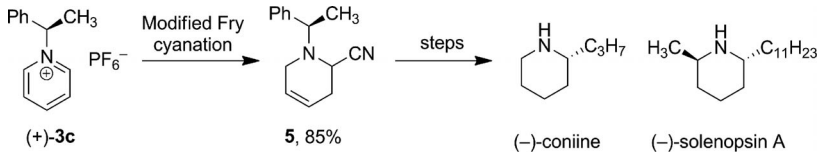
EurJOC European Journal of Organic Chemistry

α-Amino Nitrile Synthesis



(+)-**3c** **5**, 85% (–)-coniine (–)-solenopsin A

The two-step reductive cyanation of chiral pyridinium salt (+)-**3c** afforded α-amino nitrile **5** in 85% yield, which underwent an alkylation–reduction sequence followed by removal of the chiral moiety to yield the hemlock alkaloid (–)-coniine as its mandelate salt (>99:1 *er*). This reaction sequence was also used for the synthesis of the *trans*-2,6-disubstituted piperidine alkaloid (–)-solenopsin A.

Keywords: Total synthesis / Alkaloids / Asymmetric synthesis / Lithiation / Chiral resolution

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Modified Fry Cyanation of a Chiral Pyridinium Salt: Asymmetric Syntheses of (–)-Coniine and (–)-Solenopsin A

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Keywords: Total synthesis / Alkaloids / Asymmetric synthesis / Lithiation / Chiral resolution

The synthesis of chiral 2-cyano-Δ^4-tetrahydropyridine **5** was carried out in 85 % yield through a modified two-step Fry reductive cyanation of pyridinium salt (+)-**3c** that used lithium triethylborohydride as the hydride donor. An alkylation–reduction sequence provided 2-alkyl-substituted tetrahydropyridines (+)-**10a** and (+)-**10b** in 72–75 % yield after chromatographic purification. This protocol has been applied to the asymmetric syntheses of piperidine alkaloids (–)-coniine and (–)-solenopsin A.

Introduction

Piperidine derivatives are found in both the plant and animal kingdoms and are part of an important broad group of alkaloids. An ever-growing array of such substances that display various substitution patterns now exists, and their syntheses have been the subject of several reviews.[1] For example, (–)-coniine (**1**) is a toxic component of *Conium maculatum*, and (–)-solenopsin A (**2**) is one of many non-proteinaceous piperidine alkaloids that are secreted by the fire ant *Solenopsis invicta* (see Figure 1).

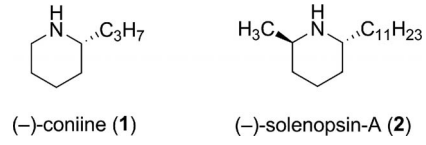
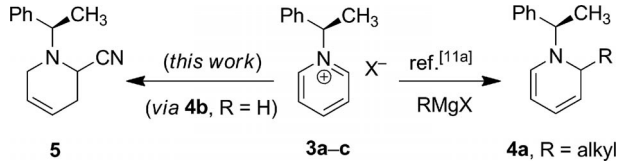


Figure 1. Structures of piperidine alkaloids **1** and **2**.

The difficulty of isolating more than milligram quantities from natural sources has led chemists to elaborate new chemical pathways for the synthesis of compounds **1** and **2**. Recent studies have included the asymmetric alkylation of imines and iminium or acyl pyridinium salts,[2] metal-catalyzed cyclizations,[3] an enantioselective vinylogous Mannich addition,[4] an aza-Michael reaction,[5] the stereoselective reduction of iminium systems,[6] the dynamic resolution of *N*-Boc-2-lithiopiperidine,[7] an asymmetric allylic imidate rearrangement of trifluoroacetimidates,[8] a Mo-catalyzed asymmetric ring-closing metathesis (RCM),[9] and chemoenzymatic resolution methods.[10] As shown in Scheme 1, chiral *N*-alkylpyridinium salts **3**, which are derived from (*R*)-(+)-1-phenylethylamine through the Zincke reaction, have occupied an interesting but somewhat understated position.[11] Marazano and Guilloteau-Bertin reported that the addition of Grignard reagents to **3a** (X^- = dodecyl sulfate) yielded unstable 1,2-dihydropyridine **4a**, which was converted in a two-step procedure into alkaloids **1** and **2**.[11a] However, the regioselectivity of the attack at C-2 decreases with bulky Grignard reagents, and the stereoselectivities do not exceed 75:25 *dr*. As far as the piperidine ring is concerned, we were interested in transforming pyridinium salt **3** into a new derivative to allow for substitution at the α-position to the nitrogen atom. For this purpose, we sought to reverse the previous reaction sequence. Accordingly, the hydride anion should first be incorporated at C-2 to afford the intermediary 1,2-dihydropyridine **4b** (R = H), which in the presence of cyanide anions could then be converted into α-amino nitrile **5**.



Scheme 1. Synthetic approaches to alkaloids **1** and **2** from pyridinium salt **3**.

For the second step and on the basis of our previous experience with α-amino nitrile chemistry, we reasoned that **5** could lead stereoselectively to 2-substituted piperidines

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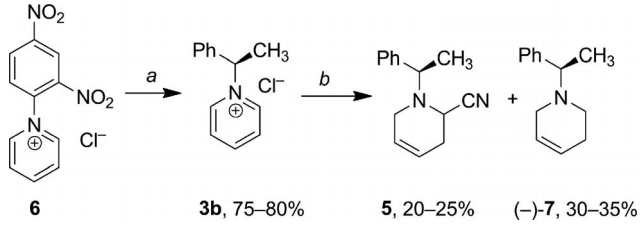
through an alkylation–reduction sequence.[12] In this paper, we report the potential of this approach to demonstrate the concise syntheses of the title alkaloids **1** and **2**. The key feature incorporates a modified two-step Fry reductive cyanation of pyridinium salt **3c** ($X^- = PF_6^-$). To the best of our knowledge, the lithiation of a chiral nonracemic 2-cyano-Δ^4-tetrahydropyridine system has never been reported in the literature.

Results and Discussion

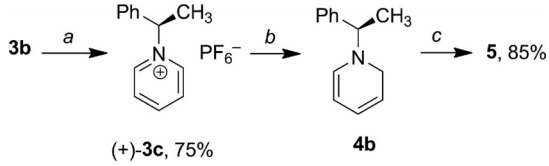
Synthesis of α-Amino Nitrile 5

The reaction of 1-(2,4-dinitrophenyl)pyridinium chloride (Zincke salt **6**) with optically pure amines offered an efficient entry to pyridinium salts **3**, which are ideally suited for our chemistry.[13] Hence, the treatment of **6** with 1 equiv. of (*R*)-(+)-1-phenylethylamine in *n*-butanol and heating to reflux for 24 h provided pyridinium chloride **3b** in 75–80% yield. The synthesis of α-amino nitrile **5** was first carried out by using the protocol described by Fry in 1963 (see Scheme 2).[14] Accordingly, pyridinium chloride **3b** (5 mmol) and 6 equiv. of NaCN were stirred at 0 °C for 4 h in a two-phase system (Et_2O/H_2O, NaCN, pH = 9.5) in the presence of 1 equiv. of $NaBH_4$. Workup and purification of the crude reaction mixture by column chromatography afforded a mixture of α-amino nitrile **5** (20–25%) and tetrahydropyridine (–)-**7** (30–35%). Neither altering the reaction conditions nor varying the hydride source improved the yields significantly. In addition, the unfavorable **5**/**7** product distribution indicated that the entire sequence of reactions took place in the two-phase system and the reductive decyanation of **5** (or the stepwise reduction of **3b** into **7**) was an unavoidable process.[15]



Scheme 2. Fry synthesis of α-amino nitrile **5** and tetrahydropyridine (–)-**7**. Reagents and conditions: (a) (*R*)-(+)-1-phenylethylamine, *n*-butanol, reflux, 24 h; (b) $NaBH_4$, NaCN/HCN, Et_2O/H_2O, pH = 9.5, 0 °C.

To overcome this drawback, it seemed a two-step procedure that included prior formation of unstable 1,2-dihydropyridine **4b** in an aprotic solvent and its subsequent transformation upon contact with an aqueous NaCN/HCN buffer system would efficiently lead to α-amino nitrile **5** (see Scheme 3). In addition, the exclusive formation of 1,2-dihydropyridine **4b** required the regiospecific addition of a hydride anion at C-2. Because this reaction sequence would be more efficiently carried out in tetrahydrofuran (THF) in the presence of a stoichiometric amount of a complex hydride, we thus searched for a pyridinium salt that would be relatively soluble in this solvent. Thus, the addition of KPF_6 to an aqueous solution of pyridinium chloride **3b** led to the immediate precipitation of the corresponding hexafluorophosphate salt (+)-**3c**, which was recovered in 75% yield.[16]



Scheme 3. Modified two-step Fry synthesis of α-amino nitrile **5**. Reagents and conditions: (a) KPF_6, H_2O, room temp. 12 h; (b) Li-Et_3BH, THF, –70 °C; (c) NaCN/HCN, pH = 9.5.

An evaluation of complex boron hydrides showed that the best yields and reaction rates were obtained by the slow addition of 1.1 equiv. of lithium triethylborohydride (1.0 M solution in THF) to a stirred suspension of pyridinium (+)-**3c** in THF at –70 °C. The resulting clear solution of **4b** was warmed to 0 °C, and an oxygen-free NaCN/HCN (pH = 9.5) buffer solution was slowly added at that temperature. The stirring was continued for 12 h to afford α-amino nitrile **5** as an epimeric mixture (50:50) in 85% yield.[17] Crystallization of the mixture in a biphasic system of diethyl ether and petroleum ether afforded single crystals {m.p. 76 °C, $[\alpha]_D^{22} = -2.5$ (c = 1.1, $CHCl_3$)}[18] that were analyzed by X-ray diffraction, which indicated that the less soluble diastereoisomer (–)-**5**-**A** displayed an absolute configuration of (1′*R*,2*S*). This study also revealed that the tetrahydropyridine ring adopts a half-chair conformation in which the nitrile group is axially oriented (see Figure 2).[19]

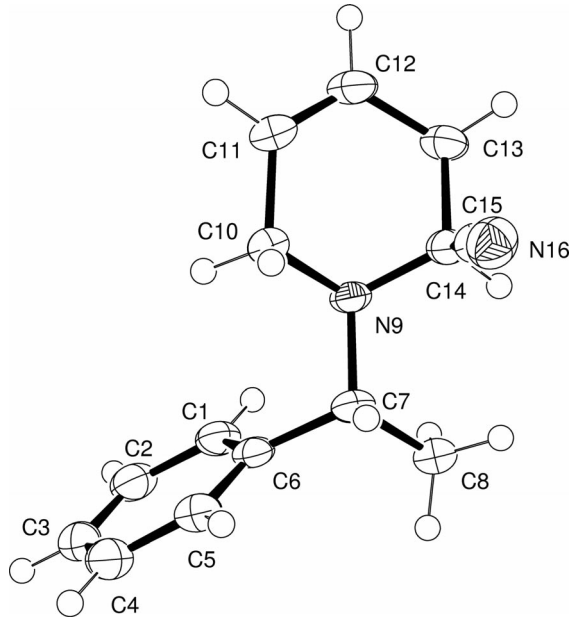
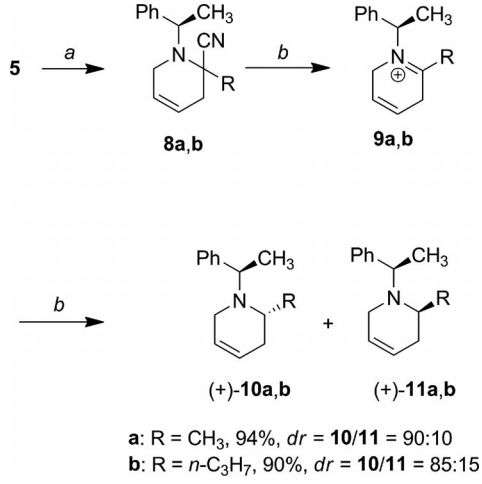


Figure 2. ORTEP drawing of α-amino nitrile (–)-**5**-**A**. Elipsoid plots were drawn with 60% probability.

Synthesis of Tetrahydropyridines 10a and 10b

To introduce the requisite side chains at C-2, lithiation of α-amino nitrile **5** (as a 50:50 epimeric mixture) was carried out in THF at –80 °C by the addition of a solution of lithium diisopropylamide (LDA, see Scheme 4).[20,21] The addition of iodomethane or *n*-propyl iodide to the resulting α-amino carbanion led to the synthesis of unstable quaternary aminonitriles **8a** and **8b**, respectively. Analogous to previous experiments, reductive decyanation was best achieved by the introduction of 4 equiv. of $NaBH_4$ at 0 °C to solutions of α-amino nitriles **8a** and **8b** (in THF/EtOH, 50:50) to provide 2-alkyl-tetrahydropyridine (+)-**10a** as a mixture with its isomer (+)-**11a** (**10a/11a**, 90:10) and (+)-**10b** as a mixture with its isomer (+)-**11b** (**10b/11b**, 85:15), respectively, in yields ranging from 90–94%.

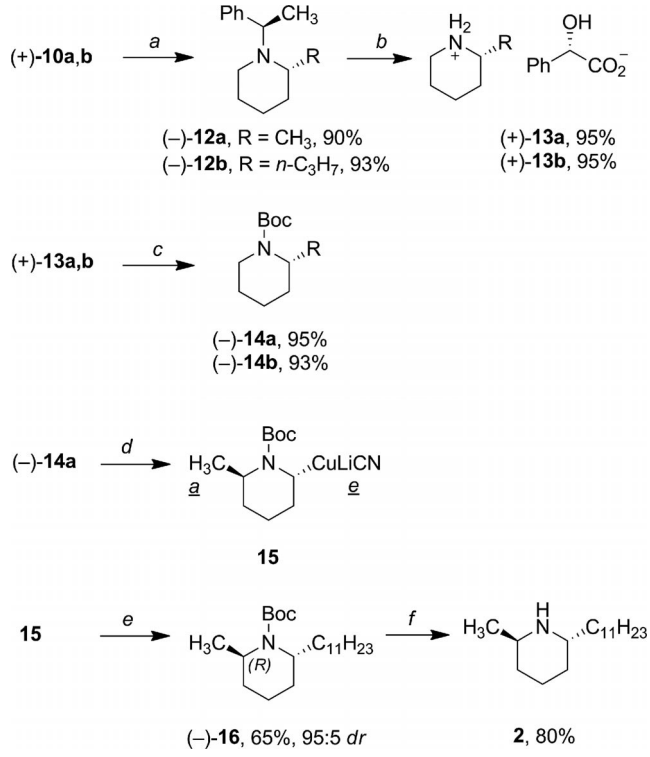


Scheme 4. Synthesis of 2-alkyl-tetrahydropyridines. Reagents and conditions: (a) LDA, THF, –80 °C to –20 °C and then CH_3I or *n*-C_3H_7I, –80 °C to room temp. (b) $NaBH_4$, THF/EtOH, 50:50, 0 °C.

At this point, the major diastereoisomers (+)-**10a** and (+)-**10b** could be obtained as sole products (72–75%) after a careful separation by chromatography. The proposed mechanism to account for the observed stereoselectivities involves the formation of planar iminium ion **9** in which incorporation of the hydride anion to the least hindered *si* face produces the (*R*,*R*) absolute configuration. Conversely, delivery of the hydride anion to the more sterically demanding *re* face produces the (*R*,*S*) absolute configuration. As expected and observed, the structural differences of the R alkyl groups do not modify the diastereoisomeric ratio.

Synthesis of *N*-Boc-(*R*)-Coniine and *N*-Boc-(*R*)-2-Methylpiperidine

In the next step, hydrogenation of the olefinic double bond of tetrahydropyridines (+)-**10a** and (+)-**10b** was carried out in methanol in the presence of Wilkinson's catalyst under hydrogen pressure at 5 bars (see Scheme 5). The selective saturation of the olefin did occur, and piperidines (–)-**12a** and (–)-**12b** were obtained as sole products in yields ranging from 90 to 93%.[22] The removal of the chiral appendage was best achieved by stirring either (–)-**12a** or (–)-**12b** in methanol in the presence of Pearlman's catalyst under hydrogen pressure at 5 bars. To avoid handling the toxic hemlock alkaloid,[23] (*R*)-(–)-coniine was obtained as its mandelate salt (+)-**13b** in 95% yield, and a similar treatment of the (*R*)-2-methylpiperidine afforded the mandelate salt (+)-**13a**.[24] For further chemical purposes [vide infra the synthesis of (–)-solenopsin A], these complexes were heated at reflux in acetonitrile in the presence of $(Boc)_2O$ and an excess amount of Hünig's base to afford *N*-*tert*-butoxycarbonyl (Boc) derivatives (–)-**14a** and (–)-**14b** in very high yields.



Scheme 5. Synthesis of *N*-Boc-(*R*)-coniine, *N*-Boc-(*R*)-2-methylpiperidine, and (–)-solenopsin A. Reagents and conditions: (a) Wilkinson's catalyst (5% by mass), MeOH, H_2 (5 bars), 72 h, room temp.; (b) 20% $Pd(OH)_2$/C, MeOH, 72 h, room temp. and then (*S*)-(+)-mandelic acid, Et_2O, room temp.; (c) $(Boc)_2O$, Hünig's base, CH_3CN, reflux, 4 h; (d) *s*BuLi, TMEDA, Et_2O, –80 °C, 2 h and then CuCN·2LiCl (THF), 1 h; (e) 1-iodoundecane, –80 °C to room temp.; (f) HCl, room temp., 3 h.

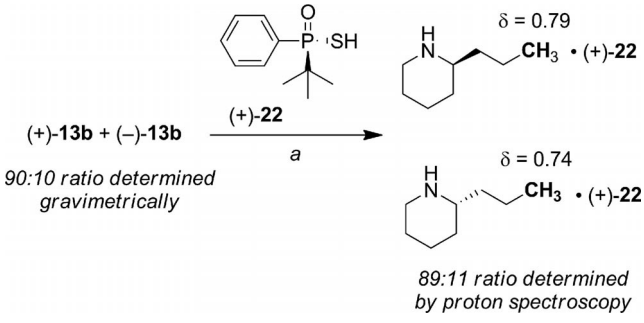
Synthesis of (–)-Solenopsin A

The synthesis of (–)-solenopsin A required the elaboration of a new stereogenic center at C-6, which displayed the *R* absolute configuration.[25,26] To place both alkyl substituents in a *trans* disposition, the lithiation procedure that was developed by Beak seemed to be the method of choice.[27] We also believed that the best synthetic approach was to incorporate the *n*-undecyl chain in a single operation.[28] Hence, the treatment of an ethereal solution of (–)-**14a** with *s*BuLi in the presence of *N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethylenediamine (TMEDA) at –80 °C led to the formation of the

corresponding stabilized carbanion (see Scheme 5). Unfortunately, the use of 1-iodoundecane as the electrophile led to the recovery of the starting material. Therefore, for the stereoselective introduction of the C-6 undecyl group to (–)-**14a**, we turned to the addition of an organocuprate reagent, as recently reported by Dieter.[29] Addition of a THF solution of CuCN·2LiCl to lithiated (–)-**14a** ensured the formation of cuprate **15**, to which the addition of 1-iodoundecane provided (–)-**16** in 65% yield with a 95:5 *dr* as shown by proton NMR spectroscopic analysis. The high diastereoselectivity of that transformation can be explained by the prior formation of a conformer in which the methyl group is axially oriented to release the $A^{1,3}$ strain between the methyl group and the *N*-Boc substituent.[30] Thus, as shown in Scheme 5, equatorial deprotonation and condensation of resulting cuprate **15** with the requisite electrophilic reagent took place with retention of configuration at C-6 to place both alkyl substituents in a *trans* geometry. Deprotection of the carbamate moiety of (–)-**16** was routinely carried out by treatment with gaseous hydrogen chloride in Et_2O to yield a crude reaction mixture, which was purified through a silica gel column with diethyl ether that was saturated with gaseous ammonia as the eluent. A trace amount of *cis* isomer (–)-isosolenopsin A eluted first followed by the more polar *trans* isomer (–)-solenopsin A, which was obtained as a colorless oil in 80% yield. The optical rotation of our synthetic solenopsin A was consistent with that reported in the literature {$[\alpha]_D^{22}$ = –1.2 (*c* = 1.0, $CHCl_3$); ref.[28d] $[\alpha]_D^{22}$ = –1.2 (*c* = 1.2, $CHCl_3$)}.

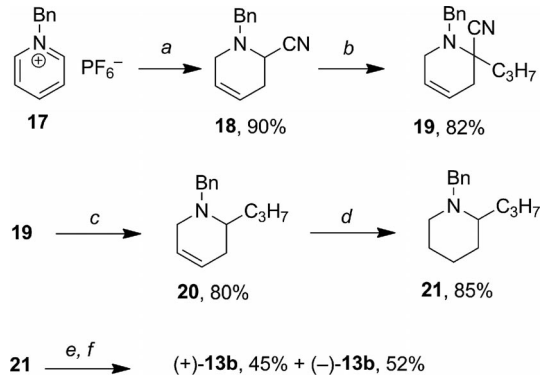
Determination of Enantiomeric Ratios of Coniine by Proton and Carbon NMR Spectroscopy

The enantiomeric composition of our sample of (*R*)-(–)-coniine was determined by proton and carbon NMR spectroscopy utilizing (*R*)-(+)-*tert*-butylphenylphosphanylthioic acid [(+)-**22**] as a chiral resolving agent (see Scheme 6).[31–34]



Scheme 6. Determination of enantiomeric ratio of (–)-coniine by proton spectroscopy. Reagents and conditions: (a) NaOH (5%)/Et_2O, 5 min and then (+)-**22** (ca. 1.1 equiv.).

With this purpose in mind, mandelate salt (–)-**13b** was obtained in 52% yield (based on isomer content) from the optical resolution of *rac*-coniine, which was synthesized from hexafluorophosphate salt **17** (see Scheme 7). In this process, single crystals were obtained by the slow crystallization of α-amino nitrile **18** from a mixture of diethyl ether and petroleum ether (see Figure 3).



Scheme 7. Synthesis and optical resolution of *rac*-coniine. Reagents and conditions: (a) Et_4BHLi, THF, –70 °C and then NaCN/HCN, pH = 9.5; (b) LDA, THF, –80 °C to –20 °C and then C_3H_7I, –80 °C to room temp.; (c) $NaBH_4$, MeOH, 0 °C; (d) Wilkinson's catalyst (5% by mass), MeOH, H_2 (5 bars), 72 h, room temp.; (e) 10% Pd/C, MeOH, 72 h, room temp.; (f) (*S*)-(+)-mandelic acid, then (*R*)-(–)-mandelic acid, Et_2O, room temp.

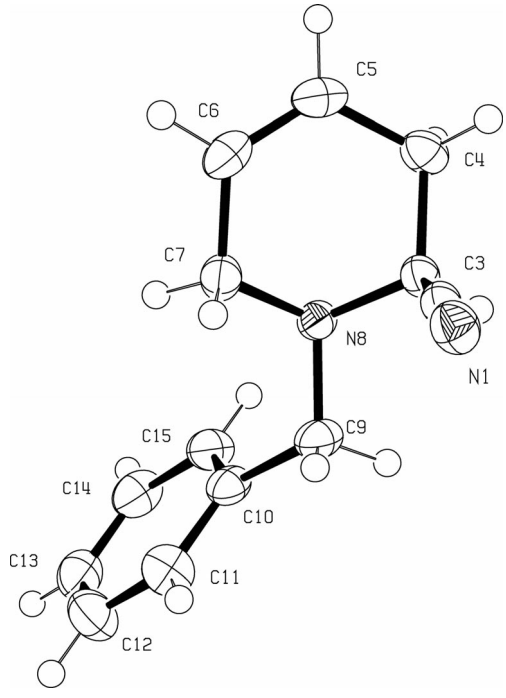


Figure 3. ORTEP drawing of α-amino nitrile **18**. Elipsoid plots were drawn with 60% probability.

Then, two standard solutions of enantioenriched (–)-coniine (90:10 *er* and 95:5 *er*) were prepared by means of an accurate gravimetric method by weighing mandelate salts (+)-**13b** and (–)-**13b**. Both enantiomers of coniine were displaced from their respective salts by treatment with base, and stoichiometric amounts of (+)-**22** were added to the

resulting mixtures. The samples were analyzed by proton NMR spectroscopy (see the detailed procedure in the Supporting Information), and the *er* values were determined by integration of the methyl resonance signals of the diastereoisomeric salts (–)-coniine·(+)-**22** and (+)-coniine·(+)-**22**, which displayed two triplet systems at δ = 0.79 and 0.74 ppm ($\Delta\delta$ = 0.05), respectively. When a similar process was carried out with an optically pure sample of mandelate (+)-**13b**, a single triplet was observed, which indicates that our synthetic sample of coniine had a >99:1 *er*.

Conclusions

The stereocontrolled syntheses of (–)-coniine (>99:1 *er*) and (–)-solenopsin A from a chiral pyridinium salt were developed. Because both enantiomers of α-phenylethylamine (PEA) are commercially available, the application of a modified Fry synthesis provided an efficient synthesis to 2-substituted enantioenriched piperidines with the requisite absolute configuration. In addition, the combination of this reaction sequence with the Beak's lithiation–transmetalation procedure afforded direct access to *trans*-2,6-disubstituted piperidines.

Experimental Section

General Methods: Purification by column chromatography was performed with 70–230 mesh silica gel using diethyl ether and petroleum ether (b.p. 60 to 80 °C). TLC analyses were carried out with alumina sheets precoated with silica gel 60 F254, and the R_f values are given. The NMR spectroscopic data were recorded with either a 500, 400, or 300 MHz spectrometer ("p" denotes "primary C"). Positive-ion mass spectra were recorded with an orthogonal acceleration quadrupole time-of-flight mass spectrometer that was equipped with a standard electrospray probe. Melting points were measured with a Kofler apparatus, and the values are reported in °C. Optical rotations were recorded at 20 °C with a 1 dm cell.

(*R*)-(+)-1-(1-Phenylethyl)pyridinium Hexafluorophosphate [(+)-3c]: (*R*)-(+)-1-phenylethylamine (5.43 g, 44.10 mmol, 1.1 equiv.) was added slowly to a suspension of 1-(2,4-dinitrophenyl)pyridinium chloride (**6**,[35] 11.50 g, 40.92 mmol) in *n*-butanol (40 mL), and the solution was heated at reflux for 24 h. The solvent was evaporated, and the resulting paste was combined with water (50 mL). The excess amount of 2,4-dinitroaniline hydrochloride was removed by filtration, and the aqueous phase was basified by the addition of concentrated aqueous ammonia (2 mL). The resulting solution was extracted with EtOAc (2 × 50 mL). The organic phases were discarded, and the pyridinium chloride solution was treated with KPF_6 (8.30 g, 45.10 mmol, 1.1 equiv.) for 12 h to afford pyridinium salt (+)-**3c** (10.0 g, 75%) as a slightly yellow powder; m.p. 86–88 °C (ethanol). $[\alpha]_D^{22}$ = +26 (*c* = 1.50, acetone); ref.[16] $[\alpha]_D^{22}$ = +9 (*c* = 1.0, methanol)]. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.06 (d, *J* = 7.0 Hz, 3 H), 6.23 (q, *J* = 7.0 Hz, 1 H), 7.41–7.50 (m, 3 H), 7.53–7.56 (dm, *J* = 4.5 Hz, 2 H), 8.17 (t, *J* = 6.9 Hz, 2 H), 8.61 (tt, *J* = 7.8, 1.3 Hz, 1 H), 9.22 (dd, *J* = 6.8, 1.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 19.7 (p), 69.6 (t), 127.2 (t), 128.5 (t), 129.16 (t), 129.36 (t), 137.8 (q), 143.4 (q), 146.1 (q) ppm. HRMS: calcd. for $C_{13}H_{14}N$ $[M]^+$ 184.11262; found 184.1132.

(1′*R*)-(–)-1-(1-Phenylethyl)-1,2,3,6-tetrahydropyridine [(–)-7]: Pale yellow oil; $[\alpha]_D^{22}$ = –7.0 (*c* = 1.10, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (d, *J* = 6.7 Hz, 3 H), 2.00–2.22 (m, 2 H), 2.38 (ddd, *J* = 12.0, 8.0, 5.0 Hz, 1 H), 2.59 (dt, *J* = 12.0, 6.0 Hz, 1 H), 2.86 (dm, *J* = 17.0 Hz, 1 H), 3.17 (dm, *J* = 17.0 Hz, 1 H), 3.42 (q, *J* = 6.7 Hz, 1 H), 5.60–5.70 (m, 1 H), 5.71–5.80 (m, 1 H), 7.19–7.35 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2 (p), 26.6 (s), 47.3 (s), 50.4 (s), 64.9 (t), 125.3 (t), 125.7 (t), 126.9 (t), 127.6 (t), 128.3 (t), 144.2 (q) ppm.

(1′*R*,2*S*)-(–)-1-(1-Phenylethyl)-1,2,3,6-tetrahydropyridine-2-carbonitrile [(–)-5-A]: ***Caution:*** Because of the possible emission of toxic HCN, the preparation of the HCN/NaCN buffer should be carried out under a well-ventilated hood. An oven-dried, one-necked Schlenk tube (200 mL), which was fitted with a magnetic stirring bar and connected to an argon inlet, was charged with pyridinium salt (+)-**3c** (5.30 g, 16.09 mmol) and THF (25 mL). The resulting suspension was cooled to –70 °C, and lithium triethylborohydride (1.0 M solution in THF, 17.70 mL, 17.7 mmol, 1.1 equiv.) was added dropwise through a syringe. The solution was warmed to 0 °C over a 2 h period. Then, an aqueous buffer solution of HCN/NaCN [35 mL, prepared from the addition of a 10% HCl solution (12 mL) to a solution of NaCN (4.73 g, 96.53 mmol, 6.0 equiv.) dissolved in water (35 mL)] was slowly added at that temperature over a period of 15 min. The stirring was continued overnight at that temperature. Then, water (25 mL) was added, and the resulting solution was covered by a layer of diethyl ether (100 mL). The organic layer was washed with water, dried with $MgSO_4$, and concentrated to afford a crude residue, which was transferred to a chromatographic column (30 × 3.5 cm, prepared with 20 g of silica, diethyl ether/petroleum ether, 20:80). The combined fractions were evaporated to yield α-amino nitriles (–)-**5-A** and (+)-**5-B** (2.90 g, 85%, 50:50 mixture of diastereoisomers) as a viscous, orange oil; R_f = 0.2 (diethyl ether/petroleum ether, 20:80). A mixture of α-amino nitriles (–)-**5-A** and (+)-**5-B** (0.3 g) was dissolved in a 50:50 mixture of diethyl ether and petroleum ether. The solution was kept at room temperature until the solvents completely evaporated. The residue was combined with petroleum ether (5 mL) to afford (–)-**5-A** (0.15 g) as colorless crystals, which were analyzed by X-ray diffraction; m.p. 76 °C. $[\alpha]_D^{22}$ = –2.5 (*c* = 1.06, $CHCl_3$). As a result of the slow epimerization of the (*S*) configuration at C-2, the optical rotation should be recorded in ethanol within 5 min. $[\alpha]_D^{22}$ = –2.5 (*c* = 1.0, ethanol); at 5 min, (*R*,*S*)/(*R*,*R*), 95:5 *dr*. $[\alpha]_D^{22}$ = +56 (*c* = 1.0, ethanol); at equilibrium, (*R*,*S*)/(*R*,*R*), 35:75 *dr*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (d, *J* = 6.6 Hz, 3 H), 2.37 (dm, *J* = 16.0 Hz, 1 H), 2.70 (dm, *J* = 16.0 Hz, 1 H), 2.85 (dm, *J* = 16.0 Hz, 1 H), 3.04 (dm, *J* = 6.6 Hz, 1 H), 3.53 (q, *J* = 6.6 Hz, 1 H), 4.29 (dd, *J* = 6.0, 1.4 Hz, 1 H), 5.61–5.71 (m, 2 H), 7.24–7.34 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5 (p), 30.0 (s), 45.7 (t), 48.0 (s), 63.1 (t), 116.8 (q), 120.7 (t), 125.9 (t), 127.3 (t), 127.4 (t), 128.6 (t), 143.6 (q) ppm. HRMS: calcd. for $C_{14}H_{16}N_2Na$ $[M + Na]^+$ 235.12112; found 235.1210; calcd. for $C_{13}H_{15}NNa$ $[M - HCN + Na]^+$ 208.11022; found 208.1110. $C_{14}H_{16}N_2$ (212.13): calcd. C 79.21, H 7.60, N 13.20; found C 79.26, H 7.59, N 13.34.

***(1′R,2R)*-(–)-1-(1-Phenylethyl)-1,2,3,6-tetrahydropyridine-2-carbonitrile (5-B):** Compound **5-B** was obtained as a mixture of diastereoisomers [(1′*R*,2*S*)/(1′*R*,2*R*), 50:50 *dr*]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 6.6 Hz, 3 H), 2.15 (dm, *J* = 16.5 Hz, 1 H), 2.46 (dm, *J* = 16.0 Hz, 1 H), 3.00–3.10 (m, 1 H), 3.53 (q, *J* = 6.6 Hz, 1 H), 3.63–3.70 (m, 2 H), 5.60–5.75 (m, 1 H), 5.80–5.85 (m, 1 H), 7.23–7.36 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (p), 29.6 (s), 46.4 (s), 47.7 (t), 63.5 (t), 116.81 (q), 121.4 (t), 125.7 (t), 127.1 (t), 127.8 (t), 128.7 (t), 128.8 (t), 129.0 (t), 143.64 (q) ppm.

(1′*R*,2*R*)-(–)-1-(1-Phenylethyl)-2-methyl-1,2,3,6-tetrahydropyridine [(+)-10a]: An oven-dried, one-necked Schlenk tube (200 mL), which

was fitted with a magnetic stirring bar and connected to an argon inlet, was flushed with argon. The flask was then cooled to –80 °C, and dry THF (20 mL) and diisopropylamine (4.78 mL, 3.39 g, 33.6 mmol) were added followed by the dropwise addition of butyllithium (2.5 M solution in hexane, 11.80 mL, 29.50 mmol). The stirring was continued for 30 min, and the solution was warmed to 0 °C over a 1 h period. The solution was then added dropwise to a Schlenk tube (200 mL) that was cooled to –80 °C and contained a 50:50 mixture of α-amino nitrile **5** (4.20 g, 19.78 mmol) dissolved in dry THF (5 mL). The solution was warmed to 0 °C over 2.0 h and then was cooled to –80 °C. Then, iodomethane (2.06 mL, 4.74 g, 33.39 mmol, 1.7 equiv.) was added dropwise, and the reaction mixture was warmed to –10 °C for 2 h. The Schlenk tube was then charged with ethanol (30 mL), and $NaBH_4$ (3.00 g, 79.30 mmol, 4.0 equiv.) was added in portions. The stirring was continued for 12 h at 0 °C. The solvents were evaporated under reduced pressure, and the crude material was dissolved in 15% ammonia solution (20 mL). The aqueous layer was extracted with dichloromethane (2 × 25 mL), and the organic phases were dried with $MgSO_4$ and concentrated. The crude oily residue (4.58 g) was transferred to a chromatographic column (50 × 2.5 cm, prepared with 30 g of silica, diethyl ether/petroleum ether, 10:90) to afford tetrahydropyridines (+)-**10a** and (+)-**11a** (3.73 g, 94% based on α-amino nitrile **5**, 85:15 mixture of diastereoisomers). A careful purification of the mixture on silica (diethyl ether/petroleum ether, 10:90) afforded tetrahydropyridine (+)-**10a** (2.96 g, 75%) as a colorless oil; R_f = 0.2 (diethyl ether/petroleum ether, 20:80). $[\alpha]_D^{22}$ = +19 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (d, J = 7.3 Hz, 3 H), 1.31 (d, J = 6.7 Hz, 3 H), 1.85 (dm, J = 17.3 Hz, 1 H), 2.47 (dm, J = 17.3 Hz, 1 H), 2.71 (dm, J = 16.5 Hz, 1 H), 2.88 (dm, J = 16.5 Hz, 1 H), 3.32–3.40 (m, 1 H), 3.64 (q, J = 6.7 Hz, 1 H), 5.48–5.54 (m, 1 H), 5.61–5.67 (m, 1 H), 7.20 (tt, J = 6.4, 1.4 Hz, 1 H), 7.28 (td, J = 6.4, 1.0 Hz, 2 H), 7.36 (d, J = 7.5, 1.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8 (p), 19.2 (p), 33.1 (s), 45.3 (s), 46.6 (t), 60.4 (t), 123.2 (t), 125.2 (t), 126.6 (t), 127.5 (t), 128.2 (t), 146.0 (q) ppm. HRMS: calcd. for $C_{14}H_{20}N$ [M + H]$^+$ 202.15902; found 202.1589. $C_{14}H_{19}N$ (201.30): calcd. C 83.53, H 9.51, N 6.96; found C 83.73, H 9.53, N 6.94.

(1′*R*,2*R*)-(–)-1-(1-Phenylethyl)-2-propyl-1,2,3,6-tetrahydropyridine [(+)-10b]: The synthesis was as reported for (+)-**10a**, but with the addition of 1-iodopropane (3.28 mL, 5.71 g, 33.59 mmol) as the electrophile. Workup and chromatographic purification of the crude oil over a silica column afforded tetrahydropyridines (+)-**10b** and (+)-**11b** (4.08 g, 90%, 90:10 mixture of diastereoisomers). Chromatographic purification of the mixture on a silica column (diethyl ether/petroleum ether, 10:90) afforded tetrahydropyridine (+)-**10b** (3.26 g, 72%) as a colorless oil; R_f = 0.2 (diethyl ether/petroleum ether, 20:80). $[\alpha]_D^{22}$ = +20 (c = 3.24, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.3 Hz, 3 H), 1.30 (d, J = 6.7 Hz, 3 H), 1.20–1.40 (m, 4 H), 1.45–1.55 (m, 1 H), 1.90 (dm, J = 18.0 Hz, 1 H), 2.37 (dm, J = 18.0 Hz, 1 H), 2.83 (dm, J = 17.5 Hz, 1 H), 2.93 (dm, J = 17.5 Hz, 1 H), 3.05–3.12 (m, 1 H), 3.67 (q, J = 6.7 Hz, 1 H), 5.50–5.55 (m, 1 H), 5.61–5.67 (m, 1 H), 7.18 (tt, J = 6.4, 1.4 Hz, 1 H), 7.26 (td, J = 6.4, 1.0 Hz, 2 H), 7.35 (d, J = 7.5, 1.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5 (p), 20.1 (s), 20.9 (p), 27.9 (s), 28.5 (s), 45.2 (s), 51.2 (t), 60.3 (t), 123.5 (t), 125.5 (t), 126.6 (t), 127.4 (t), 128.2 (t), 146.4 (q) ppm. HRMS: calcd. for $C_{16}H_{24}N$ [M + H]$^+$ 230.19087; found 230.1909. $C_{16}H_{23}N$ (229.36): calcd. C 83.79, H 10.11, N 6.11; found C 82.97, H 10.04, N 6.05.

(1′*R*,2*R*)-(–)-1-(1-Phenylethyl)-2-methylpiperidine [(–)-12a]: A low-pressure hydrogenator (50 mL) was charged with MeOH (30 mL), tetrahydropyridine (+)-**10a** (2.23 g, 11.07 mmol), and chlorotris(triphenylphosphane)rhodium(I) (0.10 g, 3% by mass). Hydrogen pressure (3.75 × 10^3 Torr, 5 bars) was applied, and the solution was stirred for 72 h at room temperature. The solution was concentrated under reduced pressure to afford a crude oily residue, which was transferred to a chromatographic column (20 × 2.0 cm, prepared with 10 g of silica, diethyl ether/petroleum ether, 50:50). The combined fractions were evaporated to afford piperidine (–)-**12a** (2.03 g, 90%) as a colorless viscous oil; R_f = 0.4 (diethyl ether/petroleum ether, 60:40). $[\alpha]_D^{22}$ = –40 (c = 1.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (d, J = 6.3 Hz, 3 H), 1.24 (d, J = 6.7 Hz, 3 H), 1.26–1.45 (m, 4 H), 1.55–1.64 (m, 1 H), 1.65–1.73 (m, 1 H), 2.12 (ddd, J = 11.9, 8.8, 3.1 Hz, 1 H), 2.30–2.80 (m, 1 H), 2.78–2.85 (m, 1 H), 4.05 (q, J = 6.7 Hz, 1 H), 7.19 (tt, J = 6.4, 1.4 Hz, 1 H), 7.28 (t, J = 6.4 Hz, 2 H), 7.41 (d, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.5 (p), 17.0 (p), 23.4 (s), 26.4 (s), 34.7 (s), 44.9 (s), 52.0 (t), 56.6 (t), 126.2 (t), 127.6 (t), 127.9 (t), 145.8 (q) ppm. HRMS: calcd. for $C_{14}H_{22}N$ [M + H]$^+$ 204.17522; found 204.1747. $C_{14}H_{21}N$ (203.32): calcd. C 82.70, H 10.41, N 6.89; found C 82.65, H 10.35, N 6.85.

(1′*R*,2*R*)-(–)-1-(1-Phenylethyl)-2-propylpiperidine [(–)-12b]: The synthesis was as reported for (–)-**12a**, but with (+)-**10b** (2.20 g) to afford piperidine (–)-**12b** (2.06 g, 93%) as a colorless viscous oil; R_f = 0.4 (diethyl ether/petroleum ether, 60:40). $[\alpha]_D^{22}$ = –10 (c = 2.72, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (t, J = 7.3 Hz, 3 H), 1.25 (d, J = 6.7 Hz, 3 H), 1.26–1.70 (m, 10 H), 2.19–2.24 (m, 1 H), 2.34–2.39 (m, 1 H), 2.72 (dq, J = 10.1, 4.0 Hz, 1 H), 4.00 (q, J = 6.7 Hz, 1 H), 7.19 (tt, J = 6.4, 1.4 Hz, 1 H), 7.28 (t, J = 6.4 Hz, 2 H), 7.41 (d, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.6 (p), 14.7 (p), 18.9 (s), 22.7 (s), 25.8 (s), 29.6 (s), 30.1 (s), 45.0 (s), 55.7 (t), 56.8 (t), 126.2 (t), 127.5 (t), 128.0 (t), 146.4 (q) ppm. HRMS: calcd. for $C_{16}H_{26}N$ [M + H]$^+$ 232.20653; found 232.2065. $C_{16}H_{25}N$ (231.37): calcd. C 83.06, H 10.89, N 6.05; found C 82.26, H 10.65, N 6.08.

***tert*-Butyl (2*R*)-(–)-Methylpiperidine-1-carboxylate [(–)-14a]:** A low-pressure hydrogenator (50 mL) was charged with methanol (30 mL), piperidine (–)-**12a** (1.50 g, 7.38 mmol), and 20% Pd(OH)$_2$/C (0.30 g, 20% by mass). Hydrogen pressure (3.75 × 10^3 Torr, 5 bars) was applied, and the homogeneous solution was stirred for 72 h at room temperature. The suspension was filtered through a short pad of Celite, and (*S*)-(+)-mandelic acid (1.15 g, 7.55 mmol) was added to the methanolic solution, which was then concentrated. The solid residue was combined with diethyl ether (20 mL) to afford (2*R*)-(–)-methylpiperidine·(*S*)-(+)-mandelic acid salt [(+)-**13a**, 1.76 g, 95% from (–)-**12a**, >98:2 *dr*] as a white solid, m.p. 119 °C; ref.[36] m.p. 118 °C. $[\alpha]_D^{22}$ = +78 (c = 1.0, $CHCl_3$); ref.[36] $[\alpha]_D^{22}$ = +60 (c = 2.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09 (d, J = 7.2 Hz, 3 H), 1.10–1.30 (m, 2 H), 1.50–1.59 (m, 3 H), 1.64–1.70 (m, 1 H), 2.18–2.26 (m, 1 H), 2.63–2.70 (m, 1 H), 2.97 (dm, J = 13.0 Hz, 1 H), 3.50–4.50 (br. s, 1 H), 4.84 (s, 1 H), 7.20 (t, J = 7.1 Hz, 1 H), 7.27 (t, J = 7.1 Hz, 2 H), 7.45 (d, J = 7.1 Hz, 2 H), 9.50–10.00 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1 (p), 21.8 (s), 22.5 (s), 30.2 (s), 43.8 (s), 52.2 (t), 74.5 (t), 126.6 (t), 127.0 (t), 128.0 (t), 142.6 (q), 178.2 (q) ppm. HRMS: calcd for $C_6H_{14}N$ [M]$^+$ 100.11262; found 100.1125. $C_{14}H_{21}NO_3$ (251.32): calcd. C 66.91, H 8.42, N 5.57; found C 66.80, H 8.40, N 5.60. Mandelate salt (+)-**13a** (0.50 g, 1.99 mmol) was dissolved in dry acetonitrile (20 mL), and to the resulting solution were successively added *N*,*N*-diisopropylethylamine (1.25 mL, 0.95 g, 7.35 mmol) and di-*tert*-butyldicarbonate (0.43 g, 1.97 mmol). The reaction mixture was heated at reflux for 4 h, and the solvent was evaporated. The residue was dissolved in water (20 mL), and the organic phase was extracted with diethyl ether (50 mL). The organic phase was dried with $MgSO_4$ and concentrated, and the resi-

due was transferred to a chromatographic column (20 × 2.0 cm, prepared with 10 g of silica, diethyl ether/petroleum ether, 60:40). The combined fractions were evaporated to yield (–)-**14a** (0.37 g, 93%) as a colorless oil; R_f = 0.6 (diethyl ether/petroleum ether, 60:40). $[\alpha]_D^{22}$ = –47 (*c* = 1.2, $CHCl_3$); ref.[36] $[\alpha]_D^{22}$ = –51 (*c* = 0.83, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.11 (d, *J* = 6.9 Hz, 3 H), 1.30–1.50 (m, 2 H), 1.45 (s, 9 H), 1.50–1.65 (m, 4 H), 2.80 (td, *J* = 13.0, 2.7 Hz, 1 H) 3.90 (dm, *J* = 13.0 Hz, 1 H), 4.32–4.41 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.7 (p), 18.7 (s), 25.7 (s), 28.5 (p), 30.1 (s), 38.7 (t), 46.1 (t), 79.0 (q), 155.0 (q) ppm. HRMS: calcd. for $C_{11}H_{21}NO_2Na$ $[M + Na]^+$ 222.1470; found 222.1469. $C_{11}H_{21}NO_2$ (199.28): calcd. C 66.29, H 10.62, N 7.03; found C 66.20, H 10.20, N 7.00.

***tert*-Butyl (2*R*)-(–)-Propyl-piperidine-1-carboxylate [(–)-14b]:** The synthesis was as reported for (–)-**14a**, but with (–)-**12b** (1.80 g, 7.78 mmol) to afford (*R*)-(–)-coniine·(*S*)-(+)-mandelic acid salt [(+)-**13b**, 2.06 g, 95% from (–)-**12b**, >98:2 *dr*] as a white solid, m.p. 125 °C; ref.[23] m.p. 117 °C. $[\alpha]_D^{22}$ = +45 (*c* = 0.97, EtOH); ref.[23] $[\alpha]_D^{22}$ = +49 (*c* = 0.6, MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.0 Hz, 3 H), 1.03–1.15 (m, 1 H), 1.16–1.32 (m, 4 H), 1.40–1.76 (m, 5 H), 2.20 (td, *J* = 12.5, 5.4 Hz, 1 H), 2.50–2.60 (m, 1 H), 2.97 (d, *J* = 12.5 Hz, 1 H), 3.60–4.50 (br. s, 1 H), 4.84 (s, 1 H), 7.20 (t, *J* = 7.1 Hz, 1 H), 7.26 (t, *J* = 7.1 Hz, 2 H), 7.44 (d, *J* = 7.1 Hz, 2 H), 8.00–10.00 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8 (p), 18.3 (s), 22.1 (s), 22.5 (s), 27.9 (s), 35.4 (t), 44.1 (s), 56.2 (t), 74.5 (t), 126.7 (t), 127.0 (t), 128.0 (t), 142.7 (q), 178.1 (q) ppm. HRMS: calcd. for $C_8H_{18}N$ $[M]^+$ 128.14392; found 128.14392. $C_{16}H_{25}NO_3$ (279.37): calcd. C 68.79, H 9.02, N 5.01; found C 68.38, H 8.96, N 5.01. The synthesis of (*R*)-(–)-*N*-Boc-coniine [(–)-**14b**, 93%] was as reported for (–)-**14a**, but with mandelate salt (+)-**13b** (0.50 g). Colorless oil; R_f = 0.6 (diethyl ether/petroleum ether, 60:40). $[\alpha]_D^{22}$ = –32.5 (*c* = 1.34, $CHCl_3$); ref.[37] $[\alpha]_D^{22}$ = –28.4 (*c* = 1.36, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.2 Hz, 3 H), 1.20–1.41 (m, 4 H), 1.45 (s, 9 H), 1.50–1.70 (m, 6 H), 2.77 (t, *J* = 14.0 Hz, 1 H) 3.96 (d, *J* = 12.0 Hz, 1 H), 4.20 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (p), 19.1 (s), 19.5 (s), 25.7 (s), 28.5 (p), 31.9 (s), 38.7 (br. s), 50.1 (br. t), 78.9 (q), 155.2 (q) ppm. HRMS: calcd. for $C_{13}H_{25}NO_2Na$ $[M + Na]^+$ 250.17830; found 250.1782. $C_{13}H_{25}NO_2$ (227.34): calcd. C 68.68, H 11.08, N 6.16; found C 68.34, H 10.48, N 5.97.

***tert*-Butyl (2*R*,6*R*)-(–)-2-Methyl-6-undecyl-piperidine-1-carboxylate [(–)-16]:** An oven-dried, one-necked Schlenk tube (200 mL), which was fitted with a magnetic stirring bar and connected to an argon inlet, was flushed with argon. The flask was then cooled to –80 °C, and a solution of compound (–)-**14a** (1.00 g, 5.02 mmol) in dry Et_2O (40 mL) was added. To this solution was added TMEDA (1.26 mL, 0.97 g, 8.35 mmol). A solution of *s*BuLi (1.4 M in cyclohexane, 5.60 mL, 7.84 mmol, 1.56 equiv.) was then added dropwise. The resulting solution was stirred between –80 and –65 °C for 3 h and was then cooled to –80 °C. A solution of the complex CuCN·2LiCl [prepared from CuCN (0.70 g, 7.81 mmol) and LiCl (0.66 g, 15.57 mmol)] in THF (20 mL) was added dropwise, and the reaction mixture was stirred between –80 °C and –60 °C for 2 h. The solution was then cooled to –80 °C, and 1-iodoundecane (2.19 g, 1.80 mL, 7.76 mmol, 1.5 equiv.) was added. The reaction mixture was warmed to room temperature over a 12 h period and then poured into water (50 mL). The organic phase was dried with $MgSO_4$ and concentrated, and the resulting residue was transferred to a chromatographic column (20 × 2.0 cm, prepared with 10 g of silica, diethyl ether/petroleum ether, 10:90). The combined fractions were evaporated to yield (–)-**16** (1.12 g, 65%) as a colorless oil; R_f = 0.42 (diethyl ether/petroleum ether, 10:90). $[\alpha]_D^{22}$ = –29 (*c* = 1.20, $CHCl_3$); ref.[38] $[\alpha]_D^{22}$ = –26.3 (*c* = 1.58, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.2 Hz, 3 H), 1.23 (d, *J* = 6.7 Hz, 3 H), 1.20–1.33 (m, 19 H), 1.46 (s, 9 H), 1.40–1.56 (m, 2 H), 1.57–1.70 (m, 3 H), 1.71–1.90 (m, 2 H), 3.75–3.82 (m, 1 H), 3.87–3.95 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (s), 14.1 (p), 20.9 (p), 22.7 (s), 23.3 (s), 27.0 (s), 27.2 (s), 28.6 (p), 29.4 (s), 29.63 (s), 29.66 (s), 29.69 (s), 29.70 (s), 29.73 (s), 31.9 (s), 34.4 (s), 47.0 (t), 51.73 (t), 78.7 (q), 155.3 (q) ppm. HRMS: calcd. for $C_{22}H_{43}NO_2Na$ $[M + Na]^+$ 376.31915; found 376.3193. $C_{22}H_{43}NO_2$ (353.58): calcd. C 74.73, H 12.26, N 3.96; found C 75.00, H 12.10, N 3.80.

(2*R*,6*R*)-(–)-2-Methyl-6-undecyl-piperidine [(–)-Solenopsin A, (–)-2]: An oven-dried, one-necked Schlenk tube (50 mL) was successively charged with compound (–)-**16** (0.5 g, 1.41 mmol) and dry Et_2O (10 mL). Then, dry Et_2O (10 mL) that was saturated with gaseous HCl was added, and the resulting solution was stirred for 12 h. The solvents were removed, and the resulting white powder was stirred in NaOH (1 M solution) to yield a crude oil, which was purified by a silica gel column (Et_2O saturated with gaseous ammonia) to afford (–)-solenopsin A (0.28 g, 80%) as a colorless oil; R_f = 0.80 (diethyl ether saturated with gaseous ammonia). $[\alpha]_D^{22}$ = –1.2 (*c* = 1.0, $CHCl_3$); ref.[39] $[\alpha]_D^{22}$ = –1.3 (*c* = 0.94, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.7 Hz, 3 H), 1.07 (d, *J* = 6.5 Hz, 3 H); 1.20–1.65 (m, 26 H), 2.83–2.91 (m, 1 H), 3.00–3.10 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (p), 19.6 (s), 21.3 (p), 22.7 (s), 26.5 (s), 29.4 (s), 29.66 (s), 29.69 (s), 29.8 (s), 30.8 (s), 31.9 (s), 33.0 (s), 34.1 (s), 45.9 (t), 50.9 (t) ppm.

(*R*)-(–)-Coniine·(+)-22: Mandelate salt (+)-**13b** (45 mg, 160 μmol, >99:1 *dr*) and its optical antipode (–)-**13b** (5.0 mg, 18 μmol, >99:1 *dr*) were mixed (5 min) in 5% NaOH (1 mL). The aqueous phase was extracted with diethyl ether (5 mL), and the organic phase was washed with water until the pH was neutral and then dried with $MgSO_4$. Then, (*R*)-(+)-*tert*-butylphenylphosphanylthioic acid (+)-**22** (0.04 g, 186 μmol, γ = 1.15, >99:1 *er*) was added to the ethereal phase, and the solvent was evaporated to afford (*R*)-(–)-coniine·(+)-**22**, (0.063 g, 99%, 90:10 *dr*). This salt was diluted with $CDCl_3$ (0.5 mL) in a 5 mm NMR tube. ^1H NMR [400 MHz, $CDCl_3$, splitting signals are indicated by an asterisk (*)]: δ = 0.75 (t, *J* = 7.4 Hz, 0.38 H), 0.79 (t, *J* = 7.4 Hz, 3 H)*, 1.11 (d, $^3J_{H,P}$ = 16.0 Hz, 9 H), 1.20–1.50 (m, 5 H), 1.61–1.85 (m, 5 H), 2.70 (td, *J* = 12.6, 3.2 Hz, 1 H), 2.81 (td, *J* = 12.6, 3.2 Hz, 0.1 H)*, 2.84–2.93 (m, 1 H), 3.30 (dm, *J* = 12.6 Hz, 1 H), 7.33–7.40 (m, 3 H), 7.90–7.98 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = [13.67 (p), 13.68 (p)]*, [18.48 (s), 18.56 (s)]*, 22.4 (s), 22.5 (s), 25.2 (p), 28.2 (s), [35.41 (s), 35.49 (s)]*, 36.3 [q, (d, $^1J_{C,P}$ = 73.5 Hz)], [44.51 (s), 44.55 (s)]*, [56.55 (s), 56.59 (s)]*, 126.9 [(t), d, $J_{C,P}$ = 11.0 Hz], 129.4 [(t), d, $J_{C,P}$ = 2.5 Hz], 132.7 [(t), d, $J_{P,H}$ = 8.8 Hz], 139.2 [q, d, $^1J_{P,H}$ = 88.0 Hz] ppm.

1-Benzyl-pyridinium Hexafluorophosphate (17)

Alkylation: In a Schlenk tube (200 mL), which was fitted with a magnetic stirring bar and connected to an argon inlet and a bubbler, was placed dry pyridine (8.70 g, 110 mmol). The flask was flushed with argon, and degassed acetone (20 mL) was added. The solution was cooled to 0 °C, and benzyl bromide (11.89 mL, 17.10 g, 100 mmol) was added by a syringe. The solution was stirred at that temperature for 4 h, and the stirring was continued at room temperature overnight. The solvent was removed by cannulation, and the solvents were evaporated in vacuo under argon to afford 1-benzyl-pyridinium bromide (22.50 g, 90%) as a highly hygroscopic white powder, which could be stored for one month under argon without any loss of quality.

Anion Exchange: 1-Benzyl-pyridinium bromide (2.50 g, 10.00 mmol) was dissolved in water (15 mL), and to this clear solu-

tion was added KPF_6 (2.00 g, 10.86 mmol). The hexafluorophosphate pyridinium salt precipitated immediately as a white solid, and the resulting suspension was stirred at room temperature for 24 h. The content of the flask was poured into a sintered-glass funnel, and the solvents were removed by filtration to yield a white powder, which was rinsed with cold ethanol (2 × 20 mL) to afford pyridinium salt **17** (3.0 g, 95%) as a white powder; m.p. 150–152 °C (ethanol). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 5.86 (s, 2 H), 7.40–7.50 (m, 3 H), 7.52–7.56 (m, 2 H), 8.18 (t, J = 7.4 Hz, 2 H), 8.62 (t, J = 7.0 Hz, 1 H), 9.19 (d, J = 5.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 63.3 (s), 128.4 (t), 128.7 (t), 129.1 (t), 129.3 (t), 134.1 (q), 144.7 (t), 145.9 (t) ppm. HRMS: calcd for $C_{12}H_{12}N$ [M]$^+$ 170.09697; found 170.0970; calcd. for $C_{24}H_{24}N_2F_6P$ [2M + PF_6]$^+$ 485.158313; found 485.1578.

1-Benzyl-1,2,3,6-tetrahydro-pyridine-2-carbonitrile (18)

Synthesis: ***Caution:*** Because of the possible emission of toxic HCN, the preparation of the HCN/NaCN buffer should be carried out under a well-ventilated hood. An oven-dried, one-necked Schlenk tube (200 mL), which was fitted with a magnetic stirring bar and connected to an argon inlet, was charged with pyridinium salt **17** (2.0 g, 6.34 mmol) and dry THF (20 mL). The resulting suspension was cooled to –70 °C, and lithium triethylborohydride (1.0 M solution in THF, 7.0 mL, 7.0 mmol, 1.1 equiv.) was added dropwise by a syringe. The solution rapidly turned yellow, and the clear homogeneous reaction mixture was warmed to 0 °C over a 1 h period. Then, an aqueous HCN/NaCN buffer solution [20 mL, prepared from the addition of 10% HCl solution (4 mL) to a solution of NaCN (1.90 g, 38.80 mmol, 6.0 equiv.) dissolved in water (16 mL)] was added at that temperature over a period of 15 min. The stirring was continued overnight at 0 °C, and water (25 mL) was added to the reaction solution. The mixture was covered by a layer of diethyl ether (75 mL), and the biphasic system was vigorously stirred for 5 min. The aqueous layer was discarded, and the cyanide anions were oxidized with an excess amount of $KMnO_4$. The organic layer was washed with water until the aqueous phase remained neutral to litmus paper, and it was then dried with $MgSO_4$ and concentrated to afford a slightly yellowish solid (1.17 g). This crude material was dissolved in dichloromethane, and the resulting solution was transferred to a chromatographic column (30 × 3.5 cm, prepared with 20 g of silica, diethyl ether/petroleum ether, 20:80). The combined fractions were evaporated to yield α-amino nitrile **18** (1.14 g, 91%) as a viscous oil that solidified upon cooling. A slow crystallization in ethanol yielded single crystals, which were analyzed by X-ray diffraction.

Recrystallization. α-Amino nitrile **18** (21.5 g) was dissolved in boiling ethanol (25 mL). After the solid had precipitated, the mixture was kept at –20 °C for 24 h. The precipitate was filtered through a sintered-glass funnel to give a light yellow powder (20.0 g, 93%); m.p. 74–76 °C (ethanol); R_f = 0.2 (diethyl ether/petroleum ether, 20:80). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.26 (dm, J = 16.5 Hz, 1 H), 2.53–2.62 (m, 1 H), 3.07 (dm, J = 17.0 Hz, 1 H), 3.20 (dm, J = 17.0 Hz, 1 H), 3.55 (d, J_{AB} = 13.1 Hz, 1 H), 3.78 (d, J_{AB} = 13.1 Hz, 1 H), 3.80 (dd, J = 6.2, 1.6 Hz, 1 H), 5.67–5.79 (m, 2 H), 7.26–7.37 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.4 (s), 48.2 (t), 49.1 (s), 60.1 (s), 116.5 (q), 121.3 (t), 125.5 (t), 127.8 (t), 128.5 (t), 129.0 (t), 136.5 (q) ppm. ^{1}H NMR (400 MHz, C_6D_6): δ = 1.64 (dm, J = 16.5 Hz, 1 H), 2.01 (dm, J = 16.5 Hz, 1 H), 2.80–2.93 (m, 2 H), 3.26 (dd, J = 6.2, 1.6 Hz, 1 H), 3.31 (d, J_{AB} = 13.2 Hz, 1 H), 3.43 (d, J_{AB} = 13.2 Hz, 1 H), 5.27–5.32 (m, 1 H), 5.35–5.40 (m, 1 H), 7.06–7.20 (m, 5 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 29.5 (s), 48.4 (t), 49.0 (s), 60.2 (s), 116.2 (q), 121.4 (t), 125.7 (t), 127.9 (t), 128.3 (t), 128.8 (t), 137.3 (q) ppm. HRMS: calcd. for $C_{13}H_{14}N_2Na$ [M + Na]$^+$ 221.10547; found 221.1055; calcd. for $C_{12}H_{13}NNa$ [M – HCN + Na]$^+$ 194.09457; found 194.0957. $C_{13}H_{14}N_2$ (198.26): calcd. C 78.75, H 7.12, N 14.13; found C 78.86, H 7.12, N 14.00.

1-Benzyl-2-propyl-1,2,3,6-tetrahydropyridine-2-carbonitrile (19): An oven-dried, one-necked Schlenk tube (200 mL), which was fitted with a magnetic stirring bar and connected to an argon inlet, was flushed with argon. The flask was then cooled to –80 °C, and dry THF (5 mL) and diisopropylamine (1.45 mL, 1.03 g, 10.18 mmol) were added followed by the dropwise addition of *n*-butyllithium (2.5 M solution in hexane, 3.60 mL, 9.0 mmol, 1.5 equiv.). The 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 to a Schlenk tube (200 mL) that was cooled to –80 °C and contained a suspension of α-amino nitrile **18** (1.20 g, 6.05 mmol) in dry THF (5 mL). The solution rapidly turned deep red in color to yield a homogeneous anion mixture, which was warmed to 0 °C over 2.0 h and then cooled to –80 °C. 1-Iodopropane (0.90 mL, 1.56 g, 9.22 mmol, 1.5 equiv.) was added dropwise, and the reaction mixture was warmed to –10 °C for 2 h and was then quenched by the addition of ethanol (2 mL). Workup was carried out under argon. A degassed mixture of diethyl ether (100 mL) and water (15 mL) that contained NaCN (0.15 g) was added to the reaction mixture. The ethereal layer was separated, dried with $MgSO_4$, and concentrated at a temperature ranging between 5 and 10 °C to yield a crude oil (1.30 g), which was dissolved in dichloromethane. The solution was transferred to a chromatographic column (30 × 3.5 cm, prepared with 20 g of silica, diethyl ether/petroleum ether, 25:75). The combined fractions were evaporated to yield α-amino nitrile **19** (1.28 g, 88%) as slightly yellow viscous oil; R_f = 0.5 (diethyl ether/petroleum ether, 20:80). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.99 (t, J = 7.3 Hz, 3 H), 1.53–1.65 (m, 2 H), 1.80–1.88 (m, 1 H), 1.93–2.01 (m, 1 H), 2.37 (dm, J_{AB} = 17.0 Hz, 1 H), 2.49 (dm, J_{AB} = 17.0 Hz, 1 H), 2.84 (dm, J_{AB} = 17.8 Hz, 1 H), 3.14 (dm, J_{AB} = 17.8 Hz, 1 H), 3.18 (d, J_{AB} = 13.0 Hz, 1 H), 4.20 (dm, J_{AB} = 13.0 Hz, 1 H), 5.60–5.68 (m, 2 H), 7.22–7.34 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.2 (p), 16.6 (s), 35.0 (s), 39.5 (s), 49.4 (s), 55.1 (s), 58.6 (q), 119.1 (q), 121.2 (t), 125.1 (t), 127.3 (t), 128.5 (t), 128.6 (t), 138.0 (q) ppm. HRMS: calcd. for $C_{16}H_{20}N_2Na$ [M + Na]$^+$ 263.15242; found 263.1522. $C_{16}H_{20}N_2$ (240.34): calcd. C 79.96, H 8.39, N 11.66; found C 80.58, H 8.44, N 11.57.

1-Benzyl-2-propyl-1,2,3,6-tetrahydropyridine (20): A one-necked flask (50 mL), which was equipped with a rubber septum, was charged with ethanol (10 mL) and α-amino nitrile **19** (2.60 g, 10.80 mmol). The solution was cooled to 0 °C, and $NaBH_4$ (1.75 g, 46.26 mmol, 4.3 equiv.) was added in portions. The stirring was continued for 48 h at that temperature, and the solvent was evaporated under reduced pressure. The crude material was dissolved in a 15% ammonia solution (20 mL), and the aqueous layer was extracted with dichloromethane (2 × 25 mL). The combined organic layers were washed with water (25 mL), dried with anhydrous sodium sulfate, and concentrated on a rotary evaporator. The crude oily residue (2.26 g) was diluted with dichloromethane (2 mL), and the resulting solution was transferred to a chromatographic column (50 × 2.5 cm, prepared with 30 g of silica, diethyl ether/petroleum ether, 50:50). The combined fractions were evaporated to afford tetrahydropyridine **20** (1.86 g, 80%) as a colorless oil; R_f = 0.5 (diethyl ether/petroleum ether, 50:50). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.90 (t, J = 7.1 Hz, 3 H), 1.30–1.42 (m, 3 H), 1.57–1.64 (m, 1 H), 1.91 (dm, J_{AB} = 14.7 Hz, 1 H), 2.23 (dm, J_{AB} = 14.7 Hz, 1 H), 2.77–2.82 (m, 1 H), 2.98 (dm, J_{AB} = 17.5 Hz, 1 H), 3.06 (dm, J_{AB} = 17.5 Hz, 1 H), 3.60 (d, J_{AB} = 13.3 Hz, 1 H), 3.68 (d, J_{AB} =

13.3 Hz, 1 H), 5.56–5.60 (m, 1 H), 5.70–5.74 (m, 1 H), 7.21 (t, J = 7.0 Hz, 1 H), 7.28 (t, J = 7.0 Hz, 2 H), 7.34 (d, J = 7.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.4 (p), 19.8 (s), 28.0 (s), 31.4 (s), 48.3 (s), 55.6 (t), 56.2 (s), 124.5 (t), 125.1 (t), 126.7 (t), 128.2 (t), 128.8 (t), 139.9 (q) ppm. HRMS: calcd. for $C_{15}H_{22}N$ [M + H]$^+$ 216.17522; found 216.1753; calcd. for $C_{15}H_{21}NNa$ [M + Na]$^+$ 238.15717; found 238.1581. $C_{15}H_{21}N$ (215.33): calcd. C 83.67, H 9.83, N 6.50; found C 83.27, H 9.71, N 6.51.

1-Benzyl-2-propyl-piperidine (21): A low-pressure hydrogenator (50 mL) was charged with THF (25 mL), tetrahydropyridine **20** (1.10 g, 5.10 mmol), and chlorotris(triphenylphosphane)rhodium(I) (Wilkinson's catalyst, 0.05 g, 5% by mass). Air was removed from the reactor by alternately filling it with hydrogen and venting it (3×). Hydrogen pressure (3.75×10^3 Torr, 5 bars) was applied, and the homogeneous solution was stirred for 72 h at room temperature. The solution was concentrated under reduced pressure to afford a crude oily residue, which was diluted with dichloromethane (2 mL). The resulting solution was transferred to a chromatographic column (20 × 2.0 cm, prepared with 10 g of silica, diethyl ether/petroleum ether, 50:50). The combined fractions were evaporated to afford piperidine **21** (0.90 g, 81%) as a colorless viscous oil; R_f = 0.5 (diethyl ether/petroleum ether, 50:50). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.90 (t, J = 7.3 Hz, 3 H), 1.25–1.70 (m, 10 H), 1.98–2.05 (m, 1 H), 2.23–2.30 (m, 1 H), 2.72 (dt, J = 11.7, 4.2 Hz, 1 H), 3.21 (d, J_{AB} = 13.5 Hz, 1 H), 3.96 (d, J_{AB} = 13.5 Hz, 1 H), 7.18–7.23 (m, 1 H), 7.25–7.34 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.6 (p), 18.8 (s), 23.7 (s), 25.2 (s), 30.3 (s), 34.1 (t), 51.7 (s), 57.6 (s), 60.7 (t), 126.5 (t), 128.1 (t), 128.9 (t), 140.1 (q) ppm. HRMS: calcd. for $C_{15}H_{24}N$ [M + H]$^+$ 218.19087; found 218.1909. $C_{15}H_{23}N$ (217.35): calcd. C 82.89, H 10.67, N 6.44; found C 82.10, H 10.50, N 6.40.

Optical Resolution of *rac*-Coniine to (*R*)-(–)-Coniine·(*S*)-(+)-Mandelic Acid [(+)-13b]: A low-pressure hydrogenator (50 mL) was charged with methanol (20 mL), piperidine **21** (1.0 g, 4.60 mmol), and 20% $Pd(OH)_2$ (Pearlman's catalyst, 0.1 g, 10% by mass). Air was removed from the reactor by alternately filling it with hydrogen and venting it (3×). Hydrogen pressure (3.75×10^3 Torr, 5 bars) was applied, and the homogeneous solution was stirred for 72 h at room temperature. The suspension was filtered through a short pad of Celite, and the vessel was washed with methanol. Then, (*S*)-(+)-mandelic acid (0.70 g, 4.60 mmol) was added to the methanolic solution, and the resulting solution was concentrated on a rotary evaporator to afford *rac*-coniine·(*S*)-(+)-mandelic acid (1.30 g) as a white solid. This solid was dissolved in diethyl ether (30 mL), and the solution was stirred at room temperature for 12 h. The precipitate was filtered, and the mother liquor was saved for the recovery of the (*S*)-(+)-coniine (vide infra). The white solid was washed with diethyl ether (10 mL) to give the (*R*)-(–)-coniine·(*S*)-(+)-mandelic acid salt (0.62 g, mixture of diastereoisomers, 75:25 *dr*); m.p. 115 °C. $[\alpha]_D^{22}$ = +46 (c = 0.94, EtOH); (*R*,*S*)/(*S*,*S*), 75:25 *dr*. This process was repeated (2×) using diethyl ether (2 × 20 mL) to give the (*R*)-(–)-coniine·(*S*)-(+)-mandelic acid salt (0.39 g, 60% based on isomer content, mixture of diastereoisomers, 92:8 *dr*); m.p. 122 °C. $[\alpha]_D^{22}$ = +46 (c = 0.94, EtOH); (*R*,*S*)/(*S*,*S*), 92:8 *dr*. This ratio was determined by proton NMR spectroscopy. This solid (0.28 g) was dissolved in methanol (1.5 mL) followed by the addition of diethyl ether (20 mL). The resulting solution was kept at 0 °C for 24 h, and the (*R*)-(–)-coniine·(*S*)-(+)-mandelic acid salt [(+)-**13b**, 0.21 g, 75%] was recovered as a single diastereoisomer [(*R*,*S*)/(*S*,*S*), ≥98:2 *dr*]. The mother liquor from the initial resolution procedure was cooled to 0 °C and stirred for 10 min with the addition of water (15 mL) that contained NaOH (0.5 g). The aqueous layer was separated and extracted with diethyl ether (2 × 20 mL). The diethyl ether extracts were combined and washed with water until the pH was neutral, and then it was dried with magnesium sulfate. (*R*)-(–)-mandelic acid (0.34 g) was added to the resulting ethereal solution, which was stirred for 25 h at room temperature. The precipitate was filtered to afford the (*S*)-(+)-coniine·(*R*)-(–)-mandelic acid salt [(–)-**13b**, 0.35 g, 52% based on isomer content] as a single diastereoisomer; m.p. 125 °C. $[\alpha]_D^{22}$ = –46 (c = 1.07, EtOH); (*S*,*R*)/(*R*,*R*), ≥98:2 *dr*.

Single-Crystal X-ray Analysis of (–)-5-A and 18: The structures were solved by direct methods with SIR-97,[40] which revealed the non-hydrogen atoms of the molecules. Refinement was performed by full-matrix least-square techniques based on F^2 with SHELXL-97[41] with the aid of the WINGX[42] 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®. CCDC-910514 [for (–)-**5-A**] and -910515 (for **18**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal Data, X-ray Data Collection and Refinement Results of α-Amino Nitrile (–)-5-A: $C_{14}H_{16}N_2$, M = 212.29, monoclinic, space group $C2$, a = 24.798(4) Å, b = 5.4404(8) Å, c = 8.9506(16) Å, α = 90°, β = 93.766(8)°, γ = 90°, V = 1204.9(3) Å^3, Z = 4, D_X = 1.17 Mg m^{-3}, μ = 0.70 cm^{-1}, λ(Mo-K_α) = 0.71073 Å, F(000) = 456, T = 150(2) K. The sample (0.60 × 0.13 × 0.13 mm) was studied with a diffractometer with graphite-monochromatized Mo-K_α radiation. The data collection (θ_{max} = 27.45°, range of hkl: h –31→32, k –6→6, l –11→11) gave 4727 reflections with 1511 unique reflections from which 1346 with $I > 2.0\sigma(I)$.

Crystal Data, X-ray Data Collection and Refinement Results of α-Amino Nitrile 18: $C_{13}H_{14}N_2$, M = 198.26, monoclinic, space group $C2/c$, a = 20.2826(9) Å, b = 6.2838(3) Å, c = 17.6042(10) Å, α = 90°, β = 97.730(2)°, γ = 90°, V = 2223.30(19) Å^3, Z = 8, D_X = 1.185 Mg m^{-3}, μ = 0.71 cm^{-1}, λ(Mo-K_α) = 0.71073 Å, F(000) = 848, T = 150(2) K. The sample (0.60 × 0.50 × 0.30 mm) was studied with a diffractometer with graphite-monochromatized Mo-K_α radiation. The data collection (θ_{max} = 27.52°, range of hkl: h –25→26, k –8→8, l –22→22) gave 8487 reflections with 2524 unique reflections from which 2110 with $I > 2.0\sigma(I)$.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of derivatives **1**–**21** and additional X-ray crystallographic data and ORTEP plots of (–)-**5-A** and **18**.

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