solution was dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator to afford 7.00 g of a yellowish oil. This oil was poured into a chromatographic column (50 × 5.0 cm), prepared with 150 g of silica and 50:50 diethyl ether/petroleum ether. The combined fractions were evaporated to afford 6.48 g (95%) of iodide **5** as yellowish oil: R_f = 0.90 (diethyl ether/petroleum ether, 50:50); GC t_R = 2.71 min (isotherm 200 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.50−1.74 (m, 6 H), 2.09 (quint, *J* = 6.1 Hz, 2 H), 3.30 (t, *J* = 6.8 Hz, 2 H), 3.40−3.53 (m, 2 H), 3.77−3.90 (m, 2 H), 4.60 (t, *J* = 2.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 3.4 (s), 19.5 (s), 25.4 (s), 30.6 (s), 33.6 (s), 62.3 (s), 66.8 (s), 98.9 (t); HRMS ($C_8H_{14}IO_2$, [M − H]$^+$) calcd for 269.0386, found 269.037. Anal. Calcd for $C_8H_{15}IO_2$ (270.11): C, 35.57; H, 5.60. Found: C, 35.64; H, 5.58.

*(1S,1′S)-(−)-6,7-Dimethoxy-2-(1-phenylethyl)-1-[3-tetrahydropyran-2-yloxy)propyl]-1,2,3,4-tetrahydroisoquinoline, (−)-**6**.* An oven-dried, 200-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube was flushed with argon. The flask was then cooled to −80 °C, and 10 mL of dry THF and 1.75 mL (1.25 g, 12.39 mmol) of diisopropylamine were added, followed by the dropwise addition of 4.40 mL (11.00 mmol) of butyllithium (2.5 M solution in hexane). Stirring was continued for 30 min, and the solution was warmed to 0 °C over a 1 h period. This solution was then added dropwise into a 200-mL Schlenk tube cooled to −80 °C (ethanol/liquid nitrogen bath), containing 25 mL of dry THF and 2.37 g (7.35 mmol) of aminonitrile (+)-**4**. The anion solution turned rapidly red, was allowed to warm to −20 °C over 2 h, and was cooled to −80 °C. Then, 2.98 g (11.03 mmol) of iodide **5** was added dropwise, and the reaction mixture was allowed to warm to −20 °C for 3 h. The contents of the flask were poured into a mixture of 100 mL of diethyl ether plus 15 mL of water containing 0.25 g of NaCN. The layers were separated, and the aqueous layer was extracted twice with 25 mL of diethyl ether. The combined organic layers were washed with 10 mL of water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to yield 3.94 g of a crude oily residue which was used in the next step without further purification. A 50-mL, one-necked flask, equipped with a rubber septum, was charged with 10 mL of ethanol and 3.94 g of crude alkylated material. The solution was cooled to −20 °C, and 1.28 g (33.83 mmol) of $NaBH_4$ was added in portions. Stirring was continued for 3 h at that temperature, and the solution was allowed to reach room temperature overnight. The solvents were evaporated under reduced pressure, the crude material was taken up with 20 mL of a 15% ammonia solution, and the aqueous layer was extracted twice with 25 mL of dichloromethane. The combined organic layers were washed with 25 mL of water, dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The crude oily residue was diluted with 5 mL of dichloromethane and poured into a chromatographic column (50 × 2.5 cm), prepared with 80 g of silica and 50:50 diethyl ether−petroleum ether. The combined fractions were evaporated to afford 2.5 g (77% based on α-aminonitrile (+)-**4**) of (−)-**6**: yellow viscous oil; R_f = 0.50 (diethyl ether/petroleum ether, 50:50); $[\alpha]^{22}_D$ −18.0 [*c* 1.0, $CHCl_3$, 90 (*S*,*S*):10 (*R*,*S*) dr]; ^{1}H NMR {isomeric mixture, major diastereoisomer, $CDCl_3$, 300 MHz} δ = 1.38 (d, *J* = 6.5 Hz, 3 H), 1.45−1.85 (m, 10 H), 2.40 (dt, *J* = 16.5, 5.0 Hz, 1 H), 2.82−2.89 (m, 1 H), 3.20−3.36 (m, 3 H), 3.44−3.58 (m, 4 H), 3.75 (q, *J* = 6.5 Hz, 1 H), 3.80 (s, 3 H), 3.87 (s, 3 H), 4.46−4.49 (m, 1 H), 6.41 (s, 1 H), 6.59 (s, 1 H), 7.23−7.32 (m, 5 H); ^{13}C NMR

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{isomeric mixture [90 (*S*,*S*):10 (*R*,*S*)], major diastereoisomer $CDCl_3$, 75 MHz, splitting signals indicated with an asterisk (*) are due to the presence of the tetrahydropyranyl group} δ = 19.6* (s), 19.7* (s), 21.0 (p), 23.3 (s), 25.5 (s), 26.5* (s), 26.8* (s), 30.76* (s), 30.80* (s), 33.3* (s), 33.5* (s), 38.9 (s), 55.8 (p), 55.9 (p), 57.8* (t), 58.0* (t), 58.4 (t), 62.1* (s), 62.3* (s), 67.5* (s), 67.7* (s), 98.8 (t), 111.0 (t), 11.4 (t), 126.64 (q), 126.71* (t), 127.7 (t), 128.2 (t), 131.1 (q), 146.5 (q), 147.2 (q); HRMS $C_{19}H_{23}NO_2$, [M − $(C_8H_{14}O_2^{\bullet})$]$^+$ calcd for 297.1728, found 297.1750. Anal. Calcd for $C_{27}H_{37}NO_4$ (439.58): C, 73.77; H, 8.48; N, 3.19. Found: C, 72.20; H, 8.10; N, 3.24.

*(1S,1′S)-(−)-3-[6,7-Dimethoxy-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]-propan-1-ol, (−)-**7**.* A 50-mL, one necked flask equipped with a water condenser and a magnetic stirring bar was charged with 2.50 g (5.68 mmol) of THIQ (−)-**6**, 6 mL of THF, and 60 mL of an aqueous 1.5 M H_2SO_4 solution. The mixture was refluxed over a 6 h period, and the THF wasw distilled under reduced pressure. The aqueous phase was basified with powdered $NaHCO_3$, and the resulting mixture was extracted twice with 50 mL of diethyl ether. The combined organic layers were washed with 10 mL of water, dried over anhydrous magnesium sulfate, and concentrated on a rotary evaporator to afford 2.00 g of a crude oil. This oil was diluted with 5 mL of dichloromethane and poured into a chromatographic column (50 × 2.5 cm), prepared with 80 g of silica and 80:20 diethyl ether/petroleum ether. The combined fractions were evaporated to afford 1.88 g (93%) of (−)-**7**: colorless viscous oil; R_f = 0.1 (diethyl ether/petroleum ether, 80:20); $[\alpha]^{22}_D$ −63.4 [*c* 1.0, $CHCl_3$, 90 (*S*,*S*):10 (*R*,*S*) dr]; ^{1}H NMR {isomeric mixture, major diastereoisomer, $CDCl_3$, 300 MHz} δ = 1.33 (d, *J* = 6.9 Hz, 3 H), 1.30−1.45 (m, 1 H), 1.65−1.85 (m, 3 H), 2.47 (dd, *J* = 17.5, 4.0 Hz, 1 H), 2.97 (ddd, *J* = 17.5, 12.0, 6.5 Hz, 1 H), 3.29−3.45 (m, 4 H), 3.68−3.73 (m, 2 H), 3.77 (s, 3 H), 3.86 (s, 3 H), 6.31 (s, 1 H), 6.59 (s, 1 H), 7.24−7.28 (m, 5 H); ^{13}C NMR {isomeric mixture, major diastereoisomer, $CDCl_3$, 75 MHz} δ = 21.0 (p), 21.7 (s), 30.9 (s), 36.7 (s), 38.3 (s), 55.8 (p), 55.9 (p), 58.3 (t), 59.2 (t), 63.5 (s), 110.9 (t), 111.3 (t), 125.5 (q), 127.3 (t), 128.0 (t), 128.4 (t), 129.5 (q), 144.28 (q), 147.42 (q), 147.47 (q); HRMS $C_{19}H_{22}NO_2$, [M −$(HO(CH_2)_3^{\bullet})$]$^+$ calcd for 296.16505, found 296.1627. Anal. Calcd for $C_{22}H_{29}NO_3$ (355.21): C, 74.33; H, 8.22; N, 3.94. Found: C, 73.20; H, 7.90; N, 3.85.

*(1S)-(−)-3-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-propa-1-ol, (−)-**8**.* A 50-mL low-pressure hydrogenator was charged with 10 mL of methanol, 2 mL of an aqueous 10% HCl solution, 0.19 g (20% in mass) of 10% Pd/C, and 0.95 g (2.67 mmol) of THIQ (−)-7. Air was removed from the reactor by alternatively filling it with hydrogen and venting it three times. Hydrogen pressure (3.75×10^3 Torr, 5 bar) was applied, and the suspension was stirred for 48 h at room temperature. The suspension was filtered over a small pad of Celite, and the vessel was washed with ethanol. The filtrate was concentrated under reduced pressure, and the resulting paste was dissolved in 10 mL of water. The solution was cooled in an ice bath and basified with solid KOH. The white oily residue was extracted twice with 50 mL of dichloromethane, and the combined organic layers were washed with 10 mL of water, dried over anhydrous magnesium sulfate, and concentrated on a rotary evaporator. The crude oily residue was diluted with 5 mL of dichloromethane and poured into a chromatographic column (20 × 2.0 cm), prepared with 10 g of silica and 70:30 dichloromethane/methanol. The combined fractions were evaporated to afford 0.55 g (82%) of (−)-**8**. *This THIQ derivative is sensitive to aerial oxidation and to the presence of CO_2. It should be kept under argon at −20 °C for storage.*[36] Analyses should be carried out promptly after chromatographic purification: colorless viscous oil; R_f = 0.4 (dichloromethane/methanol, 70:30); $[\alpha]^{22}_D$ −25 [*c* 1.0, $CHCl_3$, 90 (*S*)/10 (*R*) er]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.68−1.82 (m, 2 H), 1.91−2.02 (m, 2 H), 2.67 (dt, *J* = 16.2, 5.7 Hz, 1 H), 2.77 (dt, *J* = 16.2, 5.7 Hz, 1 H), 3.05 (dt, *J* = 11.7, 5.3 Hz, 1 H), 3.20 (dt, *J* = 11.7, 5.3 Hz, 1 H). 3.55 (ddd, *J* = 11.1, 7.9, 3.1 Hz, 1 H), 3.65 (ddd, *J* = 11.1, 6.4, 3.3 Hz, 1 H), 3.84 (s, 6 H), 3.90−4.00 (s, br Two H), 3.96 (dd, *J* = 8.1, 2.4 Hz, 1 H), 6.56 (s, 1 H), 6.59 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 28.6 (s), 30.5 (s), 35.4 (s), 39.8 (s), 55.4 (t), 55.8 (p), 56.0 (p), 62.7 (s), 109.4 (t), 111.7 (t), 126.6 (q), 130.2 (q), 147.5 (q), 147.6 (q); HRMS ($C_{14}H_{20}NO_3$) [M − H]$^+$ calcd for 250.1443, found 250.1453. Anal. Calcd for $C_{14}H_{21}NO_3$ (251.32): C, 66.91; H, 8.42; N, 5.57. Found: C, 65.48; H, 8.39; N, 5.50.

*(1S)-(−)-1-(3-Chloropropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride, (−)-**9**.* In a 200-mL, three-necked Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube and a reflux condenser, was placed 10 mL of dichloromethane and 0.21 mL (0.34 g, 2.88 mmol) of thionyl chloride. The solution was heated at 40 °C, and 10 mL of dichloromethane containing 0.52 g (2.07 mmol) of (−)-**8** was added dropwise over a 30 min period. The resulting mixture was refluxed for 3 h, and the solvent was removed under reduced pressure to afford a solid paste which was taken up with anhydrous diethyl ether to yield 0.57 g (90%) of (−)-**9**: white solid; mp = 195 °C dec; $[\alpha]^{22}_D$ −24 [*c* 0.25, $CHCl_3$, 90 (*S*):10 (*R*) er]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.09−2.32 (m, 4 H), 3.00−3.05 (m, 1 H), 3.20−3.33 (m, 2 H), 3.59−3.70 (m, 3 H), 3.87 (s, 6 H), 4.52 (s, br One H), 6.62 (s, 2 H), 9.56 (s, br, 1 H), 10.39 (s, br,1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 25.3 (s), 27.9 (s), 31.5 (s), 39.8 (s), 44.5 (s), 54.27 (t), 55.6 (p), 56.1 (p), 108.9 (t), 111.5 (t), 123.1 (q), 124.1 (q), 148.4 (q), 148.9 (q).

*2 (2-Iodoethyl)-1,3-dioxolane, **10**.* A 200-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube and a water condenser, was charged with 25 mL of acetone, 2.59 mL (4.0 g, 22.06 mmol) of 2-(2-bromoethyl)-1,3-dioxolane, and 6.62 g (44.16 mmol) of NaI. The suspension was refluxed under argon overnight, and GC indicated the consumption of starting material. The reaction mixture was filtered over a sintered glass funnel, and the solvent was evaporated under reduced pressure. The resulting paste was diluted with 50 mL of dichloromethane, and the solution was washed with 10 mL of a 0.1 M $Na_2S_2O_3$ aqueous solution. The organic solution was dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator to yield 4.70 g of an oily residue. This oil was diluted with 5 mL of dichloromethane and poured into a chromatographic column (50 × 5.0 cm) prepared with 100 g of silica and 90:10 diethyl ether/petroleum ether. The combined fractions were evaporated to afford 4.50 g (90%) of iodide **10** as a yellowish oil: R_f = 0.50 (diethyl ether/petroleum ether, 10:90); GC t_R = 2.71 min (isotherm 200 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.18−2.28 (m, 2 H), 3.23 (t, *J* = 7.4 Hz, 2 H), 3.85−4.03 (m, 4 H), 4.95 (t, *J* = 4.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = −2.0 (s), 37.9 (s), 65.0 (s), 103.9 (t).

*(1S,1′S)-(−)-1-(2-1,3-Dioxolan-2-ylethyl)-6,7-dimethoxy-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline, (−)-**11**. Alkylation.* An oven-dried, 200-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube was flushed with argon. The flask was then cooled to −80 °C, and 5 mL of dry THF and 0.77 mL (0.55 g, 5.45 mmol) of diisopropylamine were added, followed by the dropwise addition of 1.93 mL (4.82 mmol) of butyllithium (2.5 M solution in hexane). Stirring was continued for 30 min, and the solution was warmed to 0 °C over a 1 h period. This solution was then added dropwise into a 200-mL Schlenck tube cooled to −80 °C (ethanol/liquid nitrogen bath), containing 25 mL of dry THF and 1.11 g (3.44 mmol) of amino nitrile (+)-**4**. The anion solution turned rapidly yellow, then brownish-red, and was allowed to warm to −10 °C over 2 h and then cooled to −80 °C. Then, 0.94 g (4.12 mmol) of iodide **10** was added dropwise, and the reaction mixture was allowed to warm to −20 °C for 3 h. The contents of the flask were poured into a mixture of 100 mL of diethyl ether plus 15 mL of water containing 0.25 g of NaCN. The layers were separated, and the aqueous layer was extracted twice with 25 mL of diethyl ether. The combined organic layers were washed with 10 mL of water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to yield 1.64 g of a crude material, which was used in the next step without further purification.

Reductive Decyanation. A 50-mL, one-necked flask, equipped with a rubber septum, was charged with 10 mL of ethanol and 1.64 g of crude alkylated material. The solution was cooled to −20 °C, and 0.55 g (14.53 mmol) of $NaBH_4$ was added in portions. Stirring was continued for 3 h at that temperature, and the solution was allowed to reach room temperature overnight. The solvents were evaporated under reduced pressure, the crude material was taken up with 20 mL

of a 15% ammonia solution, and the aqueous layer was extracted twice with 25 mL of dichloromethane. The combined organic layers were washed with 25 mL of water, dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The crude oily residue was diluted with 2 mL of dichloromethane and poured into a chromatographic column (50 × 2.5 cm), prepared with 20 g of silica and 50:50 diethyl ether/petroleum ether. The combined fractions were evaporated to afford 1.10 g (80% based on α-aminonitrile (+)-**4**) of (−)-**11**: yellow viscous oil; R_f = 0.50 (diethyl ether/petroleum ether, 50:50); $[\alpha]^{22}_D$ −25.0 [*c* 1.0, $CHCl_3$, 85 (*S,S*):15 (*R,S*) dr]; ^{1}H NMR (isomeric mixture, major diastereoisomer $CDCl_3$, 300 MHz) δ = 1.31 (d, *J* = 6.5 Hz, 3 H), 1.50−1.57 (m, 2 H), 1.75−2.00 (m, 2 H), 2.42 (dt, *J* = 16.5, 3.7 Hz, 1 H), 2.87 (dt, *J* = 16.5, 8.7 Hz, 1 H), 3.18−3.22 (m, 2 H), 3.47 (dd, *J* = 9.6, 4.5 Hz, 1 H), 3.75 (q, *J* = 6.5 Hz, 1 H), 3.75−3.80 (m, 2 H), 3.78 (s, 3 H), 3.86 (s, 3 H), 3.82−3.95 (m, 2 H), 4.75 (t, *J* = 4.6 Hz, 1 H), 6.41 (s, 1 H), 6.56 (s, 1 H), 7.23−7.31 (m, 5 H); ^{13}C NMR (isomeric mixture, major diastereoisomer $CDCl_3$, 75 MHz) δ = 21.0 (p), 23.2 (s), 30.6 (s, 2 C), 38.7 (s), 55.8 (p), 55.9 (p), 57.9 (t), 58.3 (t), 64.8 (s, 2 C), 104.67 (t), 110.9 (t), 111.4 (t), 126.6 (q), 126.7 (t), 127.6 (t), 128.3 (t), 130.8 (q), 146.4 (q), 147.1 (q); HRMS ($C_{24}H_{31}NO_4$), $[M + H]^+$ calcd for 398.23311, found 398.2330.

*(S)-(−)-1-(2-1,3-Dioxolan-2-ylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, (−)-**12**.* A 50-mL low-pressure hydrogenator was charged with 10 mL of methanol, 1.03 g (2.59 mmol) of THIQ (−)-**11**, and 0.22 g (20% in mass) of 20% $Pd(OH)_2$ (Pearlman's catalyst). Air was removed from the reactor by alternatively filling it with hydrogen and venting it three times. Hydrogen pressure (3.75 × 10^3 Torr, 5 bar) was applied, and the suspension was stirred for 48 h at room temperature. The suspension was filtered over a small pad of Celite, and the vessel was washed with ethanol. The filtrate was concentrated under reduced pressure to afford a crude oily residue which was diluted with 5 mL of dichloromethane and poured into a chromatographic column (20 × 2.0 cm) prepared with 10 g of silica and 95:5 dichloromethane/methanol. The combined fractions were evaporated to afford 0.65 g (85%) of (−)-**12**. *This THIQ derivative is sensitive to aerial oxidation and to degradation in the presence of CO_2 (see additional signals in the ^{1}H NMR spectrum at δ = 5.00, 6.67, 7.05 ppm).* It should be kept under argon at −20 °C for storage. Analyses should be carried out promptly after chromatographic purification: colorless viscous oil; R_f = 0.2 (dichloromethane/methanol, 95:5); $[\alpha]^{22}_D$ −22 [*c* 1.0, $CHCl_3$, 85 (*S*)/15 (*R*) er]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.78−2.03 (m, 4 H), 2.58−2.84 (m, 2 H), 2.96 (ddd, *J* = 12.5, 7.22, 5.3 Hz, 1 H), 3.20 (dt, *J* = 12.5, 5.5 Hz, 1 H), 3.84−3.97 (m, 5 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 4.95 (t, *J* = 4.2 Hz, 1 H), 6.58 (s, 1 H), 6.65 (s, 1 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ = 29.3 (s), 30.2 (s, 2 C), 40.9 (s), 55.0 (t), 55.8 (p), 56.0 (p), 64.87 (s), 64.96 (s), 104.5 (t), 109.2 (t), 111.7 (t), 127.1 (q), 131.0 (q), 147.2 (q), 147.3 (q); HRMS ($C_{16}H_{22}NO_4$), $[M - H]^+$ calcd for 292.15488, found 292.1539. Anal. Calcd for $C_{16}H_{22}NO_4$ (293.36): C, 65.51; H, 7.90; N, 4.77. Found: C, 64.15; H, 7.89; N, 4.60.

(10bS)-(−)-8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline, (−)-Crispine A. **Protocol 1.** In a 200-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube, were placed 10 mL of an aqueous 2 M NaOH solution, 15 mL of diethyl ether, and 0.50 g (1.63 mmol) of hydrochloride (−)-**9**. The biphasic system was stirred for 5 h at ambient temperature to afford a slightly yellow ethereal phase. The layers were separated, and the aqueous phase was extracted twice with 10 mL of diethyl ether. The combined organic phases were washed with 10 mL of water, dried over anhydrous magnesium sulfate, and concentrated on a rotary evaporator to yield 0.38 g of a solid paste. This crude paste was diluted with 2 mL of dichloromethane and poured into a chromatographic column (10 × 1.0 cm), prepared with 5 g of silica and 70:30 dichloromethane/methanol. The combined fractions were evaporated to afford 0.34 g (90%) of (−)-crispine A as a brownish oil which solidified upon cooling: beige powder; mp = 89−90 °C (lit.[7a] mp = 88−89 °C); R_f = 0.15 (dichloromethane/methanol, 70:30); $[\alpha]^{22}_D$ −73 (*c* 1.0, $CHCl_3$, 90:10 er). **Protocol 2.** A 200-mL, one-necked Schlenk tube, fitted with a magnetic stirrer and a rubber septum, was flushed with argon and charged with 0.53 g (1.80 mmol) of THIQ (−)-**12**, 8 mL of THF, and 8 mL of an aqueous 10% HCl solution. The mixture was degassed by a bubbling of argon and was stirred at ambient temperature for 24 h, upon which a characteristic emerald green color progressively appeared. The organic solvent was evaporated under reduced pressure to afford an emerald green clear aqueous phase. The pH was raised to 4.5 (litmus paper) by the addition of 5.0 g of sodium acetate. Then, 1.2 g (19.0 mmol) of $NaBH_3CN$ was added until the complete precipitation of (−)-crispine A as yellow viscous oil. Then, 20 mL of diethyl ether was added to the aqueous solution, and the biphasic system was stirred for an additional 3 h period. The aqueous phase was made basic (pH = 9) by the addition of an excess of sodium carbonate. The layers were separated, and the aqueous phase was extracted twice with 10 mL of diethyl ether. The combined organic layers were washed with 10 mL of water, dried over anhydrous magnesium sulfate, and concentrated on a rotary evaporator to afford 0.33 g (79%) of (−)-crispine A. **Protocol 3.** A 50-mL, one-necked flask, equipped with a rubber septum, was charged with 10 mL of ethanol and 0.50 g (1.93 mmol) of crude α-aminonitrile **13**. The solution was cooled to 0 °C, and 0.57 g (15.0 mmol) of $NaBH_4$ was added in portions. The solution was allowed to reach room temperature overnight, and stirring was continued for 48 h. The solvents were evaporated under reduced pressure, and the crude material was taken up with 20 mL of a 15% ammonia solution. The aqueous layer was extracted twice with 25 mL of dichloromethane, and the combined organic layers were washed with 25 mL of water, dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator. The crude oily residue was diluted with 2 mL of dichloromethane and poured into a chromatographic column (10 × 1.0 cm), prepared with 5 g of silica and 70:30 dichloromethane/methanol. The combined fractions were evaporated to afford 0.35 g (79%) of (−)-crispine A as a brownish oil which solidified upon cooling: $[\alpha]^{22}_D$ −69 (*c* 0.8, $CHCl_3$, 85:15 er); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.65−1.78 (m, 1 H), 1.79−1.98 (m, 2 H), 2.26−2.37 (m, 1 H), 2.52−2.76 (m, 3 H), 2.96−3.10 (m, 2 H), 3.13−3.20 (m, 1 H), 3.40 (t, *J* = 8.5 Hz, 1 H), 3.84 (s, 3 H),3.85 (s, 3 H), 6.56 (s, 1 H), 6.50 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 22.2 (s), 28.0 (s), 30.5 (s), 48.3 (s), 53.1 (s), 55.87 (p), 55.93 (p), 62.9 (t), 108.9 (t), 111.3 (t), 126.2 (q), 130.9 (q), 147.23 (q), 147.34 (q); HRMS ($C_{14}H_{19}NO_2$), $[M]^+$ calcd for 233.1416, found 233.1408. Anal. Calcd for $C_{14}H_{19}NO_2$ (233.30): C, 72.07; H, 8.21; N, 6.00. Found: C, 71.46; H, 8.10; N, 5.85.

*8 9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline-3-carbonitrile, **13**.* A 200-mL, one-necked Schlenk tube, fitted with a magnetic stirrer and a rubber septum, was flushed with argon and charged with 0.70 g (2.38 mmol) of THIQ (−)-**12**, 10 mL of THF, and 10 mL of an aqueous 10% HCl solution. The mixture was degassed by a bubbling of argon and stirred at ambient temperature for 24 h, upon which a characteristic emerald green color progressively appeared. The organic solvent was evaporated under reduced pressure to afford an emerald green clear aqueous phase. The pH was raised to 4.5 (litmus paper) by the addition of 5.0 g of sodium acetate. Then, 1.58 g (32.24 mmol) of NaCN was added until the complete precipitation of α-aminonitrile **13** as yellow viscous oil. Then, 20 mL of diethyl ether was added to the aqueous solution, and the biphasic system was stirred for an additional 3 h period. The aqueous phase was made basic (pH = 9) by the addition of an excess of sodium carbonate. The layers were separated, and the aqueous phase was extracted twice with 10 mL of diethyl ether. The combined organic layers were washed with 10 mL of water, dried over anhydrous magnesium sulfate, and concentrated on a rotary evaporator to afford 0.55 g (90%) of α-aminonitrile **13** as pale yellow oil which could be utilized in the next step without purification: R_f = 0 (α-aminonitrile **13** readily decomposed on silica gel); ^{1}H NMR (isomeric mixture, 60:40 dr, $CDCl_3$, 500 MHz) δ = 1.75−1.80 (m, 0.6 H), 1.84−1.90 (m, 0.4 H), 2.17−2.41 (m, 2.4 H), 2.45−2.47 (m, 0.6 H), 2.60 (td, *J* = 11.1, 4.7 Hz, 0.4 H), 2.73−2.81 (m, 1 H), 2.90 (td, *J* = 11.2, 3.4 Hz, 0.6 H), 3.01−3.06 (m, 0.6 H), 3.16−3.22 (m, 1 H), 3.31−3.36 (m, 0.8 H), 3.46 (ddd, *J* = 10.8, 8.5, 1.5 Hz, 0.4 H), 3.79 (t, *J* = 8.0 Hz, 0.6 H), 3.83 (s, 1.2 H), 3.84 (s, 4.8 H), 4.07 (dd, *J* = 8.4, 3.0 Hz, 0.6 H), 6.51 (s, 0.4 H), 6.54 (s, 0.6 H), 6.61 (s, 0.6 H), 6.64 (s, 0.4 H); ^{13}C NMR

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(isomeric mixture, 60:40 dr, $CDCl_3$, 125 MHz) δ = 27.7 (s), 28.2 (s), 28.4 (s), 28.7 (s), 28.8 (s), 29.3 (s), 45.7 (s), 47.6 (s), 52.8 (t, 2 C), 55.9 (p, 2 C), 56.06 (p), 56.09 (p), 60.5 (t), 63.1 (t), 108.3 (t), 108.7 (t), 111.42 (t), 111.44 (t), 118.5 (q), 119.8 (q), 125.7 (q), 125.9 (q), 129.2 (q), 129.5 (q), 147.4 (q), 147.5 (q), 147.7 (q), 147.9 (q); HRMS ($C_{15}H_{18}N_2O_2Na$), $[M + Na]^+$ calcd for 281.1266, found 281.1265. Anal. Calcd for $C_{15}H_{18}N_2O_2$ (258.31): C, 69.74; H, 7.02; N, 10.84. Found C, 68.55; H, 7.03; N, 10.08.

*(−)-Crispine A·(−)-O,O′-Dibenzoyl-L-tartaric Acid·Ethanol, (−)-**14**.* To a solution of 0.33 g (1.41 mmol) of a partially resolved mixture of (−)-crispine A (90:10 er) in 10 mL of ethanol was added 0.52 g (1.45 mmol) of (−)-*O,O′*-dibenzoyl-L-tartaric acid monohydrate. The solution was heated to reflux, and the homogeneous solution was allowed to cool to room temperature slowly. The precipitate was then filtered over a sintered glass funnel to give 0.60 g (81% based on isomer content) of (−)-crispine A·(−)-*O,O′*-dibenzoyl-L-tartaric acid·ethanol as colorless crystals which were analyzed by X-ray diffraction: mp = 152−154 °C; $[\alpha]^{22}_D$ −54 (*c* 1.0, $CHCl_3$, ≥98:2 dr); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.20 (t, *J* = 7.0 Hz, 3 H), 1.75−1.90 (m, 2 H), 1.91−2.08 (m, 1 H), 2.40−2.50 (m, 1 H), 2.60−2.75 (m, 1 H), 2.82−3.10 (m, 3 H), 3.38−3.50 (m, 1 H), 3.68 (q, *J* = 7.0 Hz, 2 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 4.70−4.80 (m, 1 H), 5.83 (s, 2 H), 6.44 (s, 1 H), 6.47 (s, 1 H), 7.33 (t, *J* = 7.5 Hz, 4 H), 7.47 (t, *J* = 7.4 Hz, 2 H), 8.03 (d, *J* = 7.2 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 18.3 (p), 22.3 (s), 24.3 (s), 32.5 (s), 46.4 (s), 52.9 (s), 55.9 (p), 56.0 (p), 58.4 (s), 60.7 (t), 73.0 (t), 108.9 (t), 110.8 (t), 123.3 (q), 124.0 (q), 128.2 (t), 129.7 (q), 130.0 (t), 133.0 (t), 148.36 (q), 148.46 (q), 165.6 (q), 170.4 (q); HRMS ($C_{14}H_{20}NO_2$), $[M]^+$ calcd for 234.1494, found 234.1486. Anal. Calcd for $C_{34}H_{39}NO_{11}$ (637.25): C, 64.04; H, 6.16; N, 2.20. Found: C, 63.82; H, 6.23; N, 2.07.

*(S)-(−)-Crispine A from the Tartrate Salt (−)-**14**.* To a stirred aqueous 10% NaOH solution (10 mL) was added 0.20 g (0.31 mmol) of tartrate salt (−)-**14**. The mixture was stirred at ambient temperature for 5 min before diethyl ether (20 mL) was added, whereupon the solution was stirred for another 30 min period. The aqueous layer was separated and extracted twice with 10 mL of diethyl ether. The organic layers were washed with 10 mL of water, dried over magnesium sulfate, and concentrated under reduced pressure to afford 0.065 g (89%) of (−)-crispine A: $[\alpha]^{22}_D$ −97 [*c* 1.02, $CHCl_3$, ≥98:2 er] [lit.[6b] $[\alpha]^{22}_D$ = +100 (*c* = 1.5, $CHCl_3$)]; this value is referred to the *R* enantiomer.

*(R)-(+)-Crispine **A**.* The syntheses were as reported for (−)-crispine A but starting from *α*-aminonitrile (−)-**4** to afford (+)-**11**, $[\alpha]^{22}_D$ +23.0 [*c* 1.0, $CHCl_3$, 85 (*R,R*):15 (*S,R*) dr]; (+)-**12**, $[\alpha]^{22}_D$ +26 [*c* 1.0, $CHCl_3$, 85 (*R*):15 (*S*) er], and (+)-crispine A as a beige solid: $[\alpha]^{22}_D$ +72 [*c* 1.0, $CHCl_3$, 85 (*R*):15 (*S*) er].

*(+)-Crispine A·(+)-O,O′-Dibenzoyl-D-tartaric Acid·Ethanol, (+)-**14**.* To a solution of 0.26 g (1.11 mmol) of a mixture [85(*R*):15 (*S*)] of (+)-crispine A and (−)-crispine A in 10 mL of ethanol was added 0.40 g (1.11 mmol) of (+)-*O,O′*-dibenzoyl-D-tartaric acid monohydrate. The solution was heated to reflux, and the homogeneous solution was allowed to cool to room temperature slowly. The precipitate was then filtered over a sintered glass funnel to give 0.47 g (78% based on isomer content) of (+)-crispine A·(+)-*O,O′*-dibenzoyl-*D*-tartaric acid·ethanol ((+)-**14**): colorless crystals; mp = 152−154 °C; $[\alpha]^{22}_D$ +48 (*c* 1.0, $CHCl_3$, ≥98:2 dr). Spectral properties (^{1}H and ^{13}C) are identical to those reported for tartrate (−)-**14**.

*(R)-(+)-Crispine A from Tartrate Salt (+)-**14**.* A basic treatment (10% NaOH) of tartrate salt (+)-**14** afforded (+)-crispine A: $[\alpha]^{22}_D$ + 98 (*c* 1.0, $CHCl_3$, ≥98:2 er) in 87% yield; ^{1}H NMR (C_6D_6, 400 MHz) δ = 1.60−1.80 (m, 3 H), 2.00−2.10 (m, 1 H), 2.34−2.41 (m, 1 H), 2.48−2.60 (m, 2 H), 2.90−3.08 (m, 3 H), 3.32 (t, *J* = 8.5 Hz, 1 H), 3.45 (s, 3 H),3.48 (s, 3 H), 6.49 (s, 1 H), 6.56 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 22.3 (s), 28.5 (s), 30.5 (s), 48.5 (s), 53.1 (s), 55.5 (p), 55.7 (p), 63.2 (t), 110.3 (t), 112.7 (t), 126.7 (q), 131.7 (q), 148.34 (q), 148.44 (q).

*(S)-(−)-Crispine A·(+)-**15**.* (*S*)-(−)-Crispine A (50 *μ*mol, ≥98:2 er) and C_6D_6 (0.7 mL) were mixed in a 5 mm NMR tube, and (+)-**15** (60 *μ*mol) was added. The ^{13}C and ^{1}H NMR data were collected on a 500 MHz spectrometer. The chemical shifts (ppm) were internally referenced to the TMS signal (0 ppm): ^{1}H NMR (C_6D_6, 500 MHz, 300 K, transients = 456) δ = 1.20−1.50 (m, 2 H), 1.54 (d, $^3J_{PH}$ = 15.8 Hz, 9 H), 1.63−1.69 (m, 1 H), 2.00−2.07 (m, 1 H), 2.10−2.22 (m, br, 1 H), 2.30−2.40 (m, br, 1 H), 2.50−2.60 (m, br, 1 H), 2.70−2.74 (m, 1 H), 3.25−3.35 (m, br, 1 H), 3.45 (s, 3 H), 3.47 (s, 3 H), 3.70−3.90 (m, br, 1 H), 4.90−5.05 (m, br, 1 H), 6.22 (s, 1 H), 6.26 (s, 1 H), 7.35 (td, $^3J_{HH}$ = 7.6 Hz, $^4J_{PH}$ = 2.8 Hz, 2 H), 8.54−8.58 (m, 3 H); ^{13}C NMR (C_6D_6, 125 MHz, NS = 1693) δ = 21.9 (s), 24.3 (s), 25.4 (p), 32.0 (s), 36.4 [q, d, $^1J_{PH}$ = 75.0 Hz], 45.8 (s), 52.2 (s), 55.3 (p), 55.5 (p), 60.0 (t), 109.8 (t), 111.5 (t), 123.6 (q), 125.1 (q), 127.1 [t; (d, $^2J_{PH}$ = 11.0 Hz)], 129.6 [t; (d, $^4J_{PH}$ = 2.4 Hz)], 133.4 [t; (d, $^3J_{PH}$ = 9.2 Hz)], 139.1 [q; (d, $^1J_{PH}$ = 90.0 Hz)], 149.0 (q), 149.2 (q); ^{31}P NMR (C_6D_6, 121 MHz) δ = 82.14.

*(+)-Crispine A (85:15 er)·(+)-**15**:* ^{1}H NMR (C_6D_6, 400 MHz, 295 K) δ = 1.60−1.80 (m, H-1a, H-2a and H-2b, 3H), 2.00−2.10 (m, H-1b, 1 H), 2.38 (m, H-3a, 1 H), 2.47−2.60 (m, H-5a and H-6a, 2 H), 2.90−3.07 (m, H-3b, H-6b and H-5b, 3 H), 3.32 (t, ^3J = 7.15 Hz, H-10b, 1 H), 3.44 (s, MeO-9, 3 H), 3.48 (s, MeO-8, 3 H), 6.49 (s, H-7, 1 H), 6.56 (s, H-10, 1 H); ^{13}C NMR (C_6D_6, 100 MHz, 295 K) δ = 22.3 (C-2), 28.5 (C-6), 30.5 (C-1), 48.5 (C-5), 53.1 (C-3), 55.50 (CH_3−O-9), 55.70 (CH_3−O-8), 63.2 (C-10b), 110.3 (C-10), 112.7 (C-7), 126.7 (C-6a), 131.7 (C-10a), 148.34 (C-8), 148.44 (C-9).

*(R)-(+)-Crispine A·(+)-**15**:* (*R*)-(+)-Crispine A (130 *μ*mol) and C_6D_6 (0.7 mL) were mixed in a 5 mm NMR tube, and (+)-**15** (149 *μ*mol) was added. The ^{13}C and ^{1}H NMR data were collected on a 400 MHz spectrometer. The chemical shifts (ppm) were internally referenced to the TMS signal (0 ppm): ^{1}H NMR (C_6D_6, 400 MHz, 295 K) δ = 1.10−1.30 (m, H-1a and H-2a, 2H), 1.42 (d, $^3J_{HP}$ = 15.8 Hz, 9 H), 1.50−1.60 (m, H-2b, 1 H), 1.90−2.00 (m, H-1b, 1 H), 2.18−2.30 (m, H-3a and H-6a, 2 H), 2.40−2.50 (m, H-5a, 1 H), 2.70−2.80 (m, H-6b, 1 H), 3.05−3.15 (m, H-5b, 1 H), 3.34 (s, MeO-9, 3 H), 3.38 (s, MeO-8, 3 H), 3.60−3.70 (m, H-3b, 1 H), 4.50−4.60 (m, H-10b, 1 H), 6.04 (s, H-10, 1 H), 6.20 (s, H-7, 1 H), 7.10−7.20 (m, 3 H), 8.30−8.35 (m, 2 H); ^{13}C NMR (C_6D_6, 100 MHz, 295 K) δ = 21.9 (C-2), 24.5 (C-6), 25.4 (C-CH_3-*t*-Bu), 31.8 (C-1), 36.2 (d, $^1J_{CP}$ = 75.0 Hz, *C*-CH_3-*t*-Bu), 45.8 (C-5), 52.1 (C-3), 55.34 (CH_3−O-8), 55.42 (CH_3−O-9), 59.9 (C-10b), 109.8 (C-10), 111.5 (C-7), 123.6 (C-6a), 125.1 (C-10a), 126.8 (d, $^2J_{PH}$ = 11.0 Hz, C_m), 129.3 (d, $^4J_{PH}$ = 2.4 Hz, C_p), 133.2 (d, $^3J_{PH}$ = 9.2 Hz, C_o), 139.5 (d, $^1J_{PH}$ = 90.0 Hz, C_i), 148.94 (C-8), 149.03 (C-9).

*rac-Crispine A·(+)-**15**:* *rac*-Crispine A (140 *μ*mol) and C_6D_6 (0.7 mL) were mixed in a 5 mm NMR tube, and (+)-**15** (145 *μ*mol) was added. The ^{13}C and ^{1}H NMR data were collected on a 400 MHz spectrometer. The chemical shifts (ppm) were internally referenced to the TMS signal (0 ppm): ^{1}H NMR (C_6D_6, 500 MHz, 300 K, transients = 136) δ = 1.20−1.45 (m, 2 H), 1.54 (d, $^3J_{HP}$ = 15.8 Hz, 9 H), 1.60−1.80 (m, 1 H), 2.00−2.17 (m, 1 H), 2.25−2.45 (m, br, 2 H), 2.50−2.60 (m, br, 1 H), 2.75−2.81 (m, 0.5 H), 2.87−2.91 (m, 0.5 H), 3.17−3.30 (m, br, 1 H), 3.45 (s, 1.5 H), 3.48 (s, 3 H), 3.50 (s, 1.5 H), 3.70−3.90 (m, br, 1 H), 4.60−4.70 (m, br, 0.5 H), 4.85−4.95 (m, br, 0.5 H), 6.17 (s, 0.5 H), 6.29 (s, 0.5 H), 6.30 (s, 0.5 H), 6.32 (s, 0.5 H), 7.24−7.27 (m, 1 H), 7.35 (td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HP}$ = 2.8 Hz, 2 H), 8.54−8.58 (m, 2 H); ^{13}C NMR [C_6D_6, 125 MHz, 300 K, transients =664, splitting signals are indicated with an asterisk (*)] δ = [22.0 (s), 22.1 (s)]*, [24.5 (s), 24.7 (s)]*, 25.6 (p), [31.9 (s), 32.1 (s)]*, 36.5 [q, (d, $^1J_{CP}$ = 75.0 Hz)], 45.8 (s), 52.2 (s), [55.40 (p), 55.43 (p), 55.50 (p)*, 55.57 (p)]*, [59.95 (t), 60.03 (t)]*, [109.81 (t), 109.88 (t)]*, [111.55 (t), 111.61 (t)]*, [123.8 (q), 123.9 (q)]*, [125.36 (q), 125.43 (q)]*, 127.1 [t; (d, $^3J_{CP}$ = 11.0 Hz)], 129.3 [t; (d, $^4J_{CP}$ = 2.4 Hz), 133.4 [t; (d, $^2J_{PH}$ = 8.9 Hz), 139.9 [q, (d, $^1J_{PH}$ = 88.5 Hz)], [149.0 (q), 149.1 (q), 149.2 (q)]*.

*Crystal Data, X-ray Data Collection, and Refinement Results of Tartrate (−)-**14**.* $C_{34}H_{39}NO_{11}$, *M* = 637.66, monoclinic, space group $P2_1$, *a* = 9.3851(6) Å, *b* = 11.1429(7) Å, *c* = 15.4073(11) Å, *α* = 90, *β* = 97.742(2), *γ* = 90°, *V* = 1596.57(18) Å^{-3}, *Z* = 2, D_x = 1.326 Mg m^{-3}, *μ* = 0.99 cm^{-1}, *λ* (Mo *Kα*) = 0.71073 Å, *F*(000) = 676, *T* = 100(2) K. The sample (0.28 × 0.24 × 0.13 mm) was studied on a diffractometer with graphite-monochromatized Mo K*α* radiation. The data collection (Θ_{max} = 27.48°, range of *HKL*: *H* −10→12, *K* −14→13, *L* −20→20) gave 14460 reflections with 3846 unique reflections from which 3606 with $I > 2.0\sigma(I)$. The structures were solved by direct

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methods with SIR-97,[37] which revealed the non-hydrogen atoms of the molecules. Refinement was performed by full-matrix least-squares techniques based on F^2 with SHELXL-97[38] with the aid of the WINGX[39] program. All non-hydrogen atoms were refined with anisotropic thermal parameters. H atoms were finally included in their calculated positions. Figures were drawn with ORTEP-3 for Windows.[40] CCDC-807857 [(−)-**14**] contains the supplementary crystallographic data for this paper. These data can be obtained from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR and ^{13}C NMR spectra and ORTEP view for the preparation of derivatives **1**−**14**, (−)- and (+)-crispine A, electroanalytical study and determination of enantiomeric ratios of (−)- and (+)-crispine A by ^{1}H and ^{13}C NMR (S86−S114), and crystallographic data of derivative (−)-**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ DEDICATION

Dedicated to Dr. Jacques Royer, with respect and admiration for his contribution to alkaloid chemistry.

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