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FULL PAPER

Formal Synthesis of (–)-Perhydrohistrionicotoxin Using a Thorpe-Ziegler Cyclization Approach. Synthesis of Functionalized Aza-Spirocycles.

Dr. Van Ha Vu,[b] Christelle Bouvry,[a] Dr. Thierry Roisnel,[a] Dr. Stéphane Golhen,[a] Prof. Dr. Jean-Pierre Hurvois *[a]

Abstract: The formal synthesis of (–)-PHTX is described. Our approach was based on the anodic cyanation of (*S*)-1-(1-phenylethyl)-piperidine (–)-**1** to afford α-aminonitrile **2** in 85% yield in a 53:47 dr. The presence of the α-phenylethyl group as the chiral auxiliary ensured the control of the absolute configuration of the future C6 spiro-center during the alkylation step of **2**, which was carried out with 1-bromo-4-chlorobutane. Next, elaboration of the 1-azaspiro[5,5]undecane-7-one ring system was achieved in a two-step sequence, involving (a) a Thorpe-Ziegler annulation, and (b) the hydrolysis–decarboxylation of enaminonitrile (–)-**5** to afford spiroketone (+)-**6** in >99:1 dr. Finally, the incorporation of the future C7 butyl chain was carried out stereoselectively through a new reaction sequence which involved the synthesis of tricyclic oxazolidinone (–)-**11** and alkylation of the intermediary *syn*-fluorohydrin (+)-**13** with *n*BuMgCl to form oxazolidinone (+)-**15** in an overall 19% yield from (–)-**1**.

Introduction

Histrionicotoxin (HTX-283A, figure 1) was isolated in 1971 by Daly and co-workers from the skin extracts of 800 specimens of poison frogs belonging to the neotropical family Dendrobatidae. The 1-azaspiro-[5,5]-undecan-8-ol structure and the absolute configuration of this new alkaloid were elucidated by an X-ray diffraction study.[1]

To date, approximately 20 new alkaloids have been isolated from dendrobatid frogs, all of which share the same spiro-ring system substituted at the C2 and C7 positions by unsaturated alkyl chains.[2,3] Recently, methanol extracts of ants of the species *Carabella bicolor* were found to contain histrionicotoxins indicating that alkaloids accumulated in the skin of amphibians arise from a dietary source.[4]

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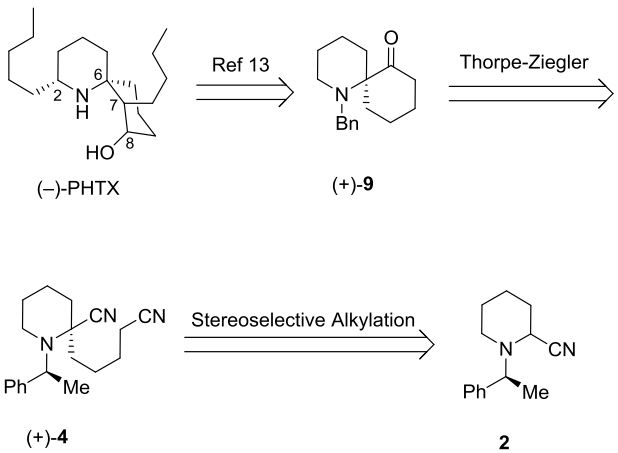
Several studies have shown that natural histrionicotoxins, and their more potent synthetic analogues, such as perhydrohistrionicotoxin (PHTX), are non-competitive blockers of the nicotinic acetyl choline receptor (nAChR).[5]

Figure 1. Representation of (–)-HTX-283A and its saturated analogue (–)-PHTX.

These interesting biological properties coupled with the construction of the unusual heterocyclic core of these alkaloids has provided a sustained interest in the community of organic chemists.[6] In the last decade, total or formal syntheses of members of the histrionicotoxin family have been achieved by the application of well-designed methodologies, such as: SmI_2-induced ring expansion,[7] cross-methathesis-hydrogenation,[8] free-radical induced cyclizations,[9] intramolecular nitrone cycloaddition,[10] dienyne metathesis,[11] and rearrangement of deprotonated aziridines.[12]

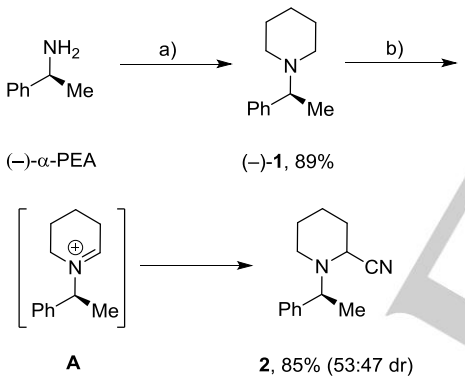


Scheme 1. Retrosynthetic analysis of (–)-PHTX from α-aminonitrile **2**.

In this contribution, we wish to present a new route to chiral spiro-piperidine (+)-**9**, a known intermediate to unnatural (–)-PHTX.[13] The retrosynthetic analysis is presented in scheme 1 and is based on the electrochemical synthesis of α-aminonitrile **2**, while an asymmetric alkylation would control the absolute configuration of the future C6 atom. We also hypothesized, that a Thorpe-Ziegler annulation sequence could be efficient for the formation of the C7-C8 bond of the 1-azaspiro-[5,5]undecane heterocyclic system.

Results and Discussion

This work began with the synthesis of α-aminonitrile **2** according to a reaction sequence described previously (Scheme 2).[14] Thus, heating (–)-α-phenylethylamine (α-PEA) with 1.2 equivalents of 1,5-dibromopentane in DMSO for 4 h in the presence of an excess of K_2CO_3, provided (–)-**1** in 89% yield. We then carried out an analytical study to determine the best conditions for the electrochemical synthesis by dissolving piperidine (–)-**1** in methanol in the presence of $LiClO_4$•$3H_2O$ as the supporting electrolyte and 2.5 equivalents of NaCN.[15]



Scheme 2. Anodic cyanation of piperidine (–)-**1**. Reagents and conditions: (a) (*S*)-(–)-α-PEA, 1,5-dibromopentane, K_2CO_3, DMSO, 50 °C, 2 h, then 100 °C, 2 h. (b) MeOH/$LiClO_4$, NaCN, Ep = 1.0 V (ECS).

The cyclic voltammogram (Figure 2) was carried out using a vitreous carbon electrode at a scan rate of 0.05 V.s^{-1}, and potentials were recorded versus a saturated calomel electrode (SCE). As is typical for tertiary amines, an irreversible bielectronic system was recorded at Ep_1 = +1.0 V corresponding to the oxidation of (–)-**1** to iminium cation **A** which was directly converted into α-aminonitrile **2** upon condensation with cyanide anions at the anode surface. Under these conditions, a macroscale electrolysis of (–)-**1** was carried out on a 10 g scale in an undivided cell equipped with a glassy carbon electrode (diameter = 10 cm) as anode and a carbon rod as cathode at a *controlled potential* of + 1.0 V. After consumption of 2.1 Faradays per mole of substrate, the electrolysis was stopped. Aqueous work-up and purification of the crude reaction mixture on a silica column afforded α-aminonitrile **2** in 85% yield as a mixture (53:47) of diastereoisomers.

The quaternary α-aminonitrile (+)-**3** was synthesized in two steps: the deprotonation of **2** and alkylation of the resulting α-cyano-carbanion (Scheme 3). Treatment of an epimeric mixture (53:47) of α-aminonitrile **2** with 1.4 equivalents of LDA produced the intermediary red anion solution. Addition of 1-bromo-4-chlorobutane gave α-aminonitrile (+)-**3** in 90% yield after chromatographic purification. Of note, quaternary α-aminonitriles of the type of (+)-**3** proved to be unstable when exposed to a mild acidic medium. Therefore, to avoid a Retro-Strecker type decomposition, the purification step and characterization should be carried out with care.[16] The reaction sequence provided two diastereoisomers which could be differentiated by distinct resonance signals of the benzylic protons of the α-PEA group. This signal resonated in the major diastereoisomer as a quartet (*J* = 6.8 Hz) at δ = 4.45. Hence, comparison of the relative integrations of these two diagnostic protons indicated an alkylation event with a 90:10 dr.

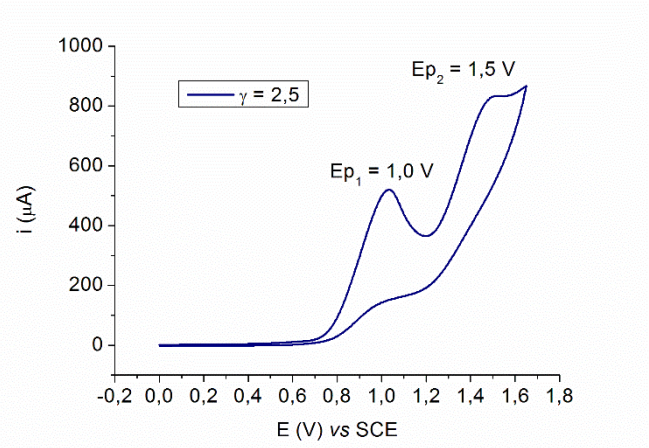


Figure 2. Cyclic Voltammogram of piperidine (–)-**1** (15 mmol). MeOH/$LiClO_4$•$3H_2O$ (0.1 M), glassy carbon electrode, ν = 0.05 Vs^{-1}, NaCN (35 mmol).

The dinitrile (+)-**4** was synthesized by prolonged treatment of (+)-**3** with NaCN in DMSO for 72 h in the presence of catalytic amounts of Bu_4NI. Substitution of the terminal chlorine atom proceeded well, providing dinitrile (+)-**4** in 95% yield in a 90:10 dr which could be improved to >99:1 dr by a slow crystallization in diethyl ether at –20 °C. A single crystal X-ray analysis, revealed the absolute configuration of the newly created chiral center to be *S* (Figure 3).

Next, we investigated the formation of the C7-C8 bond through a Thorpe-Ziegler annulation sequence. This transformation is typically accomplished in the presence of various organic or mineral bases such as: *t*BuOK,[17] morpholine,[18] K_2CO_3,[19] sodium methyl phenyl amide,[20] LiHMDS,[21] $NaNH_2$,[22] while Murahashi accomplished this cyclization under base-free conditions by iridium hydride complex catalysis.[23] However, based on our previous experiments, we

believed that LDA should remain the base of choice to perform the reaction under non-epimerizing conditions.[24]

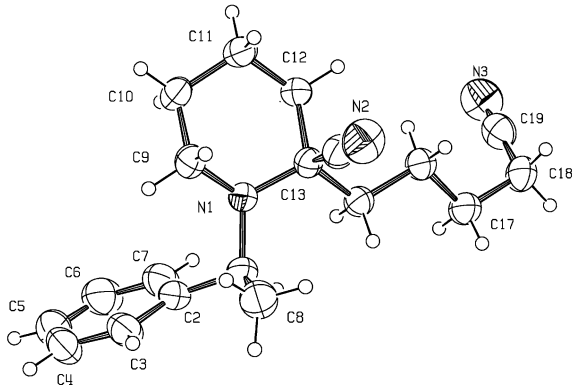
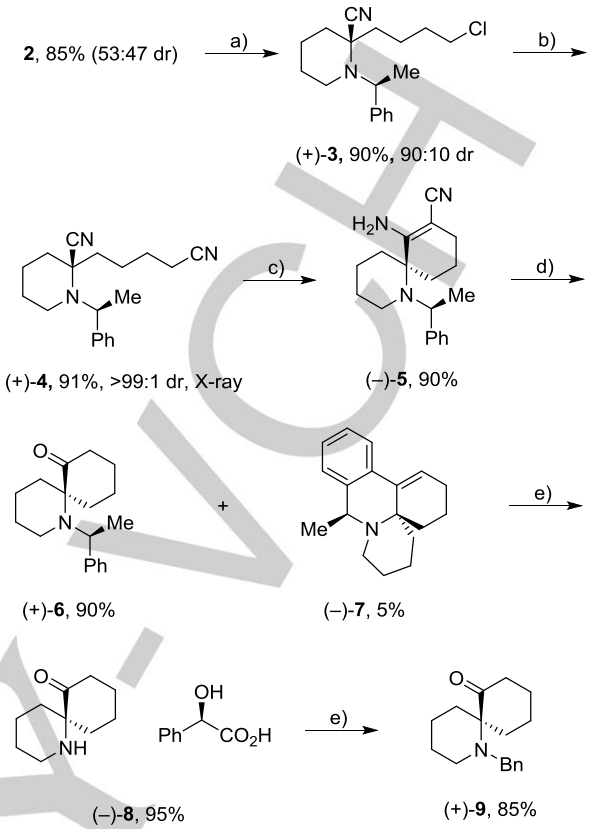


Figure 3. ORTEP view of derivative (+)-**4**. Thermal ellipsoid plots are drawn at 40% probability.

Thus, the addition of 1.3 equivalents of LDA onto a THF solution of dinitrile (+)-**4** cooled to –80 °C and stirring the solution at 0 °C for 12 h, resulted in the formation of enaminonitrile (–)-**5** in 90% yield after filtration on a chromatography column. The spectroscopic data of (–)-**5** (^{1}H and ^{13}C NMR) were consistent with the formation of a single diastereoisomer providing evidence that cyclization occurred without epimerization at the future C6 carbon. In addition, the high-resolution mass spectrum supported the molecular formula $C_{19}H_{25}N_3Na$ through a signal at m/z 318.1946 $(M + Na)^+$.

Having secured the absolute configuration of the C6 spiro-center, we set ketone (+)-**6** as the next synthetic target. We were inspired by a protocol previously proposed by Piers and Abeysekera aiming to perform hydrolysis-decarboxylation of enaminonitrile (–)-**5** in the same flask.[17b] Heating our sample in a 1:10 mixture of phosphoric acid in glacial acetic acid, resulted in poor conversion (<30%) and formation of unidentified products presumably through a polymerization process. Neither alteration of the reaction parameters nor varying the medium composition impacted significantly the overall yield and the reaction rate. To get more insight into this process, we sought to isolate the intermediate β-keto-nitrile derived from (–)-**5**. Scrutinizing the literature data revealed that such derivatives could be obtained from acid hydrolysis of enaminonitriles.[25] Our first experiments were carried out by stirring enaminonitrile (–)-**5** for 16 h at room temperature, in a two-phase system consisting of a mixture of 37% hydrochloric acid and toluene. Unfortunately, no reaction occurred under these conditions, and we reasoned that significantly higher yields should be obtained at a more elevated temperature. Indeed, heating the medium for 2 h at 100-110 °C cleanly produced ketone (+)-**6** (30% yield) together with unreacted enaminonitrile (–)-**5**. On increasing the reaction time to 15 h, the ketone (+)-**6** was recovered as the sole product in 80% yield after chromatographic purification.



Scheme 3. Formal synthesis of (–)-HTX. reagents and conditions: (a) LDA, THF, –80 °C to 0 °C, 2 h, then 1-bromo-4-chlorobutane, –80 °C to rt. (b) NaCN, Bu_4NI (10% mol), DMSO, 72 h, rt. (c) LDA, THF, –80 °C to 0 °C, 12 h. (d) Toluene, HCl 35%, reflux, 15 h. (e) 10% Pd/C, MeOH, H_2 (1 bar), 20 °C, 24 h. (f) BnBr, DMSO, Na_2CO_3, 72 h, 20 °C.

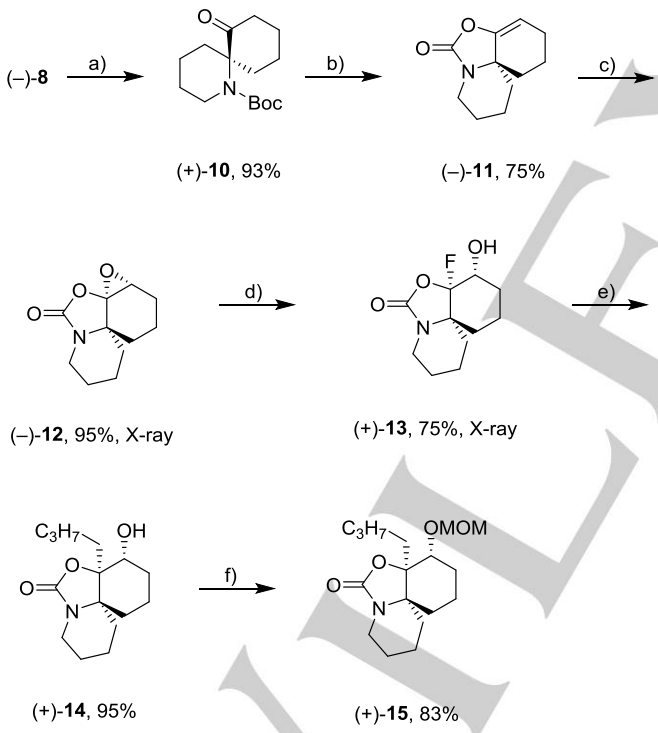
Structural determination was straightforward. In the ^{13}C NMR spectrum, the C7 quaternary carbon gives a resonance signal at δ = 216.2 ppm and both ^{1}H and ^{13}C NMR analysis suggested product formation without erosion of chirality. Taken together, these results indicated that protonation of the enaminonitrile is slow and that decarboxylation of the intermediary β-keto-acid occurred at high temperature.

Further optimization provided more information about the reactivity of spiroketone (+)-**6** under acidic conditions. Close examination of the ^{1}H NMR spectrum of the crude reaction mixture revealed the presence of an additional ethylenic doublet of doublet (^3J = 4.8, 3.2 Hz) signal at δ = 6.10 ppm corresponding to the vinylic proton of more polar hexahydrophenanthridine (–)-**7** (Scheme 3) which was isolated in 5% yield after purification by column chromatography (dichloromethane/methanol 7:3). To determine the origin of this unexpected compound, a control experiment with spiroketone (+)-**6** was conducted (15 h, 110 °C) as synthesis of (+)-**6**. Indeed, the hexahydrophenanthridine (–)-**7** was obtained in 30% yield, together with unreacted starting material, providing evidence of an intramolecular Friedel-Crafts type process.

All that remained to carry out the formal synthesis of (–)-PHTX was to replace the α-PEA group by a benzyl substituent

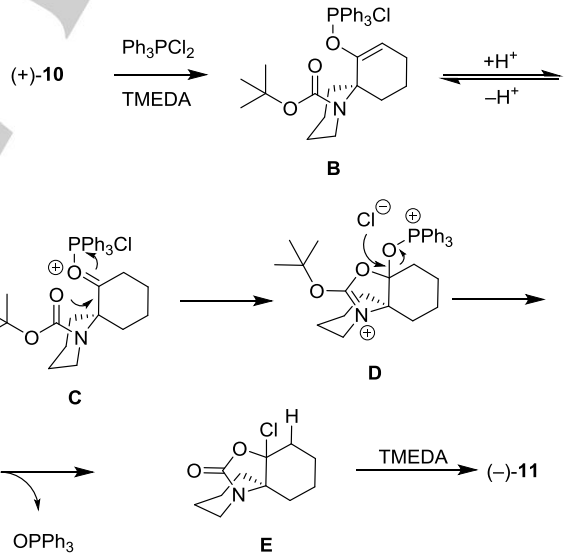
(Scheme 3). Gratifyingly, removal of the chiral appendage was easily carried out in the presence of 10% Pd/C in methanol under a hydrogen pressure of 1 bar. The expected spiropiperidine was obtained as its mandelate salt (–)-**8** (m.p. = 141-142 °C) in nearly quantitative yield. Due to a strong steric hindrance around the nitrogen atom, the alkylation step necessitated a prolonged reaction time. Nevertheless, treatment of the mandelate salt (–)-**8** with an excess (2 equiv.) of benzylbromide in DMSO for 72 h afforded spiropiperidine (+)-**9** in 85% yield after chromatographic purification. The optical rotation of our sample was recorded in chloroform ($[\alpha]^{22}_D$ = +15.0, *c* 1.0, $CHCl_3$) and proved to be identical to that reported in the literature ($[\alpha]^{22}_D$ = +15.0, *c* 2.06, $CHCl_3$).[26]

With an efficient stereoselective route to enantiopure spiropiperidine (–)-**8** in hand, we sought to develop a new and reliable route for the introduction of the butyl chain at the future C7 position (Scheme 4). With this purpose in mind, we turned to recent studies devoted to the Cu-catalyzed cross-coupling condensation between alkyl-chlorides and Grignard reagents.[27] Therefore, we screened several reagents that were expected to perform the chlorination of (+)-**10**. Access to the starting material was straightforward.



Scheme 4. Synthesis of oxazolidinone (+)-**15**. Reagents and conditions (a) Boc_2O, DIPEA, acetonitrile, reflux, 3 h. (b) TMEDA, Ph_3PCl_2, acetonitrile, rt, 4 h. (c) Oxone, $Na_2B_4O_7$•$10H_2O$, acetone, CH_2Cl_2, 0 °C, 4 h. (d) BF_3•Et_2O, Et_2O, 0 °C, 1 h. (e) *n*BuMgBr, $CuCl_2$ (5 mol%), THF, rt, 2 h. (f) NaH, MOMCl, NaI (10 mol%), THF, rt, 16 h.

Refluxing the mandelate salt (–)-**8** in acetonitrile for 3 h in the presence of Boc_2O and an excess of DIPEA afforded piperidine (+)-**10** in 93% yield. We found only a few reports in the literature where transfer of two chlorine atom takes place at the carbonyl group. Our preliminary experiments which were carried out with traditional chlorinating reagents such as PCl_5, proved to be problematic and afforded a mixture of products.[28] We also explored the chlorination of (+)-**10** with dichlorotriphenylphosphorane (Ph_3PCl_2) as an alternative to the previous method.[29,30] The reaction was carried out in the presence of TMEDA as the base and afforded oxazolidinone (–)-**11** as the sole product. A detailed examination of the spectrum of (–)-**11** confirmed the proposed structure. The downfield value (δ = 5.14 ppm) for the resonance signal of 1-H coupled with a characteristic ^3J value of 3.7 Hz confirmed the presence of an ethylenic double bond. The ^{13}C NMR spectrum contained also two characteristic signals resonance lines at δ = 99.7 and 150.1 which could be easily attributed to the C7 and C8 carbon atoms, respectively. This cyclization process could be explained as follows (Scheme 5). First, treatment of (+)-**10** with Ph_3PCl_2/TMEDA activates the C7 carbon through the probable formation of vinyloxyphosphorane **B** which is in equilibrium with the cationic intermediate **C**.[31] Second, the presence of a highly electrophilic carbon in close proximity of the carbonyl group, induced a cyclization process to form intermediate **D** which decomposed into oxazolidinone **E** with loss of isobutylene and $OPPh_3$.[32] Finally, elimination of HCl from **E**, leads to oxazolidinone (–)-**11**.



Scheme 5. Proposed mechanism for the cyclization of (+)-**10**.

With this unexpected derivative in hand, we set epoxide (–)-**12** as the next synthetic target. The reaction was best achieved by stirring (–)-**11** in a mixture of dichloromethane, acetone and Oxone, while the pH of the reaction medium was maintained at *ca.* 9–10 by the continuous addition of an aqueous solution of sodium tetraborate.[33] Under these *in situ* conditions, epoxide (–)-**12** was isolated (95%) as a colorless solid (m.p. = 110-111 °C)

with >92:8 dr. A single crystal X-ray study revealed the stereochemical outcome of the epoxidation process. The ORTEP view (Figure 4) indicated that addition of the assumed dimethyldioxirane intermediate occurred on the less hindered *Re* face of oxazolidinone (–)-**11**. With epoxide (–)-**12** available in good yield, several attempts were made to install the future C7 alkyl chain with concomitant epoxide ring opening. Unfortunately, reacting (–)-**12** with an excess of *n*BuLi (2 equiv.) in the presence of BF_3•Et_2O (5 equiv.) as the Lewis acid met with failure, with no perceptible formation of the expected product probably due to the sensitivity of the oxazolidine ring to these reaction conditions.[34]

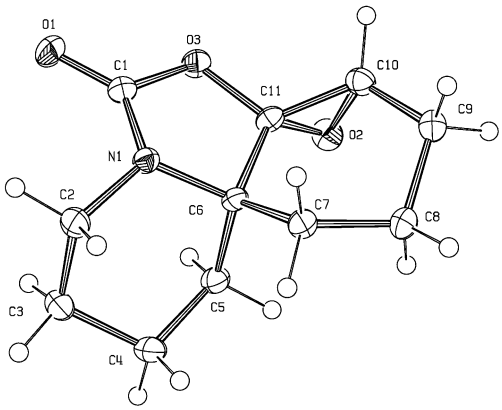


Figure 4. ORTEP view of epoxide (–)-**12**. Thermal ellipsoid plots are drawn at 40% probability.

The search for a more robust method led to consider the coupling between an alkyl fluoride and a Grignard reagent.[35] Thus, treatment of epoxide (–)-**12** in diethyl ether with 2.2 equivalents of BF_3•Et_2O as the nucleophilic fluoride source, gave fluorohydrin (+)-**13** as a colorless solid (m.p. = 113–114 °C) in 75% yield and >98:2 dr.

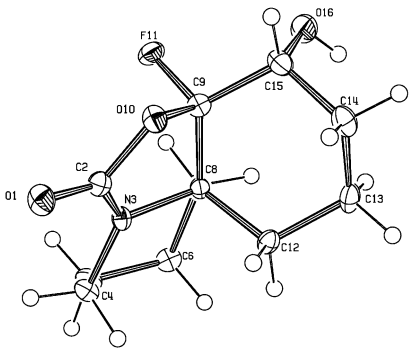


Figure 5. ORTEP view of *syn*-fluorohydrin (+)-**13**. Thermal ellipsoid plots are drawn at 40% probability.

The relative *syn*-configuration within (+)-**13** was established from an X-ray analysis (Figure 5) performed on one single crystal obtained from a slow crystallization of (+)-**13** in a mixture of diethyl ether and petroleum ether.[36] In the penultimate step, the butyl chain was introduced by modifying the protocol developed by Terao and Kambe.[35] Indeed, we rapidly observed that an efficient coupling could be achieved between (+)-**13** and a Grignard reagent. Thus, the addition of two equivalents of *n*BuMgCl to a THF solution of (+)-**13** containing a catalytic amount of $CuCl_2$ (5 mol%) resulted in the isolation of (+)-**14** (95%) whose absolute configuration probably corresponds to that drawn in scheme 4. Evidence for the presence of the butyl chain in (+)-**15** was provided by ^{1}H and ^{13}C NMR techniques and high-resolution mass spectra with $[M + Na]^+$ at 290.1735. Finally, and for our further chemical purposes, the protection of the secondary alcohol function was carried out in the presence of MOMCl to provide (+)-**15** as a single diastereoisomer after purification on a chromatography column.

Conclusions

In summary, anodic cyanation and Thorpe-Ziegler annulation proved to be an efficient combination to construct in a stereoselective fashion the 1-azaspiro[5.5]undecane ring system of the histrionicotoxin alkaloids. Apart from the generally high yields in each individual step, we present an efficient and scalable synthesis of oxazolidinone (+)-**15** which may serve as an advanced precursor to the synthesis of (–)-PHTX. This work is currently under investigation in the laboratory and will be reported in due course.

Experimental Section

Experimental section

General Techniques: Purification by chromatography column was performed with 70–230 mesh silica gel. TLC analyses were carried out on alumina sheets precoated with silica gel 60 F254; R_f values are given for guidance. The ^{1}H NMR spectra were recorded with a 400 MHz or a 300 MHz spectrometer. The ^{13}C NMR spectra were recorded with a 100 MHz or a 75 MHz spectrometer. Positive-ion mass spectra were recorded on an orthogonal acceleration quadrupole time-of-flight mass spectrometer equipped with a standard electrospray probe. Melting points were measured on a Kofler apparatus, the values reported in °C, and were uncorrected. Optical rotations were recorded at 20 °C in a 1 dm cell. For air-sensitive reactions, the glassware was oven-dried (90 °C) for 24 h and cooled under a stream of argon before use. All commercially available reagents were used as supplied and THF was distilled over sodium benzophenone ketyl. Diisopropylamine was distilled from solid potassium hydroxide.

Electrochemical techniques. Cyclic voltammetry experiments were carried out on a potentiostat using a three-electrode device with a glassy carbon (GCE, diameter = 2 mm) as the working electrode, a saturated calomel electrode (SCE) as the reference and a platinum wire as the auxiliary electrode. The experiments were carried out in methanol containing $LiClO_4$•$3H_2O$ (0.1 mol L^{-1}) as the supporting electrolyte.

Preparative electrolysis was carried out at controlled potential in a single compartment cell. The solution was stirred with a magnetic stirring bar and the electrolysis was stopped after the consumption of 2.1 F/mole.

*(S)-(–)-1-(1-phenylethyl)-piperidine, (–)-**1***. To a solution of (*S*)-phenylethylamine (4.14 mL, 3.99 g, 33.00 mmol) in DMSO (20 mL) was added 1,5-dibromopentane (5.39 mL, 9.10 g, 39.67 mmol, 1.20 equiv.) and powdered K_2CO_3 (10.00 g, 72.36 mmol, 2.19 equiv.). The reaction mixture was heated at 50 °C for 2 hours and then at 100 °C for an additional 2 hours period. After cooling, the reaction mixture was poured over 50 mL of brine and the resulting mixture was extracted with 30 mL of dichloromethane (x 3). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford a crude oil which was transferred to a chromatography column (diethyl ether/petroleum ether, 1:1). The combined fractions were evaporated to afford piperidine (–)-**1** (5.60 g, 90%). Colorless oil. $[\alpha]^{22}_D$ = –27.3 (*c* 1.2, $CHCl_3$). R_f = 0.5 (diethyl ether/petroleum ether, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.36 (d, *J* = 6.8 Hz, 3 H); 1.32–1.41 (m, 2 H); 1.50–1.57 (m, 4 H); 2.30–2.44 (m, 4 H); 3.39 (q, *J* = 6.8 Hz, 1 H); 7.20–7.25 (m, 1 H); 7.27–7.33 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 19.4 (p); 24.6 (s); 26.3 (s); 51.5 (s); 65.2 (t); 126.6 (t); 127.8 (t); 128.0 (t); 144.0 (q). IR (film, cm^{-1}): 2970, 2930, 2751, 1490, 1450, 1372, 939, 698. HRMS (ESI$^+$, CH_3OH, $C_{13}H_{20}N$ [M + H]$^+$) calcd for 190.1595, found 190.1594. Anal. Calcd for $C_{13}H_{19}N$ (189.3): C, 82.48; H, 10.12; N, 7.40. Found: C, 82.20; H, 10.10; N, 7.39.

*1-((S)-1-phenylethyl)-piperidine-2-carbonitrile, **2***. A 1000 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, 9.90 g (52.34 mmol) of piperidine (–)-**1**, 4.90 g of $LiClO_4$•$3H_2O$, and 6.40 g (130.60 mmol, 2.48 equiv.) of NaCN. The working potential is adjusted to + 1.00 V/SCE and after the consumption of 10 600 C (2.10 F/mol), the electrolysis was stopped. Then, 1000 mL of brine were added to the electrolysis solution and the reaction mixture was extracted with 2 × 200 mL of diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated to afford 10.5 g of a crude oil which was poured into a chromatography column (50 × 5.0 cm, ethyl acetate/pentane, 10:90). The combined fractions were evaporated to afford to α-aminonitrile **2** (9.59 g, 85%) as a mixture (53:47) of diastereoisomers. Yellow oil. R_f = 0.45 (ethyl acetate/pentane, 10:90). **Caution**: *$LiClO_4$ may lead to severe explosions when the material is evaporated to dryness*. *The excess of NaCN was destroyed by the addition of $KMnO_4$ onto the resulting aqueous phase. Due to the possible release of HCN, the electrolysis should be carried out under a well-ventilated hood*. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.33 (d, *J* = 6.6 Hz, 1.41 H), 1.37 (d, *J* = 6.6 Hz, 1.59 H), 1.32–1.45 (m, 1 H), 1.50–1.79 (m, 4.06 H); 1.87 (tt, *J* = 12.0, 4.2 Hz, 0.47 H), 1.95–2.02 (m, 0.47 H), 2.16 (td, *J* = 12.2, 2.8 Hz, 0.47 H), 2.35 (td, *J* = 11.6, 2.9 Hz, 0.53 H), 2.60 (dm, *J* = 11.0 Hz, 0.47 H), 3.20 (dm, *J* = 11.8 Hz, 0.53 H), 3.47 (q, *J* = 6.6 Hz, 0.53 H); 3.52 (q, *J* = 6.6 Hz, 0.47 H), 3.59 (t, *J* = 3.0 Hz, 0.53 H), 4.24 (t, *J* = 3.3 Hz, 0.47 H), 7.21–7.37 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 20.5 (s), 20.7 (s), 21.0 (p), 21.5 (p), 25.1 (s), 25.3 (s), 28.9 (s), 29.2 (s), 45.6 (s), 48.2 (s), 49.7 (t), 51.7 (t), 63.1 (t), 63.2 (t), 117.0 (q), 117.2 (q), 127.2 (t), 127.3 (t), 127.5 (t), 128.5 (t), 128.8 (t), 143.9 (q), 144.7 (q). IR (film, cm^{-1}): 2973, 2938, 2214, 1491, 1452, 1124, 939, 700. HRMS (ESI$^+$, CH_3OH, $C_{14}H_{18}N_2Na$ [M + Na$^+$]) calcd for 237.1367, found 237.1367. Anal. Calcd for $C_{14}H_{18}N_2$ (214.3): C, 78.46; H, 8.47; N, 13.07. Found: C, 78.75; H, 8.46; N, 13.00.

*(R)-2-(4-chlorobutyl)-1-((S)-1-phenylethyl)-piperidine-2-carbonitrile, (+)-**3***. An oven dried, 200-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, was flushed with argon and was charged with 15 mL of dry THF and 3.75 mL (2.69 g, 26.57 mmol, 1.70 equiv.) of diisopropylamine. The solution was cooled to –80 °C before the addition of 8.76 mL (21.90 mmol, 1.40 equiv.) of *n*-butyllithium (2.5 M solution in hexane). Stirring was continued at 0 °C for 30 minutes and the LDA solution was transferred (*via* a cannula) into a 200-mL Schlenk tube cooled to –80 °C, containing 3.35 g (15.63 mmol) of a mixture (53:47 *dr*) of α-aminonitrile **2** dissolved in 10 mL of dry THF. The solution turned rapidly red and was warmed to 0 °C for 2.0 h and then was cooled to –80 °C. Then, 2.33 mL (3.47 g, 20.22 mmol, 1.29 equiv.) of 1-bromo-4-chlorobutane were added dropwise and the reaction mixture was warmed to 0 °C and was stirred at that temperature for 12 h. The solvents were evaporated under reduced pressure, and the crude material was taken-up with 20 mL of water. The aqueous layer was extracted with 2 × 25 mL of diethyl ether and the organic phases were dried over $MgSO_4$ and concentrated. The crude oily residue (5.40 g) was poured into a chromatography column prepared with 20 g of silica and 1:2 diethyl ether/petroleum ether. The combined fractions were concentrated to afford 4.28 g (90%) of α-aminonitrile (+)-**3** as a mixture [90 (*S,R*):10 (*S,S*) dr] of diastereoisomers. Colorless oil. $[\alpha]^{22}_D$ = +2.8 (*c* 1.0, C_6H_6). R_f = 0.30 (petroleum ether/diethyl ether, 95:5). ^{1}H NMR (isomeric mixture, 90 (*S,R*):10 (*S,S*) dr, major diastereoisomer, $CDCl_3$, 400 MHz) δ = 1.20–1.40 (m, 1 H), 1.55 (d, *J* = 6.8 Hz, 3 H), 1.64–2.04 (m, 11 H), 2.55–2.65 (m, 2 H), 3.55 (t, *J* = 6.1 Hz, 2 H), 4.44 (q, *J* = 6.8 Hz, 1 H), 7.25 (t, *J* = 5.2 Hz, 1 H), 7.35 (t, *J* = 6.0 Hz, 2 H), 7.44 (d, *J* = 7.0 Hz, 2 H). IR (film, cm^{-1}): 2937, 2214, 1493, 1444, 1119, 698.^{13}C NMR ($CDCl_3$, 100 MHz) δ = 11.5 (p), 20.8 (s), 22. 2 (s), 25.4 (s), 32.5 (s), 36.2 (s), 37.3 (s), 42.9 (s), 44.4 (s), 53.8 (t), 59.7 (q), 121.8 (q), 126.6 (t), 128.1 (t), 144.1 (q). HRMS (ESI$^+$, CH_3OH, $C_{18}H_{25}ClN_2Na$ [M + Na]$^+$) calcd for 327.1604, found 327.1601. Anal. Calcd for $C_{18}H_{25}ClN_2$ (304.8): C, 70.92; H, 8.27; N, 9.19. Found C, 70.78; H, 8.30; N, 9.16.

*(S)-2-(4-cyanobutyl)-1-((S)-1-phenylethyl)-piperidine-2-carbonitrile, (+)-**4***. α-Aminonitrile (+)-**3** (3.04 g, 9.97 mmol) was dissolved in 25 ml DMSO in the presence of 1.40 g (28.57 mmol, 2.86 equiv.) of NaCN and 0.30 g (0.81 mmol, 0.08 equiv.) of *n*Bu_4NI. The reaction mixture was stirred at room temperature for 72 h and was poured onto 200 ml of water. The products were extracted with 100 mL of diethyl ether (x 3) and the combined organic phases were washed with water, dried over $MgSO_4$ and concentrated. The crude oily residue was poured into a chromatography column prepared with 20 g of silica diethyl ether. The fractions were concentrated to afford a highly viscous oil which was dissolved in a minimum of diethyl ether and was kept at –20 °C for 24 h. The precipitate was filtered on a sintered-glass funnel to afford 2.67 g (91%) of α-aminonitrile (+)-**4** as a single diastereoisomer. R_f = 0.42 (diethyl ether). Slightly brown flakes. $[\alpha]^{22}_D$ = +7.2 (*c* 1.0, C_6H_6). Mp = 79–80°C. ^{1}H NMR (C_6D_6, 400 MHz) δ = 0.70–0.80 (m, 2 H), 1.00–1.20 (m, 5 H), 1.26 (t, *J* = 7.3 Hz, 2 H), 1.30–1.45 (m, 4 H), 1.41 (d, *J* = 6.8 Hz, 3 H), 1.51 (tt, *J* = 13.0, 3.8 Hz, 1 H), 2.35 (dm, *J* = 12.2 Hz, 1 H), 2.48 (td, *J* = 12.2, 2.7 Hz, 1 H), 4.12 (q, *J* = 6.8 Hz, 1 H), 7.10 (tm, *J* = 6.0 Hz, 1 H), 7.21 (tt, *J* = 6.0, 2.2 Hz, 2 H), 7.27 (dm, *J* = 6.0 Hz, 2 H). ^{13}C NMR (C_6D_6, 100 MHz,) δ = 11.3 (p), 16.1 (s), 22.0 (s), 22.2 (s), 25.1 (s), 25.2 (s), 35.7 (s), 36.9 (s), 42.7 (s), 53.6 (t), 59.1 (q), 118.6 (q), 121.0 (q), 126.6 (t), 126.9 (t), 128.1 (t), 144.2 (q). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.30–1.42 (m, 1 H), 1.54 (d, *J* = 6.8 Hz, 3 H), 1.57–1.85 (m, 8 H), 1.90–2.39 (m, 3 H), 2.36 (t, *J* = 6.6 Hz, 2 H), 2.59–2.67 (m, 2 H), 4.41 (q, *J* = 6.8 Hz, 1 H), 7.26 (t, *J* = 8.0 Hz, 1 H), 7.35 (t, *J* = 8.0 Hz, 2 H), 7.42 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz,) δ = 11.7 (p), 17.1 (s), 22.1 (s), 22.6 (s), 25.4 (s), 25.5 (s), 36.2 (s), 37.3 (s), 43.0 (s), 53.9 (t), 59.7 (q), 119.2 (q), 122.0 (q), 126.6 (t), 126.9 (t), 128.2 (t), 144.1 (q). IR (film, cm^{-1}): 2967, 2860, 2245, 2210, 1443, 1071, 699. HRMS (ESI$^+$, CH_3CN/CH_3OH, $C_{18}H_{25}N_2$ [M – HCN + H]$^+$ calcd for 269.2017, found 269.2017. Anal. Calcd for $C_{19}H_{25}N_3$ (295.4): C, 77.25; H, 8.53; N, 14.22. Found C, 77.46; H, 8.50; N, 14.20.

*(S)-7-amino-1-((S)-1-phenylethyl)-1-azaspiro[5.5]undec-7-ene-8-carbonitrile, (–)-**5***. An oven dried, 200-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, was flushed with argon, and was successively charged with 20 mL of dry THF and 2.41 mL (1.72 g, 17.10 mmol, 1.4 equiv.) of diisopropylamine. The flask was cooled to –80 °C and 6.34 mL

(15.85 mmol, 1.3 equiv.) of *n*-butyllithium (2.5 M solution in hexane) were added to the previous solution. Stirring was continued for 30 min at 0 °C and the resulting LDA solution was then added dropwise into a 200-mL Schlenk tube cooled to –80 °C containing 3.60 g (12.20 mmol) of α-aminonitrile (+)-**4** dissolved in 50 mL of dry THF. The solution was warmed to 0 °C and stirring was continued at that temperature for 12 h. The solvents were evaporated under reduced pressure, and the crude material was taken-up with 20 mL of water. The aqueous layer was extracted with 50 mL of diethyl ether (x 2) and the organic phases were dried over $MgSO_4$ and concentrated. The crude oily residue is poured into a chromatography column containing 40 g of silica and 1:2 petroleum ether/diethyl ether. The fractions were collected and concentrated to afford 3.24 g (90%) of enaminonitrile (–)-**5** *as a single diastereoisomer*. Vitreous solid. R_f = 0.30 (petroleum ether/diethyl ether, 7:3). $[\alpha]^{22}_D$ = –200.7 (*c* 0.9, $CHCl_3$).^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.36 (d, *J* = 6.8 Hz, 3 H), 1.39–1.85 (m, 10 H), 2.10–2.28 (m, 2 H), 2.37 (td, *J* = 11.8, 2.8 Hz, 1 H), 3.20 (dm, *J* = 11.8 Hz, 1 H), 3.83 (q, *J* = 6.8 Hz, 1 H), 5.01 (s, 2 H), 7.20–7.31 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 19.8 (s), 20.0 (s), 21.9 (p), 22.8 (s), 24.4 (s), 26.7 (s), 35.3 (s), 42.0 (s), 59.6 (t), 61.1 (q), 74.8 (q), 121.1 (q), 126.9 (t), 128.2 (t), 128.8 (t), 148.8 (q), 162.3 (q). IR (film, cm^{-1}): 3468, 3361, 2930, 2181, 1615, 1573. HRMS (ESI^+, CH_3OH, $C_{19}H_{25}N_3Na$ $[M + Na]^+$) calcd for 318.1946, found 318.1944. Anal. Calcd for $C_{19}H_{25}N_3$ (295.4): C, 77.25; H, 8.53; N, 14.22. Found C, 77.00; H, 8.55; N, 14.17.

*(S)-1-((1S)-1-phenylethyl-1-azaspiro[5.5]undecan-7-one, (+)-**6**.* To a solution of enaminonitrile (–)-**5** (4.00 g, 13.54 mmol) in toluene (60 mL) were added 10 ml of 37% hydrochloric acid. The resulting biphasic system was refluxed for 15 h and was poured onto a 10% Na_2CO_3 solution (150 mL). The solution was stirred for 1 h while maintaining the pH of the aqueous phase at 12. The organic phase was discarded and the aqueous layer was extracted with 50 mL of diethyl ether (x 2). The combined organic phases (toluene plus diethyl ether) were washed with water, dried over $MgSO_4$ and concentrated. The crude oil was poured on a chromatography column containing 40 g of a slurry of silica gel and 7:3 pentane/diethyl ether. The combined fractions were concentrated to give 3.30 g (90%) of spiropiperidine (+)-**6**. Colorless oil. R_f = 0.30 (petroleum ether/diethyl ether, 7:3). $[\alpha]^{22}_D$ = +47.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.18–1.29 (m, 1 H), 1.36–1.50 (m, 1 H), 1.49 (d, *J* = 6.8 Hz, 3 H), 1.51–1.80 (m, 7 H), 1.90–2.00 (m, 1 H), 2.06 (ddd, *J* = 16.3, 11.9, 4.3 Hz, 1 H), 2.24 (dm, *J* = 13.1 Hz, 1 H), 2.36 (dm, *J* = 14.5 Hz, 1 H), 2.44 (ddd, *J* = 18.5, 14.5, 6.3 Hz, 1 H), 2.71 (dt, *J* = 11.9, 4.4 Hz, 1 H), 3.21 (ddd, *J* = 11.9, 10.6, 3.4 Hz, 1 H), 4.15 (q, *J* = 6.8 Hz, 1 H), 7.14 (t, *J* = 7.2, Hz, 1 H), 7.27 (t, *J* = 7.8 Hz, 2 H), 7.37 (dm, *J* = 7.2 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 20.1 (p), 20.9 (s), 21.6 (s), 26.3 (s), 27.1 (s), 35.7 (s), 37.8 (s), 40.5 (s), 43.2 (s), 56.5 (t), 69.3 (q), 125.8 (t), 126.8 (t), 128.0 (t), 148.6 (q), 216.2 (q). IR (film, cm^{-1}): 2928, 2858, 1705, 1445. HRMS (ESI^+, CH_3OH, $C_{18}H_{26}NO$ $[M + H]^+$) calcd for 272.2014, found 272.2010. Anal. Calcd for $C_{18}H_{25}NO$ (271.4): C, 79.66; H, 9.28; N, 5.16. Found C, 79.70; H, 9.24; N, 5.13.

*(4aS,10S)-10-methyl-2,3,4,5,6,7,8,10-octahydropyrido[2,1-e]phenanthridine, (–)-**7**.* To a solution of spiropiperidine (+)-**6** (0.50 g, 1.84 mmol) in toluene (20 mL) were added 2 ml of 37% HCl. The resulting biphasic system was refluxed for 15 h and poured onto a 10% Na_2CO_3 solution (50 ml) while maintaining the pH of the aqueous phase at 12. The organic phase was separated, and the aqueous layer was extracted with 50 mL of diethyl ether (x 2). The combined organic phases (toluene plus diethyl ether) were washed with water, dried over $MgSO_4$ and concentrated. The crude oil was poured on a chromatography column containing 10 g of silica and 7:3 of dichloromethane/ methanol. Unreacted piperidine (+)-**6** (0.35 g) was eluted first, followed by the more polar hexahydrophenanthridine (–)-**7** (0.14 g, 30%). Colorless oil. R_f = 0.30 (dichloromethane/methanol, 7:3). $[\alpha]^{22}_D$ = –159.3 (*c* 1.37, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.17–1.25 (m, 1 H), 1.32 (d, *J* = 6.8 Hz, 3 H), 1.33–1.37 (m, 2 H), 1.43–1.58 (m, 3 H), 1.66–1.85 (m, 3 H), 2.14 (dt, *J* = 17.0, 4.0 Hz, 1 H), 2.10–2.31 (m, 1 H), 2.69 (dd, *J* = 10.4, 4.4 Hz, 1 H), 2.82 (dm, *J* = 14.5 Hz, 1 H), 3.28 (ddd, *J* = 14.5, 12.7, 3.2 Hz, 1 H), 4.10 (q, *J* = 6.8 Hz, 1 H), 6.10 (dd, *J* = 4.8, 3.2 Hz, 1 H), 7.09 (d, *J* = 8.0 Hz, 1 H), 7.11–7.20 (m, 2 H), 7.32 (dd, *J* = 7.3, 1.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 18.1 (s), 19.2 (s), 19.6 (s), 26.06 (p), 26.09 (s), 27.8 (s), 32.1 (s), 44.2 (s), 53.2 (t), 53.9 (q), 125.2 (t), 125.0 (t), 126.0 (t), 126.3 (t), 126.5 (t),133.3 (q), 138.9 (q), 139.0 (q). HRMS (ESI^+, CH_3OH, $C_{18}H_{24}N$ $[M + H]^+$) calcd for 254.1908, found 254.1910. Anal. Calcd for $C_{18}H_{23}N$ (253.4): C, 85.32; H, 9.15; N, 5.53. Found C, 85.46; H, 9.13; N, 5.55.

*(S)-1-azaspiro[5.5]undecan-7-one•(R)-mandelic acid, (–)-**8**.* A 100-mL low-pressure hydrogenator was charged with 60 mL of methanol, 3.0 g (11.05 mmol) of spiropiperidine (+)-**6** and 0.3 g (10% in mass) of 10% Pd/C. Air was removed from the reactor by alternately venting it three times with argon and filling it with hydrogen. The pressure (7.5 × 10^2 Torr, 1 bar) was applied, and the solution was stirred for 24 h at room temperature. The suspension was filtered over a short pad of Celite and the vessel was washed with methanol. Then, 1.68 g (11.04 mmol) of (*R*)-(–)-mandelic acid were added to the methanolic solution which was concentrated on a rotary evaporator to afford 3.34 g (95%) of mandelate salt (–)-**8** as a white solid. Mp: 141–142 °C. $[\alpha]^{22}_D$ = –13.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.20–1.31 (m, 1 H), 1.48–1.71 (m, 7 H), 1.76 (td, *J* = 12.4, 4.4 Hz, 1 H), 1.86–1.95 (m, 1 H), 1.96–2.03 (m, 1 H), 2.12 (dm, *J* = 12.8 Hz, 1 H), 2.35–2.45 (m, 2 H), 2.87–3.01 (m, 1 H), 3.30–3.40 (m, 1 H), 4.91 (s, 1 H), 7.19 (tt, *J* = 6.4, 1.0 Hz, 1 H), 7.24–7.30 (m, 3 H), 7.48 (d, *J* = 7.0 Hz, 2 H), 6.5–8.5 (s, br. 2 H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ = 18.6 (s), 20.6 (s), 21.7 (s), 27.3 (s), 29.1 (s), 35.3 (s), 38.2 (s), 40.6 (s), 65.3 (q), 74.2 (t), 126.6 (t), 126.8 (t), 127.8 (t), 142.4 (q), 177.7 (q), 207.9 (q). IR (neat, cm^{-1}): 3157, 3060, 1724, 1606, 1584, 724. HRMS (ESI^+, CH_3OH, $C_{10}H_{18}NO$ $[M]^+$) calcd for 168.1388, found 168.1388. Anal. $C_{18}H_{24}NO_4$ (319.4): C, 67.69; H, 7.89; N, 4.39. Found C, 67.94; H, 7.90; N, 4.33.

*(S)-1-benzyl-1-azaspiro[5.5]undecan-7-one, (+)-**9**.* To a solution of mandelate salt (–)-**8** (0.32 g, 1.0 mmol) in DMSO (3 mL) were successively added 0.150 g (1.41 mmol, 1.40 equiv.) of Na_2CO_3 and 0.342 g (2.0 mmol, 2.0 equiv.) of benzyl bromide. The reaction mixture was stirred at room temperature for 72 h and was poured onto 50 ml of water. The products were extracted with 150 mL diethyl ether (x 2) and the combined organic phases were washed with water, dried over $MgSO_4$ and concentrated. The crude reaction mixture was poured on a chromatography column prepared with 20 g of silica and 6:4 petroleum ether/diethyl ether. The combined fractions were concentrated to afford 0.220 g (85%) of piperidine (+)-**9.** Colorless oil. R_f = 0.30 (petroleum ether/diethyl ether, 60:40). $[\alpha]^{22}_D$ = + 15.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.42–1.49 (m, 2 H), 1.51–1.74 (m, 5 H), 1.84–1.91 (m, 2 H), 1.92–2.03 (m, 2 H), 2.23 (ddd, *J* = 12.9, 9.0, 3.4 Hz, 1 H), 2.36 (dt, *J* = 13.7, 7.1 Hz, 1 H), 2.62–2.80 (m, 2 H), 2.77 (dt, *J* = 13.7, 6.8 Hz, 1 H); 3.60 (d, *J* = 14.5 Hz, 1 H), 3.85 (d, *J* = 14.5 Hz, 1 H), 7.24 (tt, *J* = 7.2, 1.0 Hz, 1 H), 7.33 (t, *J* = 7.8 Hz, 2 H), 7.43 (dm, *J* = 7.2 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 20.4 (s), 20.9 (s), 21.9 (s), 28.1 (s), 30.1 (s), 36.0 (s), 39.5 (s), 45.9 (s), 52.7 (s), 68.3 (q), 126.6 (t), 128.1 (t), 128.2 (t), 140.8 (q), 215.9 (q). IR (film, cm^{-1}): 2939, 1732, 1494.8, 1447, 740, 699.0. HRMS (ESI^+, CH_3OH, $C_{17}H_{24}NO$ $[M + H]^+$) calcd for 258.1858, found 258.1858. Anal. Calcd for $C_{17}H_{23}NO$ (257.4): C, 79.33; H, 9.01; N, 5.44. Found C, 79.25; H, 8.95; N, 5.40.

tert-Butyl-(S)-7-oxo-1-azaspiro[5.5]undecane-1-carboxylate, (+)-**10**. To a suspension of mandelate salt (–)-**8** (0.40 g, 1.25 mmol) in acetonitrile (25 mL) were successively added 0.273 g (1.23 mmol, 1.0 equiv.) of Boc_2O and 0.88 mL (0.65 g, 5.05 mmol, 4.04 equiv.) of DIPEA. The reaction mixture was refluxed for 3 h and was poured onto 50 ml of brine. The products were extracted with 50 mL diethyl ether (x 2) and the combined organic phases were washed with water, dried over $MgSO_4$ and concentrated. The crude reaction mixture was poured on a chromatography column prepared with 20 g of silica and 4:1

dichloromethane/diethyl ether. The combined fractions were concentrated to afford 0.31 g (93%) of carbamate (+)-**10**. White solid, m.p. = 110–111 °C. R_f = 0.77 (dichloromethane/diethyl ether, 4:1). $[\alpha]^{22}_D$ = + 60.2 (*c* 0.93, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.42 (s, 9 H), 1.45–2.00 (m, 11 H), 2.25–2.42 (m, 2 H), 2.65 (ddd, *J* = 13.5, 9.1, 6.0 Hz, 1 H), 3.00 (tm, *J* = 14.0 Hz, 1 H), 3.85 (d, *J* = 13.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 18.5 (s), 21.0 (s), 24.1 (s), 26.7 (s), 28.4 (p), 29.7 (s), 33.8 (s), 39.4 (s), 41.2 (s), 65.3 (q), 80.9 (q), 156.1 (q), 209.2 (q). IR (neat, cm^{-1}): 2930, 1705, 1679, 1486, 1380, 1014. HRMS (ESI$^+$, CH_3OH, $C_{15}H_{25}NO_3Na$ [M + Na]$^+$) calcd for 290.1732, found 290.1731. Anal. Calcd for $C_{15}H_{25}NO_3$ (267.4): C, 67.38; H, 9.43; N, 5.24. Found C, 67.31; H, 9.41; N, 5.23.

*(S)-2,3,8,9,10,11-hexahydro-1H,6H-benzo[4,5]oxazolo[3,4-a]pyridin-6-one, (–)-**11***. To a solution of carbamate (+)-**10** (0.35 g, 1.31 mmol) in anhydrous acetonitrile (15 mL) were successively added 0.78 mL (0.60 g, 5.20 mmol, 4.0 equiv.) of TMEDA and 0.87 g, 2.61 mmol, 2.0 equiv.) of dichlorotriphenylphosphorane. The reaction mixture was stirred under an argon atmosphere for 4 h and was poured onto 50 ml of brine. The products were extracted with 50 mL dichloromethane (x 2) and the combined organic phases were washed with water, dried over $MgSO_4$ and concentrated. The crude reaction mixture was poured on a chromatography column prepared with 20 g of silica and 1:1 petroleum ether/diethyl ether. The combined fractions were concentrated to afford 0.19 g (75%) of oxazolidinone (–)-**11**. Colorless oil. R_f = 0.5 (petroleum ether/diethyl ether, 1:1). $[\alpha]^{22}_D$ = –202 (*c* 0.67, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.40–1.70 (m, 6 H), 1.71–1.90 (m, 3 H), 2.14–2.20 (m, 2 H), 2.27 (dt, *J* = 12.0, 3.4 Hz, 1 H), 2.86 (ddd, *J* = 15.0, 11.9, 4.0 Hz, 1 H), 3.80 (dm, *J* = 15.0 Hz, 1 H), 5.14 (t, *J* = 3.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 17.9 (s), 20.0 (s), 21.7 (s), 24.3 (s), 27.6 (s), 30.5 (s), 39.7 (s), 59.2 (q), 99.7 (t), 150.0 (q), 155.6 (q). IR (neat, cm^{-1}): 2941, 2864, 1770, 1706, 1087, 1005. HRMS (ESI$^+$, CH_3OH, $C_{11}H_{15}NO_2Na$ [M + Na]$^+$) calcd for 216.1000, found 216.1000. Anal. Calcd for $C_{11}H_{15}NO_2$ (193.2): C, 68.37; H, 7.82; N, 7.25. Found C, 68.60; H, 7.83; N, 7.25.

*(3aS,4aS,11aS)-octahydro-6H-oxireno[2",3":2',3']benzo[1',2':4,5]oxazolo[3,4-a]pyridine-6-one, (–)-**12***. To a 250 mL three necked flask, were successively added 30 mL of acetone, 15 mL of dichloromethane, a 0.05 M solution of $Na_2B_4O_7$•$10H_2O$ in water (100 mL) and 0.79 g (4.08 mmol) of oxazolidinone (–)-**11**. The resulting biphasic system was cooled to 0°C with an ice bath. A solution of Oxone (15.0 g, 24.43 mmol, 6.0 equiv.) in water (30 mL) and a solution of $Na_2B_4O_7$•$10H_2O$ (6.04 g, 15.84 mmol, 3.9 equiv.) in water (30 mL) were added separately over a 1 h period. Stirring was continued for 3 h, and 50 mL of dichloromethane were added to the reaction mixture. The organic layer was separated, washed with water, dried over $MgSO_4$ and concentrated to yield to give 0.918 g of a crude oil with was poured on a chromatography column prepared with 15 g of silica and 3:2 diethyl ether/dichloromethane. The combined fractions were concentrated to afford 0.81 g (95%) of epoxide (–)-**12**. White solid, m.p. = 96–97 °C. R_f = 0.5 (diethyl ether/dichloromethane, 3:2). $[\alpha]^{22}_D$ = –34 (*c* 1.3, C_6H_6). ^{1}H NMR (C_6D_6, 400 MHz) δ = 0.54 (tdd, *J* = 12.9, 3.8, 1.6 Hz, 1 H), 0.69–1.16 (m, 7 H), 1.29–1.47 (m, 4 H), 2.26 (ddd, *J* = 14.0, 12.5, 3.2 Hz, 1 H), 3.08 (t, *J* = 1.5 Hz, 1 H), 3.78 (dm, *J* = 14.0 Hz, 1 H). ^{13}C NMR (C_6D_6, 100 MHz) δ = 14.7 (s), 18.8 (s), 23.8 (s), 24.0 (s), 25.8 (s), 27.3 (s), 38.7 (s), 56.2 (q), 57.2 (t), 88.1 (q), 153.6 (q). IR (neat, cm^{-1}): 2930, 1762, 1747, 1000, 754. HRMS (ESI$^+$, CH_3OH, $C_{11}H_{15}NO_3Na$ [M + Na]$^+$) calcd for 232.0949, found 232.0949. Anal. Calcd for $C_{11}H_{15}NO_3$ (209.2): C, 63.14; H, 7.23; N, 6.69. Found C, 63.00; H, 7.21; N, 6.65.

*(4R,4aS,11aR)-4a-fluoro-4-hydroxyoctahydro-1H,6H-benzo[4,5]oxazolo[3,4-a]pyridin-6-one, (+)-**13***. An oven dried, 100-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, was flushed with argon and was charged with 30 mL of dry Et_2O and 0.30 g (1.43 mmol) of epoxide (–)-**12**. The solution was cooled to 0 °C and 0.85 mL [0.98 g, 3.20 mmol (46.5% BF_3 basis), 2.24 equiv.] of freshly distilled BF_3•Et_2O were slowly added to the previous solution. Stirring was continued for 1 h and the reaction mixture was poured onto a biphasic system constituted by 50 mL of Et_2O and 50 mL of a 0.05 M ammonium chloride–ammonium hydroxide buffer. The organic layer was separated, washed with water, dried over $MgSO_4$ and concentrated to yield to give 0.250 g of a crude residue with was poured on a chromatography column prepared with 15 g of silica and 7:3 diethyl ether/petroleum ether. The combined fractions were concentrated to afford 0.245 g (75%) of *syn*-fluorohydrin-(+)-**13**. White solid, m.p. = 113–114 °C. R_f = 0.25 (diethyl ether/ petroleum ether, 7:3). $[\alpha]^{22}_D$ = +49 (*c* 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.20–1.32 (m, 1 H), 1.37–1.64 (m, 3 H), 1.66–1.94 (m, 6 H), 1.96–2.03 (m, 1 H), 2.32–2.40 (m, 2 H), 2.90 (td, *J* = 12.9, 3.5 Hz, 1 H), 3.75 (dt, *J* = 12.9, 1.4 Hz, 1 H), 4.25–4.29 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 14.3 (s), 19.0 (s), 23.7 (s), 25.6 [d, $^3J_{CF}$ = 8.8 Hz), (s)], 28.5 [(d, $^3J_{CF}$ = 4.7 Hz), (s)], 31.5 [(d, $^3J_{CF}$ = 4.5 Hz), (s)], 38.1 (s), 61.5 [d, $^2J_{CF}$ = 22.8 Hz), (q)], 67.5 [d, $^2J_{CF}$ = 24.9 Hz, (q)], 113.5 [d, $^1J_{CF}$ = 240.0 Hz, (q)], 152.9 (q). IR (neat, cm^{-1}): 3450, 2950, 2872, 1752, 1415, 937. HRMS (ESI$^+$, CH_3OH, $C_{11}H_{16}NO_3FNa$ [M + Na]$^+$) calcd for 252.10112, found 252.1008. Anal. Calcd for $C_{11}H_{16}FNO_3$ (229.2): C, 57.63; H, 7.04; N, 6.11. Found C, 57.60; H, 7.05; N, 6.00.

*(4R,4aR,11aR)-4a-butyl-4-hydroxy-octahydro-1H,6H-benzo[4,5]oxazolo[3,4-a]pyridin-6-one, (+)-**14***. An oven dried, 100-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, was flushed with argon and was successively charged with 20 mL of dry THF, 0.27 g (1.17 mmol) of *syn*-fluorohydrin-(+)-**13** and 8 mg (0.05 equiv.) of $CuCl_2$. The solution was cooled to 0 °C and 1.70 mL (3.40 mmol, 2.0 equiv.) of a 2 M solution of BuMgCl in THF were slowly added. Stirring was continued for 2 h at room temperature and the reaction mixture was poured onto 50 mL a 5% aqueous ammonium hydroxide solution and 100 mL of a mixture of diethyl ether and dichloromethane (9:1). The organic layer was separated, washed with water, dried over $MgSO_4$ and concentrated to yield to give a crude residue with was poured on a chromatography column prepared with 15 g of silica and 4:1 pentane/acetone. The combined fractions were concentrated to afford 0.30 g (96%) of (+)-**14**. Colorless oil. R_f = 0.5 (pentane/acetone, 4:1). $[\alpha]^{22}_D$ = +5 (*c* 0.54, $CHCl_3$). ^{1}H NMR ($CHCl_3$, 400 MHz) δ = 0.92 (t, *J* = 7.0 Hz, 3 H), 1.24–1.84 (m, 17 H), 2.11 (dm, *J* = 12.3 Hz, 1 H), 2.26 (dm, *J* = 12.3 Hz, 1 H), 2.81–2.90 (m, 1 H), 3.87 (s, 1 H), 3.73 (dd, *J* = 13.5, 4 Hz, 1 H). ^{13}C NMR ($CHCl_3$, 100 MHz) δ = 14.0 (p), 18.9 (s), 20.3 (s), 23.1 (s), 23.6 (s), 25.1 (s), 26.7 (s), 30.3 (s), 35.5 (s), 40.6 (s), 40.8 (s), 63.2 (q), 72.2 (q), 86.3 (t), 159.3 (q). IR (neat, cm^{-1}): 3421, 2943, 1748, 1277, 1011. HRMS (ESI$^+$, CH_3OH, $C_{15}H_{25}NO_3Na$ [M + Na]$^+$) calcd for 290.1732, found 290.1735. Anal. Calcd for $C_{15}H_{25}NO_3$ (267.3): C, 67.38; H, 9.42; N, 5.24. Found C, 67.60; H, 9.41; N, 5.24.

*(4a,4aR,11aR)-4a-butyl-4-(methoxymethoxy)octahydro-1H,6H-benzo[4,5]oxazolo[3,4-a]pyridine-6-one, (+)-**15***. An oven dried, 100-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, was flushed with argon and was successively charged with 20 mL of dry THF, 0.30 g (1.12 mmol) of oxazolidinone-(+)-**14**, and 16 mg (0.1 equiv.) of NaI. The solution was cooled to 0 °C, and 0.22 g (4.9 equiv.) of NaH (60% in mineral oil) were slowly added followed by the addition of 0.34 mL (0.36 g, 4.47 mmol, 4.0 equiv.) of MOMCl. Stirring was continued for 16 h at room temperature and the reaction mixture was poured onto a 1:1 water/diethyl ether biphasic system (50 mL). The organic layer was separated, washed with water, dried over $MgSO_4$ and concentrated to yield to give a crude residue with was poured on a chromatography column prepared with 15 g of silica and 7:3 petroleum ether/diethyl ether. The combined fractions were concentrated to afford 0.29 g (83%) of (+)-**15**. Colorless oil. R_f = 0.5 (petroleum ether/diethyl ether, 7:3). $[\alpha]^{22}_D$ = +26 (*c* 0.78, $CHCl_3$). ^{1}H NMR ($CHCl_3$, 400 MHz) δ = 0.93 (t, *J* = 7.0 Hz, 3 H), 1.26–1.90 (m, 15 H), 1.95 (dm, *J* = 14.3 Hz, 1 H), 2.07 (dm, *J* = 10.7 Hz, 1 H), 2.26 (dt, *J* = 12.5, 2.8 Hz, 1 H), 2.80–2.90 (m, 1 H), 3.38 (s, 3 H), 3.70 (s, 1 H), 3.74 (dd, *J* = 13.6,

4.0 Hz, 1 H), 4.58 (d, J_{AB} = 7.0 Hz, 1 H), 4.99 (d, J_{AB} = 7.0 Hz, 1 H). ^{13}C NMR ($CHCl_3$, 100 MHz) δ = 14.0 (p), 18.8 (s), 20.3 (s), 23.2 (s), 23.7 (s), 25.5 (s), 26.6 (s), 30.5 (s), 34.6 (s), 35.8 (s), 40.7 (s), 55.8 (t), 63.1 (q), 86.8 (t), 92.2 (s), 159.0 (q). IR (neat, cm^{-1}): 2940, 1750, 1280, 998. HRMS (ESI$^+$, CH_3OH, $C_{17}H_{29}NO_4Na$ [M + Na]$^+$) calcd for 334.1994, found 334.1989. Anal. Calcd for $C_{17}H_{29}NO_4$ (311.4): C, 65.57; H, 9.39; N, 4.50. Found C, 65.78; H, 9.35; N, 4.48.

Single Crystal X-ray Analysis of Collection and Refinement Results of derivatives.

The structures were solved by direct methods with SIR-97,[37] 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[38] with the aid of the WINGX program.[39] All non-hydrogen atoms were refined with anisotropic thermal parameters. H atoms were finally included in their calculated positions. CCDC-1849125 [(+)-**4**], CCDC-1849126 [(–)-**12**], CCDC-1849127 [(+)-**13**], contain 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

Crystal data, X-ray data collection and refinement results of derivative (+)-4: $C_{19}H_{25}N_3$, M = 295.42, orthorhombic, space group $P2_1$, $P2_1$, $P2_1$, a = 8.6755(3), b = 9.1517(3), c = 22.2914(7) Å, α = 90°, β = 90°, γ = 90°, V = 1769.84(10) Å^{-3}, Z = 4, D_x = 1.109 Mg m^{-3}, μ = 0.66 cm^{-1}, λ (Mo–$K\alpha$) = 0.71073 Å, F(000) = 640, T = 293(2) K. The sample (0.12×0.10×0.04 mm) was studied on a diffractometer with graphite monochromatized Mo–$K\alpha$ radiation. The data collection (Θ_{max} = 26.018°, range of *HKL* : H –10→10, K –11→11, L –27→27) gave 6226 reflections with 3472 unique reflections from which 2621 with $I > 2.0\sigma(I)$.

Crystal data, X-ray data collection and refinement results of derivative (–)-12: $C_{11}H_{15}NO_3$, M = 209.24, monoclinic, space group $P2_1$, a = 8.6960(9), b = 6.4354(8), c = 9.48(10) Å, α = 90°, β = 101.882°, γ = 90°, V = 519.16(10) Å^{-3}, Z = 2, D_x = 1.339 Mg m^{-3}, μ = 0.97 cm^{-1}, λ (Mo–$K\alpha$) = 0.71073 Å, F(000) = 224, T = 150(2) K. The sample (0.58×0.36×0.21 mm) was studied on a diffractometer with graphite monochromatized Mo–$K\alpha$ radiation. The data collection (Θ_{max} = 27.479°, range of *HKL*: H –10→11, K –8→8, L –12→11) gave 4505 reflections with 1275 unique reflections from which 1232 with $I > 2.0\sigma(I)$.

Crystal data, X-ray data collection and refinement results of derivative (+)-13: $C_{11}H_{16}FNO_3$, M = 229.25, orthorhombic, space group $P2_1$, $P2_1$, $P2_1$, a = 9.1060(14), b = 9.5383(17), c = 12.1808(15) Å, α = 90°, β = 90°, γ = 90°, V = 1058.0(3) Å^{-3}, Z = 4, D_x = 1.439 Mg m^{-3}, μ = 1.15 cm^{-1}, λ (Mo–$K\alpha$) = 0.71073 Å, F(000) = 488, T = 150(2) K. The sample (0.58×0.54×0.34 mm) was studied on a diffractometer with graphite monochromatized Mo–$K\alpha$ radiation. The data collection (Θ_{max} = 27.450°, range of *HKL* : H –11→8, K –8→11, L –15→11) gave 4518 reflections with 1384 unique reflections from which 1262 with $I > 2.0\sigma(I)$.

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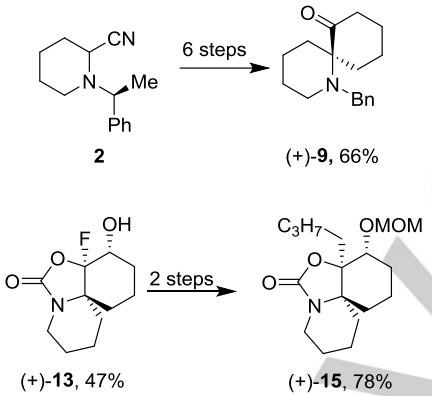
FULL PAPER

The stereoselective synthesis of spiropiperidone (+)-**9**, a known intermediate to PHTX, has been achieved in an overall 66% yield from **2**. The introduction of the future C7 butyl chain of the title alkaloid has been achieved by condensing the fluorohydrin (+)-**13** with the corresponding Grignard reagent.



2 (+)-**9,** 66%

(+)-**13**, 47% (+)-**15**, 78%

Alkaloid Synthesis

*Van Ha Vu, Thierry Roisnel, Stéphane Golhen, Christelle Bouvry, Jean-Pierre Hurvois **

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Formal Synthesis of (–)-Perhydrohistrionicotoxin Using a Thorpe-Ziegler Cyclization Approach. Synthesis of Functionalized Aza-Spirocycles.