Published in final edited form as:
European J Org Chem. 2013 May 1; 2013(15): . doi:10.1002/ejoc.201300200.

Total synthesis of (+)-antofine and (-)-cryptopleurine

Weijiang Ying and **James W. Herndon**
Department of Chemistry and Biochemistry, New Mexico State University, MSC 3C, Las Cruces, NM 88003 USA

James W. Herndon: jherndon@nmsu.edu

Abstract

The tylophorine alkaloid anticancer compounds antofine and cryptopleurine have been synthesized in optically active form. Both syntheses employ optically pure α-amino acids as the starting materials, require only seven steps from known 2-ethynylpyrrolidine or 2-ethynylpiperidine derivatives, and are free of protecting groups. Key steps include an alkyne hydration and a chromium carbene complex based net [5+5]-cycloaddition step. Alkyne hydration was accompanied by racemization of the resulting β-aminoketone under most of the conditions examined, and successful minimization of this side reaction was achieved through careful pH control and choice of metal additive. Final ring closure involves a Bischler-Napieralski reaction using a carbamate (antofine) or urea (cryptopleurine) precursor.

Keywords

Alkynes; Carbene Ligands; Chromium; Cycloaddition; Racemization; Hydration

Introduction

Antofine (**1**, Scheme 1) and cryptopleurine (**2**), members of the tylophorine class of alkaloids, are among the most potent known cytotoxic agents,[1] and exhibit low nanomolar levels of *in vitro* activity against a wide variety of tumor cell lines. These compounds display additional activities against numerous unrelated maladies, including antiviral,[2] antibacterial,[3] and anti-inflammatory.[4] The tylophorine alkaloids have been the focus of a great deal of synthetic activity.[5] Despite their tremendous potency, they have not been used clinically due to their toxicity.[6] Since antofine and cryptopleurine show nanomolar levels of activity against a variety of cell lines, they could potentially be effective anticancer agents if the neurotoxicity issue can be overcome. There has thus been tremendous interest by various research groups in the production of analogs that show higher polarity and thus lesser ability to penetrate the blood-brain barrier.[1]

Successful development of anticancer agents based on these structures requires a flexible total synthesis amenable to variation at multiple positions. Several successful total syntheses of these compounds have been reported.[5] Early total syntheses of antofine and crytopleurine were racemic however several asymmetric synthetic routes have recently been reported. Most total syntheses target intermediate amines **4a/b** followed by Pictet-Spengler condensation with formaldehyde / HCl to form the D ring as the final step. Common approaches to antofine employ either formation of the C-ring from a cis stilbene precursor or

Correspondence to: James W. Herndon, jherndon@nmsu.edu.

Supporting Information. Complete experimental procedures for known starting materials **10a-d**, failed synthetic routes from **11b** and **11c**, and photocopies of ^{1}H and ^{13}C NMR spectra for compounds in the successful synthetic routes from **11a, 11b**, and **11d**.

connection of an E-ring intact species to a phenanthrene derivative, or a combination of these events. [7, 8, 9, 10, 11, 12, 13] Other strategies include a pyridine-based strategy[14] and a cyclohexadienone photorearrangement approach.[15] Enantioselective approaches are less common[9b] and include attachment of an unnatural proline derivative to an intact phenanthrene[16] or attachment to an ethynylbiphenyl that undergoes platinum-catalyzed cyclization,[17] formation from a seco (no C ring) antofine derivative through diaryl cyclization,[18] and enantioselective construction of the E-ring through alkene metathesis[19] or 1,3-dipolar cycloaddition.[20] Some antofine syntheses also result in cryptopleurine using a synthetic route analogous to that employed for antofine.[10, 17, 19d, 20] Additional total syntheses of cryptopleurine include the annulation of the D and E rings onto a phenanthrene for racemic[21] and optically pure[22] cryptopleurine, and an enantioselective route employing chiral hydrazine methodology.[23] Preparation of cyptopleurine from the seco (no C-ring) analog julandine or the corresponding amide has also been reported.[24]

A somewhat unconventional synthesis was recently reported by this research group, which involves construction of the B and C rings in a single step (Scheme 2).[25] This synthesis employs the coupling of an alkyne ketone (**5a**) and a γ,δ-unsaturated carbene complex (**6**) in a net [5+5]-cycloaddition process.[26] This synthetic route entails far different disconnections than previous syntheses. The six carbons of the B-ring derive from two distinct entities, and thus this synthesis is especially ideal for preparation of B-ring analogs through variation in the structure of the alkyne group or the carbene complex.[27] This synthesis was incredibly short but racemic. Attempted synthesis of optically pure antofine was thwarted by difficulties joining the aromatic ring core to a proline-derived entity. Tactics based on carbonyl anion chemistry or additions to either homoproline nitrile or Weinreb amide derivatives were unsuccessful. If starting compound **5a** could be prepared in optically pure form, a total synthesis of optically pure antofine could result since none of the subsequent steps touch the lone chiral center. In this manuscript, a successful union of a proline-derived entity with an A-ring precursor to afford alkyne-ketone **5a** followed by subsequent transformation to (+)-antofine (unnatural enantiomer) is reported. This method is further utilized in an enantioselective total synthesis of the structurally related natural product (-)-cryptopleurine (natural enantiomer).

Results and Discussion

In response to failed attempts to prepare β-amino ketone derivative **5a** in optically pure form noted in the previous publication,[25] an additional idea for the preparation of compounds of general structure **5** was explored (Scheme 3). This alternate procedure entails Sonogashira coupling of 2-ethynyl-*N*-heterocycle derivatives with known dihaloveratrole derivative **9**,[17] followed by alkyne hydration and a second Sonogashira coupling with trimethylsilylacetylene. These derivatives will then serve as precursors to antofine according to the previous synthetic route in Scheme 2 when n =1, Y = COOMe and homologues where n = 2 can potentially serve as precursors to cryptopleurine. Since preparation of cryptopleurine from **5** (n = 2) had not been previously reported, a variety of nitrogen groups (Y) were examined (see subsequent schemes for definition of Y groups.

Preparation of enantiomerically pure 2-ethynylpyrrolidine derivatives from proline has ample precedent.[28] The natural enantiomer of proline was employed for the synthesis of alkynylproline **10a** (Scheme 4), thus targeting (+)-antofine, the unnatural enantiomer of antofine. The synthesis of cryptopleurine employs a known resolution procedure for pipecolic acid[29] followed by transformation to the ethynyl derivatives **10b-d**. This synthesis targets (-)-cryptopleurine, the natural enantiomer. Syntheses of **10b-d** from proline or pipecolic acid using literature procedures are included in the Supporting Information. The

first Sonogashira coupling step involving 4-bromo-5-iodoveratrole (**9**) and all of the 2-ethnynylheterocycles **10** depicted in Scheme 4 proceeded in high yield.

The critical event in the synthesis is the alkyne hydration of bromo-alkyne derivatives **11a-d** (see Table 1 and Scheme 5). Mercury-mediated alkyne hydration of a propargylic amine derivatives is reported to proceed without racemization, however only the rotation value and not the ee was reported.[30] Additional examples contain multiple stereocenters and the apparent retention of stereochemistry may thus reflect thermodynamic preferences rather than true retention of configuration.[31] Racemization can occur through either a reversible β-elimination process[32] or reversible Mannich reaction under the acidic conditions typically employed for alkyne hydration. Regiochemistry is expected to favor **12** over **13** due to the electron rich nature of the benzene ring.

Alkyne hydration of **11a-d** was examined under a variety of conditions (Table 1 and Scheme 5) in order to optimize the formation of regioisomer **12** and maximize the retention of optical purity. The five-membered ring system **11a** that would ultimately lead to antofine was examined initially. Under the standard conditions for alkyne hydration involving catalytic mercuric acetate in aqueous acetic acid and formic acid the reaction was poorly regioselective affording substantial amounts of undesired regioisomer **13a** and proceeded largely with racemization of the chiral center (entry 1). The unexpected poor regioselectivity was attributed to neighboring group participation by the carbonyl oxygen of the carbomethoxy group. To overcome this intramolecular process the concentration of water was increased and this led to a dramatic improvement in regioselectivity (entry 2). Use of mercuric acetate required excessive reaction times and this was likely contributing to the racemization problems in entries 1 and 2. Use of the more reactive mercuric trifluoroacetate led to substantial decreases in reaction time and racemization (entries 3-5). There is still racemization to some extent, which was attributed to the highly acidic solution that was generated as the reaction progressed. Increasing the amount of mercuric oxide and adding sodium bicarbonate at the end of the reaction eliminated the racemization process (entry 6). Use of ruthenium[33] and gold-catalyzed[34] alkyne hydration procedures were ineffective (entries 7 and 8). Although mercury is not “green”,[35] it is easily removed from the system through precipitation as mercuric sulfide, which has no solubility in any solvent except aqueous strong acids.

The six-membered ring systems that would ultimately lead to cryptopleurine were examined next. Homologous carbamate derivative **11b** was far more prone to racemization during alkyne hydration (entries 9-12). Even under the optimal conditions established for five-membered ring systems, the carbamate derivative **11b** afforded the desired ketone **12b** with significant racemization (entry 9). Use of a more active gold catalyst led to the desired ketone in high yield in largely racemized form (entry 12) however this catalyst system was only effective when conducted in refluxing dioxane. Systems that would render the nitrogen a poorer leaving group were next examined (entries 13-17). The benzylamine derivative **11c** afforded a low yield of the alkyne hydration product **12c** accompanied by the retro-Mannich product **14** (entry 13). Use of a urea protecting group was more promising (entries 14-17). The phenothiazine urea was chosen because of the anticipated ease of removal using an oxidative procedure.[36] In all cases using mercuric trifluoroacetate-mediated alkyne hydration, the regioselectivity was 6:1 and racemization was undetectable when the reaction was conducted at 0 °C (entries 15,16). The gold-catalyst afforded the desired product **12d** in low yield accompanied by a moderate degree of racemization.

The enantiomeric excesses of the products in Table 1 were assessed through a combination of specific rotation and NMR studies of adducts **16** (Scheme 6) obtained through Sonogashira coupling of optically pure alkyne derivative **15** with ketones **12a** or **12d** of

varying enantiomeric purity. Significant differences were noted in both the ^{1}H NMR and ^{13}C NMR spectra for the diastereomers of adduct **16a**. The diastereomers of adduct **16d** exhibited minimal differences in the ^{1}H NMR (only the aromatic H depicted as H_A was clearly separated in the two diastereomers) however several differences were noted in ^{13}C NMR spectra (see Supporting Information). In addition, the ketones **12a** obtained from entries 1 and 10 were converted to antofine (see ahead) and the optical rotation of **12a** was calculated based on comparison of the observed rotation of the synthesized antofine with that reported for the final natural product. Similarly the ketone **12b** from entry 9 and ketone **12d** from entry 16 were converted to cryptopleurine and their optical rotation was calculated based on comparison of the synthesized crypropleurine with that reported for the natural product. The diastereomeric ratios from the NMR spectra of **16a** and **16d** were in good agreement with the ee values calculated through optical rotation of **12a** and **12d** respectively.

Completion of the total synthesis of (+)-antofine

The completion of the total synthesis of antofine is depicted in Scheme 7 and involves transformation of bromoketone-carbamate **12a** to the corresponding silylethynyl derivative **5a**, followed a similar series of reactions employed in the racemic synthesis (Scheme 2). In this investigation, the carbene complex-alkyne coupling afforded a mixture of silylated and desilylated versions of **7a**, whereas in the previous racemic synthesis only the desilylated material was observed. This difficulty can likely be attributed to the different brands of silica gel used in the chromatographic purification, and the latest batch is of insufficient acidity to cause complete desilylation. The crude partially silylated mixture from the alkyne-carbene complex coupling was subjected to the dehydrogenation procedure previously employed, and only the desilylated phenanthrene derivative **17a** was obtained after chromatographic purification. Presumably, the bulky trimethylsilyl group is less stable in the bay region of the phenanthrene ring, and is more easily protiodesilylated. Bischler-Napieralski cyclization followed by amide reduction afforded (+)-antofine (**1**). The observed rotation when starting with the **12a** from entry 6 was +93°, which agrees with the literature rotation values for this compound (+85°)[16] and (+111°).[18a]

Completion of the total synthesis of scalemic (-)-cryptopleurine via the carbomethoxy route

The completion of the total synthesis of (-)-cryptopleurine (Scheme 8) involves the same series of steps as reported for antofine employing bromoketone-carbamate **12b** produced in entry 9 of Table 1. After the final step, the observed rotation for the cryptopleurine was -74°, which suggests an ee of 69% based on the reported value of -109°.[19b]

Completion of the total synthesis of (-)-cryptopleurine via the urea route

Completion of the total synthesis of cryptopleurine from urea-ketone **12d** (Scheme 9) involves a similar series of steps as reported for antofine employing bromoketone urea derivative **12d** produced in entries 15/16 of Table 1. The initial plan for the conversion of phenanthrene-urea **17d** to cryptopleurine was to remove the urea group from phenanthrene **8d** to afford free amine **4b** (Scheme 1) and claim a formal total synthesis.[19b, 21a] The phenothiazine group was chosen because of the ability to undergo oxidative hydrolysis under relatively mild oxidative conditions.[36] This process however never proceeded in acceptable yield. The Bischler-Napieralski reaction was attempted using the urea derivative directly. Using conditions that are identical to that used for the carbamate, cyclization was quite facile, resulting in compound **8d**. Bischler-Napieralski reactions employing ureas have very limited precedent and requires super acid and high temperatures.[37] After the final step,

the observed rotation for the cryptopleurine was -103° which is in agreement with the literature values reported for this compound of -108.7° [19b] and -87.2°.[21a]

Conclusions

In conclusion, the synthesis of optically pure antofine and cryptopleurine from readily-available optically pure starting materials has been accomplished. Key steps include alkyne hydration, a chromium carbene complex mediated net [5+5]-cycloaddition process, and an unusual Bischler-Napieralski cyclization reaction that employs a urea starting material to construct an amide. These latter steps afford the final natural products in only two chromatographic separation processes. The alkyne hydration process was especially difficult in that competing racemization occurred, however through careful control of the acidity, conditions were developed that eliminate competing racemization.

Experimental

General Experimental

Nuclear Magnetic Resonance (^{1}H and ^{13}C) spectra were recorded on a Varian 300 MHz spectrometer. Chemical shifts are reported in parts per million (δ) downfield from the reference tetramethylsilane. Coupling constants (*J*) are reported in hertz (Hz). The following symbols have been used to indicate multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). A Perkin-Elmer 1720X spectrometer was used to record the infrared spectra and band positions are reported in reciprocal centimeters (cm^{-1}). Only key diagnostic bands are reported, C-H stretching frequencies in the region 2800-3100 cm^{-1} are not reported. Mass spectra (MS) were obtained at the University of California at Riverside. Flash column chromatography was performed using thick walled glass columns and “flash grade” silica. Thin layer chromatography was done using precoated 0.25mm silica gel plates purchased from Sorbtech. The relative proportion of solvents in mixed chromatography solvents refers to the volume: volume ratio. All commercially available reagents were purchased in reagent grade and used without purification. THF and dioxane were distilled from sodium benzophenone ketyl. All reactions were performed in an inert atmosphere created by a slight positive pressure (ca. 0.1 psi) of nitrogen.

Preparation of (+)-N-carbomethoxy-2-ethynylpyrrolidine (10a)

A mixture of *t*-Boc-protected ethynylproline (1 eq, 1.018 g, 5.214 mmol), 12.5M aqueous HCl (3 eq, 1.35 mL, 15.6 mmol), and diethyl ether (20 mL) was vigorously stirred overnight at 0 °C, and then refluxed for 1-2 h before removal of solvent on a rotary evaporator. After azeotropic drying using toluene (3× 10 mL), anhydrous methanol (20 mL) was added, and the solution was cooled to 0 °C. Potassium carbonate (2.2 eq, 1.585 g, 11.47 mmol) and methyl chloroformate (1.2 eq, 0.483 mL, 591 mg, 6.257 mmol) were then added. The reaction was stirred for 9 h at room temperature before removal of solvent on a rotary evaporator. After water (30 mL) was added, the mixture was extracted with diethyl ether (3× 30 mL). The combined organic layer was washed (brine), dried over sodium sulfate, and concentrated on a rotary evaporator. The residue was purified by silica gel flash chromatography (hexanes/ethyl acetate 5:1) to give colorless oil (777 mg, 97%) identified as alkyne-carbamate **10a**. $[\alpha]_D^{20}$ = -138.1 ($CHCl_3$, c =1.45). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.65-4.40 (m, 1H, R_2CH-N), 3.73 (s, 3H, OCH_3), 3.60-3.20 (m, 2H, RCH_2-N), 2.26 (s, 1H, ≡C*H*), 2.20-1.65 (m, 4H, R-CH_2CH_2-R); ^{13}C NMR (75 MHz, $CDCl_3$, rotamer peaks in parenthesis): δ 155.1, 83.8, 70.1, 52.5, 48.3 (47.8), 46.0 (45.7), 32.9 (33.8), 24.4 (23.5); IR (neat): 3287, 3246, 2983, 2956, 2880, 1702, 1451, 1384, 1195, 1122 cm^{-1}; HRMS: calcd for $C_8H_{12}NO_2$ $[MH]^+$ 154.0863, found 154.0864.

Preparation of alkynylproline 11a via Sonogashira coupling of (+)-*N*-carbomethoxy-2-ethynylpyrrolidine (10a) with 1-bromo-2-iodo-4,5-dimethoxybenzene (9)

A solution of terminal alkyne **10a** (1.5 eq, 491 mg, 3.205 mmol) in diisopropylamine (6 mL) was added to a mixture of iodide **9** (1 eq, 733 mg, 2.137 mmol), $Pd(PPh_3)_4$ (0.05 eq, 123.5 mg, 0.107 mmol), and copper(I) iodide (0.10 eq, 40.7 mg, 0.214 mmol) in diisopropylamine (4 mL) dropwise via several portions over 3-5 h. The reaction mixture was stirred for another 1-3 h, diluted with diethyl ether, filtered through a short pad of silica gel, and washed with diethyl ether. After concentration on a rotary evaporator, the residue was purified by silica gel flash chromatography (5:1 to 2:1 hexanes/ethyl acetate) to give a pale yellow semisolid (771 mg, 98%) identified as arylalkyne **11a**. $[\alpha]_D^{20}$ = -144.7 ($CHCl_3$, c = 1.98). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.99 (s, 1H, Ar-*H*), 6.95-6.82 (m, 1H, Ar-*H*), 4.90-4.65 (m, 1H, R_2CH-N), 3.86 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.75 (br s, 3H, $COOCH_3$), 3.65-3.25 (m, 2H, RCH_2-N), 2.40-1.90 (m, 4H, R-CH_2CH_2-R); ^{13}C NMR (75 MHz, $CDCl_3$, rotamer peaks in parentheses): δ 155.1, 149.6 (149.6), 147.9, 116.9 (116.7), 115.3, 115.1, 114.9, 92.3, 80.8, 56.1(2C), 52.5, 48.8 (49.2), 46.0 (45.6), 34.0 (33.2), 23.6 (24.5); IR (neat): 3084, 2954, 2842, 1704, 1699, 1596, 1506, 1447, 1385, 1326, 1262, 1223, 1209, 1172, 1120, 1093, 1030 cm^{-1}; HRMS: calcd for $C_{16}H_{19}NO_4Br$ $[MH]^+$ 368.0492, found 368.0500.

Preparation of bromo-ketone 12a via hydration of alkyne 11a

To a solution of arylacetylene **11a** (1 eq, 647 mg, 1.757 mmol) in wet THF (THF/H_2O = 40:1, 71.6 mL THF, 1.79 mL H_2O) at room temperature (or 0 °C), were added red mercuric oxide (1 eq, 1.2 g, 5.537 mmol) and mercuric trifluoroacetate (1.6 eq, 1.199 g, 2.811 mmol). After stirring for 1-3 h, the reaction was quenched with H_2S gas (made from HCl and FeS) at 0 °C for 10 min followed by addition of saturated $NaHCO_3$ solution (10 mL). After filtration (Celite), the aqueous phase was extracted with ether (3× 20 mL). The combined organic layer was washed with water and brine, dried over sodium sulfate, and concentrated on a rotary evaporator. The residue was purified by silica gel flash chromatography (3:1 to 2:1 hexanes/ethyl acetate) to give pale yellow oil (670 mg, 98%) identified as bromo-ketone **12a**. $[\alpha]_D^{20}$ = - 42.7 ($CHCl_3$, c =3.91). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (s, 1H, Ar-*H*, ortho to C=O), 7.03 (s, 1H, Ar-*H*, ortho to Br), 4.40-4.22 (m, 1H, R_2CH-N), 3.90 (s, 6H, 2 × OCH_3), 3.66 (s, 3H, $COOCH_3$), 3.51-3.27 (m, 2H, RCH_2-N), 3.15-2.80 (m, 2H, $C(=O)CH_2$-R), 2.19-1.98 (m, 1H, R-CH_2CH_2-R), 1.97-1.68 (m, 3H, R-CH_2CH_2-R); ^{13}C NMR (75 MHz, $CDCl_3$, rotamer peaks in parenthesis): δ 200.1, 155.3, 154.1 (151.5), 148.1 (148.5), 131.9 (132.2), 116.5 (116.5), 112.6 (112.3), 111.1 (111.3), 56.2 (2C), 54.7 (53.9), 52.1 (52.3), 46.3 (46.8), 45.9 (46.7), 30.6 (31.6), 23.6 (22.9); IR (neat): 3084, 2955, 2879, 1694, 1593, 1507, 1451, 1384, 1260, 1168 cm^{-1}; HRMS: calcd for $C_{16}H_{21}NO_5Br$ $[MH]^+$ 386.0598, found 386.0609.

Preparation of alkyne-carbamate-ketone 5a through Sonogashira coupling of bromo-ketone 12a and trimethylsilylacetylene

A solution of trimethylsilylacetylene (5 eq, 0.472 mL, 325 mg, 3.313 mmol) in diisopropylamine (3 mL) was added to a mixture of bromo-ketone **12a** (1 eq, 256 mg, 0.663 mmol), bis(triphenylphosphine)palladium(II) chloride (0.1 eq, 46.5 mg, 0.0663 mmol), copper(I) iodide (0.04 eq, 5.1 mg, 0.0265 mmol), and triphenylphosphine (0.2 equiv, 34.8 mg, 0.131 mmol) in diisopropylamine (2 mL) at 70 °C under as argon atmosphere via several portions over 3-5 h. The reaction was stirred for another 2-5 h at 70 °C and then diluted with diethyl ether and filtered through a short pad of silica gel. After concentration on a rotary evaporator, the residue was purified by silica gel flash chromatography (3:1 hexanes/ethyl acetate) to give pale yellow oil (266 mg, 99%) identified as alkyne-carbamate-ketone **5a**. $[\alpha]_D^{20}$ = - 90.9 ($CHCl_3$, c =2.28). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (nearly

coalescing singlets,[38] 1H, Ar-*H*, ortho to C=O), 6.97 (s, 1H, Ar-*H*, ortho to alkyne), 4.39 (m, 1H, R_2CH-N), 3.94 (s, 6H, 2 × OCH_3), 3.60 (s, 3H, $COOCH_3$), 3.20-3.57 (m, 4H), 2.20 (m, 1H, R-CH_2CH_2-R), 1.70-1.93 (m, 3H, R-CH_2CH_2-R), 0.25 [s, 9H, $Si(CH_3)_3$]. The spectral data were in agreement with those previously reported for the racemic compound.[25]

Preparation of phenanthrene 17a through coupling of alkyne 5a and carbene complex 6 followed by dehydrogenation

A solution of carbene complex **6** (1.2 eq, 271 mg, 0.934 mmol) in dioxane (7.8 mL) was added to a solution of keto-alkyne **5a** (1 eq, 314 mg, 0.778 mmol) in anhydrous dioxane (7.8 mL) at 100 °C under nitrogen atmosphere over 50 min. The reaction was refluxed for 23 h and then allowed to cool to room temperature and diluted with diethyl ether. After filtration over a short pad of silica gel and concentration on a rotary evaporator a yellow oil was obtained which was used directly in the next step without further purification.[39] The residue after evaporation was dissolved in xylene (7.8 mL) and 10% palladium on carbon (0.25 eq, 207 mg, 0.195 mmol) was added. The reaction mixture was refluxed for 2 days and then filtered through Celite and concentrated on a rotary evaporator. The residue was purified by silica gel flash chromatography (4:1 to 3:1 hexanes/ethyl acetate) to give a pale yellow solid (211 mg, 66% over two steps) identified as phenanthrene **17a**. $[\alpha]_D^{20}$ = +88.0 ($CHCl_3$, c = 3.26). m.p. 179-181 °C. ^{1}H NMR (300 MHz, $CDCl_3$, rotamer peaks in brackets): δ 8.19 (br s, 1H, Ar-*H*, C ring), [7.64 (br s, 1H)], 7.93 (br s, 1H, Ar-*H*, bay region of A ring), 7.86 (d, *J* = 2.4 Hz, 1H, Ar-*H*, bay region of B ring), 7.74 (d, *J* = 8.7 Hz, 1H, Ar-*H*, B ring, *m* to OMe), 7.40 (s, 1H, Ar-*H*, non-bay region of A ring), 7.19 (dd, *J* = 1.8, 8.7 Hz, 1H, Ar-*H*, B ring *o* to OMe), 4.45-4.30 (m, 1H, R_2CH-N), 4.23 (br s, 3H, OCH_3), 4.13 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 3.78 (br s, 3H, $COOCH_3$), 3.65-3.47 (m, 1H, RCH_2-N), 3.46-3.30 (m, 1H, RCH_2-N), 2.83-2.56 (m, 2H, $ArCH_2$-R), 2.15-1.95 (m, 1H, R-CH_2CH_2-R), 1.93-1.77 (m, 2H, R-CH_2CH_2-R), 1.76-1.55 (m, 1H, R-CH_2CH_2-R); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.9, 155.7, 149.8, 148.8, 130.6, 129.5, 127.1, 125.9, 124.5, 115.3, 106.3, 105.3, 105.0, 103.9, 103.5, 57.5, 56.7, 56.0, 55.6, 52.1, 46.6, 38.2, 29.0, 23.5; Mass Spec (EI): 409 (M^+, 15), 281 (8), 128 (100); HRMS: calcd for $C_{24}H_{27}NO_5$ 409.1892, found 409.1889.[40]

Preparation of (+)-antofine (1) through cyclization and reduction of phenanthrene 17a

Trifluoromethanesulfonic anhydride (5 eq, 265 mg, 0.158 mL, 0.94 mmol) was added over 8 min to a solution of phenanthrene **17a** (1 eq, 77 mg, 0.188 mmol) and 4-dimethylaminopyridine (3 eq, 69 mg, 0.564 mmol) in dry dichloromethane (2.8 mL) at 0 °C under nitrogen. The reaction was stirred for 16 h while the ice-water bath was kept in place but without any further addition of ice. Then saturated aqueous sodium bicarbonate solution (5 mL) was then added, and the mixture was extracted with dichloromethane (3× 8 mL). The combined organic layer was washed successively with 20% aqueous acetic acid (5 mL) and saturated aqueous sodium bicarbonate solution (5 mL), dried over sodium sulfate, and concentrated on a rotary evaporator. This crude material (amide **8a**) was used in the next step without purification. Lithium aluminum hydride (10 eq, 71 mg, 1.88 mmol) was added to a solution of the above residue in anhydrous THF (3.8 mL). The reaction was refluxed for 3 h and cooled to 0 °C. The reaction was carefully quenched with ethyl acetate (5 mL), followed by addition of water (3 mL). The mixture was extracted with ethyl acetate (3× 10 mL). The combined organic layer was washed with brine (3 mL), dried over sodium sulfate, and concentrated on a rotary evaporator. The residue was purified by basic aluminum oxide flash chromatography (ethyl acetate) to give a light-yellow solid (+)-antofine (59.4 mg, 87% over two steps). $[\alpha]_D^{20}$ = +93 ($CHCl_3$, c = 1.49). m.p. 208-211 °C. ^{1}H NMR ($CDCl_3$): δ 7.91 (s, 1H, Ar-*H*, A ring bay region), 7.86 (d, 1H, J = 2.5 Hz, Ar-*H*, B ring bay region), 7.81 (d, 1H, J= 9.0 Hz, Ar-*H*, B ring *m* to OMe), 7.30 (s, 1H, Ar-*H*, A ring), 7.20 (dd, 1H, J= 9.0, 2.5 Hz, Ar-*H*, B ring *o* to OMe), 4.70 (d, 1H, J= 14.7 Hz, N-CH_2Ar), 4.11 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 3.72 (d, 1H, J = 14.7 Hz, N-CH_2Ar), 3.63

(m, 1H, R_2CH-N), 3.48 (br t, 1H, J = 6.5 Hz, RCH_2-N), 3.34 (dd, 1H, J= 13.8, 1.8 Hz, $ArCH_2R$), 2.92 (dd, IH, J = 13.8, 10.2 Hz, $ArCH_2R$), 2.50 (m, 1H, RCH_2-N), 2.26 (m, 1H, R-CH_2CH_2-R), 2.02 (m, 1H, R-CH_2CH_2-R), 1.93 (m, 1H, R-CH_2CH_2-R), 1.79 (m, 1H, R-CH_2CH_2-R); ^{13}C NMR ($CDCl_3$): δ 157.4, 149.3, 148.3, 130.2, 127.0, 126.5, 125.5, 124.2, 124.1, 123.5, 114.8, 104.8, 103.9, 60.2, 56.0, 55.9, 55.4, 55.0, 53.7, 33.5, 31.2, 21.6. The spectral data were in agreement with those previously reported for this compound.[25]

N-phenothiazinecarbonyl protected 2-ethynylpiperidine 10d

A mixture of (2*R*)-*t*-butyl 2-ethynyl-piperidinecarboxylate (1.05 eq, 1.51 g, 7.22 mmol) (see Supporting Information) and 12M HCl (3 eq, 1.9 mL, 23.1 mmol) in diethyl ether (70 mL) was refluxed overnight before removal of solvents on a rotary evaporator. After azeotropic drying using toluene (3× 10 mL), anhydrous dichloromethane (60 mL) and phenothiazine-10-carboxylchloride (0.95 eq, 1.795 g, 6.859 mmol) were added. Then triethylamine (3 eq, 2.89 mL, 2.082 g, 20.577 mmol) was added at 0 °C. After stirred at room temperature overnight, water (30 mL) was added, the mixture was extracted with dichloromethane (3× 20 mL). The combined organic layer was washed with brine, dried over sodium sulfate, and concentrated on a rotary evaporator. The residue was purified by silica gel flash chromatography (dichloromethane) to give a colorless oil (2.103 g, 92%). $[\alpha]_D^{20}$ = + 28.1 ($CHCl_3$, c =11.06). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (dd, *J* = 1.3, 8.1 Hz, 2H, Ptz-*H*, *o* to S), 7.31 (dd, *J* = 1.3, 7.5 Hz, 2H, Ptz-*H*, *o* to N), 7.24 (dt, *J* = 1.3, 7.5 Hz, 2H, Ptz-*H*, *m* to N), 7.10 (dt, *J* = 1.3, 7.5 Hz, 2H, Ptz-*H*, *m* to S), 5.26 (br s, 1H, R_2CH-N), 3.69-3.57 (m, 1H, equatorial RCH_2-N), 2.91 (dt, *J* = 3.0, 13.2 Hz, 1H, axial RCH_2-N), 2.30 (d, *J* = 2.1 Hz, 1H, ≡C-*H*), 1.85-1.52 (m, 4H, R-$CH_2CH_2CH_2$-R), 1.51-1.35 (m, 1H, R-$CH_2CH_2CH_2$-R), 1.30-1.05 (m, 1H, R-$CH_2CH_2CH_2$-R); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.0, 141.2, 128.8, 127.5, 127.4, 125.0, 122.3, 80.9, 72.8, 45.3, 43.2, 30.1, 24.8, 19.7; IR (neat): 3293, 3060, 2942, 2861, 1662, 1460, 1401, 1320, 1252, 1168, 1129, 1033 cm^{-1}; HRMS: calcd for $C_{20}H_{19}N_2OS$ $[MH]^+$ 335.1213, found 335.1224.

Preparation of alkynylproline 11d via Sonogashira coupling of alkyne-urea (10d) with 1-bromo-2-iodo-4,5-dimethoxybenzene

A procedure analogous to that for **11a** was employed using alkyne **10d** (1.35 eq, 1.002 g, 2.218 mmol), bromide-iodide **9** (1.0 eq, 761 mg, 2.995 mmol), $Pd(PPh_3)_4$ (0.05 eq, 128 mg, 0.111 mmol), and copper(I) iodide (0.1 eq, 42 mg, 0.222 mmol). After final chromatographic purification a pale yellow semisolid (1.134 g, 93%) identified as alkyne-bromide **11d** was obtained. $[\alpha]_D^{20}$ = + 44.6 ($CHCl_3$, c = 2.90). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (dd, *J* = 1.3, 8.1 Hz, 2H, Ptz-*H*, *o* to S), 7.30 (dd, *J* = 1.3, 7.5 Hz, 2H, Ptz-*H*, *o* to N), 7.20 (dt, *J* = 1.5, 7.8 Hz, 2H, Ptz-*H*, *m* to N), 7.08 (dt, *J* = 1.5, 7.5 Hz, 2H, Ptz-*H*, *m* to S), 7.01 (s, 1H, Ar-*H*, *o* to Br), 6.89 (s, 1H, Ar-*H*, *o* to alkyne), 5.57-5.45 (m, 1H, R_2CH-N), 3.88 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.75-3.65 (m, 1H, equatorial RCH_2-N), 3.09 (dt, *J* = 3.0, 13.2 Hz, 1H, axial RCH_2-N), 2.01-1.83 (m, 2H, R-$CH_2CH_2CH_2$-R), 1.73 (td, *J* = 4.5, 12.9 Hz, 1H, R-$CH_2CH_2CH_2$-R), 1.69-1.57 (m, 1H, R-$CH_2CH_2CH_2$-R), 1.56-1.44 (m, 1H, R-$CH_2CH_2CH_2$-R), 1.33-1.15 (m, 1H, R-$CH_2CH_2CH_2$-R); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8, 149.7, 148.0, 141.3, 128.6, 127.54, 127.47, 125.0, 122.1, 117.0, 116.7, 115.2, 115.0, 89.6, 83.7, 56.2, 56.1, 46.3, 43.4, 30.5, 25.0, 20.1; IR (neat): 3062, 2939, 2856, 1663, 1508, 1460, 1440, 1401, 1321, 1254, 1231, 1206, 1168, 1031, 1008 cm^{-1}; HRMS: calcd for $C_{28}H_{26}N_2O_3SBr$ $[MH]^+$ 549.0842, found 549.0838.

Preparation of bromo-ketone 12d via hydration of alkyne 11d

A procedure analogous to that for **12a** was employed using bromo-alkyne **11d** (1 eq, 136 mg, 0.248 mmol) mercuric trifluoroacetate (1.2 eq, 127 mg, 0.297 mmol) and red mercuric oxide (2.4 eq, 129 mg, 0.594 mmol). Chromatographic purification afforded two fractions, a

pale yellow oil (98 mg, 70%) identified as desired bromo-ketone **12d** and brown semisolid identified as the undesired regioisomeric bromo-ketone **13d** (11 mg, 8%). Bromo-ketone **12d**: $[\alpha]_D^{20}$ = -3.3 ($CHCl_3$, c = 2.54). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.1 Hz, 2H, Ptz-*H*, *o* to S), 7.26 (ddd, *J* = 0.6, 1.2, 7.8 Hz, 2H, Ptz-*H*, *o* to N), 7.19 (ddt, *J* = 0.6, 1.5, 7.5 Hz, 2H, Ptz-*H*, Ptz-*H*, *m* to N), 7.18 (s, 1H, Ar-*H*, *o* to C=O), 7.06 (ddt, *J* = 0.6, 1.2, 7.5 Hz, 2H, Ptz-*H*, *m* to S), 7.02 (s, 1H, Ar-*H*, *o* to Br), 4.97-4.78 (m, 1H, R_2CH-N), 3.92 (s, 6H, 2 × OCH_3), 3.79 (br d, *J* = 13.5 Hz, 1H, equatorial RCH_2-N), 3.35 (dd, *J* = 9.0, 15.9 Hz, 1H, $COCH_2$-R), 3.19 (dd, *J* = 4.8, 15.9 Hz, 1H, $COCH_2$-R), 2.83 (dt, *J* = 2.7, 13.5 Hz, 1H, axial RCH_2-N), 1.75-1.05 (m, 6H, R-$CH_2CH_2CH_2$-R); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.6, 157.5, 151.4, 148.2, 141.5, 132.2, 128.7, 127.6, 127.3, 124.9, 121.8, 116.4, 112.7, 111.1, 56.3, 56.2, 49.7, 42.6, 42.1, 27.7, 24.6, 19.1; IR (neat): 3060, 2936, 2852, 1659, 1592, 1506, 1460, 1408, 1370, 1257, 1213, 1167, 1033 cm^{-1}; HRMS: calcd for $C_{28}H_{28}N_2O_4SBr$ $[MH]^+$ 567.0948, found 567.0948. Bromo-ketone **13d**: $[\alpha]_D^{20}$ = + 3.4 ($CHCl_3$, c = 1.18). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.1 Hz, 2H, Ptz-*H*, *o* to S), 7.31 (dd, *J* = 1.5, 7.8 Hz, 2H, Ptz-*H*, *o* to N), 7.23 (dd, *J* = 1.2, 7.5 Hz, 2H, Ptz-*H*, *m* to N), 7.11 (dt, *J* = 0.6, 7.5 Hz, 2H, Ptz-*H*, *m* to S), 7.02 (s, 1H, Ar-*H*, *o* to Br), 6.72 (s, 1H, Ar-*H*, *o* to alkyl), 4.82 (t, *J* = 4.8 Hz, 1H, CORC*H*-N), 4.10-3.55 (m, 3H, $ArCH_2CO$ and RCH_2-N), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.14 (dt, *J* = 3.3, 13.6 Hz, 1H, RCH_2-N), 2.16-2.02 (m, 1H), 1.80-1.05 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.5, 158.5, 148.7, 148.3, 141.2, 128.8, 127.6, 127.5, 125.9, 125.2, 122.6, 115.3, 114.8, 114.3, 62.0, 56.13, 56.05, 46.7, 45.2, 25.8, 24.1, 20.9; IR (neat): 3060, 2955, 2934, 2856, 1726, 1659, 1508, 1460, 1406, 1309, 1258, 1219, 1166, 1033 cm^{-1}.

Preparation of alkyne-ketone 5d via Sonogashira coupling of bromo-ketone 12d and trimethylsilylacetylene

A procedure analogous to that for **5a** was employed using bromo-ketone **12d** (1 eq, 567 mg, 1 mmol), trimethylsilylacetylene (5 eq, 0.712 mL, 5 mmol), $Pd(PPh_3)_2Cl_2$ (0.3 eq, 211 mg, 0.3 mmol), triphenylphosphine (0.6 eq, 157 mg, 0.6 mmol) and copper(I) iodide (0.12 eq, 23 mg, 0.12 mmol). After final chromatographic purification a pale yellow semisolid (485 mg, 83%) identified as alkyne-ketone **5d** was obtained. $[\alpha]_D^{20}$ = +1.8 ($CHCl_3$, c = 0.47). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (dd, *J* = 0.9, 7.5 Hz, 2H, Ptz-*H*, *o* to S), 7.30 (s, 1H, Ar-*H*, *o* to C=O), 7.21 (dd, *J* = 1.2, 7.5 Hz, 2H, Ptz-*H*, *o* to N), 7.13 (dt, *J* = 1.5, 7.5 Hz, 2H, Ptz-*H*, *m* to N), 7.01 (dt, *J* = 0.9, 7.5 Hz, 2H, Ptz-*H*, *m* to S), 6.93 (s, 1H, Ar-*H*, *o* to alkyne), 5.05-4.91 (m, 1H, R_2CH-N), 3.92 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.88 (br d, 1H, *J* = 13.2 Hz, equatorial RCH_2-N) 3.67 (dd, *J* = 7.8, 16.5 Hz, 1H, $COCH_2$-R), 3.35 (dd, *J* = 6.0, 16.5 Hz, 1H, $COCH_2$-R), 2.86 (dt, *J* = 2.4, 13.2 Hz, 1H, axial RCH_2-N), 1.69-1.13 (m, 6H, R-$CH_2CH_2CH_2$-R), 0.21 [s, 9H, $Si(CH_3)_3$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.1, 157.1, 151.2, 149.2, 141.5, 133.6, 128.4, 127.4, 127.1, 124.7, 121.6, 116.2, 115.1, 111.3, 104.6, 99.8, 56.0, 55.9, 49.7, 42.3, 41.8, 28.2, 24.8, 19.2, -0.2; IR (neat): 3061, 2956, 2934, 2856, 2145, 1727, 1664, 1591, 1510, 1460, 1407, 1266, 1252, 1219, 1124 cm^{-1}; HRMS: calcd for $C_{33}H_{37}N_2O_4SiS$ $[MH]^+$ 585.2238, found 585.2241.

Formation of phenanthrene 17d through coupling of ketone-alkyne 5d with carbene complex 6 followed by dehydrogenation

A procedure analogous to that for **17a** was employed using alkyne-ketone **12d** (1 eq, 593 mg, 1.014 mmol) carbene complex **6** (1.5 eq, 441 mg, 290 mmol), and 10% palladium on carbon (0.25 eq, 270 mg, 0.253 mmol). After final chromatographic purification a pale yellow semisolid (412 mg, 69% over two steps) identified as compound **17d** was obtained. $[\alpha]_D^{20}$ = - 31.5 ($CHCl_3$, c = 2.66). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (br s, 1H, Ar-*H*, C ring), 7.90 (s, 1H, Ar-*H*, bay region of A ring), 7.83 (d, *J* = 2.1 Hz, 1H, Ar-*H*, bay region of B ring), 7.72 (d, *J* = 9.0 Hz, 1H, Ar-*H*, B ring *m* to OMe), 7.46 (d, *J* = 7.5 Hz, 2H, Ptz-*H*, *o* to S), 7.39 (s, 1H, Ar-*H*, non-bay region of A ring), 7.25-7.15 (m, 3H, Ar-*H* + Ptz-*H*), 7.09

(dt, *J* = 1.5, 7.5 Hz, 2H, Ptz-*H*, *m* to N), 7.01 (dt, *J* = 1.5, 7.5 Hz, 2H, Ptz-*H*, *m* to S), 5.04-4.86 (m, 1H, R_2CH-N), 4.30 (s, 3H, OCH_3), 4.15 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 4.03-3.87 (m, 1H, equatorial RCH_2-N), 3.50 (dd, *J* = 5.1, 13.2 Hz, 1H, $ArCH_2$-R), 3.28 (dd, *J* = 10.2, 13.5 Hz, 1H, $ArCH_2$-R), 3.16 (dt, *J* = 2.4, 13.5 Hz, 1H, axial RCH_2-N), 1.93-1.33 (m, 6H, R-$CH_2CH_2CH_2$-R); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8, 157.2, 149.7, 148.7, 141.4, 130.6, 129.8, 129.6, 127.4, 127.3, 126.9, 126.0, 124.7, 124.5, 120.3, 115.2, 105.8, 103.9, 103.8, 56.5, 56.0, 55.5, 51.9, 42.3, 33.4, 26.0, 24.5, 18.8; IR (neat): 3002, 2951, 2858, 1728, 1654, 1460, 1269, 1254, 1161, 1036 cm^{-1}; HRMS: calcd for $C_{36}H_{35}N_2O_4S$ $[MH]^+$ 591.2312, found 591.2325.

Preparation of (-)-cryptopleurine through cyclization and reduction of phenanthrene 17d

A procedure analogous to that for antofine was employed using phenanthrene **17d** (1 eq, 110 mg, 0.187 mmol), trifluoromethanesulfonic anhydride (6 eq, 316 mg, 1.122 mmol), 4-dimethylaminopyridine (4 eq, 92 mg, 0.748 mmol), and lithium aluminum hydride (15 eq, 71 mg, 1.868 mmol). After final chromatographic purification a white solid (47 mg, 79% over two steps) identified as (-)-cryptopleurine was obtained. mp 191-193 °C; $[\alpha]_D^{20}$ = -103 ($CHCl_3$, c = 2.13); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (s, 1H, Ar-*H*, bay region of A ring), 7.88 (d, *J* = 2.4 Hz, 1H, Ar-*H*, bay region of B ring), 7.77 (d, *J* = 9.3 Hz, 1H, Ar-*H*, B ring *m* to OMe), 7.23 (s, 1H, Ar-*H*, non-bay region of A ring), 7.19 (dd, *J* = 2.4, 9.0 Hz, 1H, B ring *o* to OMe), 4.43 (d, *J* = 15.6 Hz, 1H, $ArCH_2$-N), 4.10 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 3.62 (d, *J* = 15.6 Hz, 1H, $ArCH_2$-N), 3.27 (br d, *J* = 11.8 Hz, 1H, equatorial RCH_2-N), 3.05 (dd, *J* = 3.3, 16.8 Hz, 1H, equatorial $ArCH_2$-R), 2.88 (dd, *J* = 10.2, 16.2 Hz, 1H, axial $ArCH_2$-R), 2.47-2.21 (m, 2H, R_2CH-N + axial RCH_2-N), 2.02 (br d, *J* = 12.0 Hz, 1H, R-$CH_2CH_2CH_2$-R), 1.88 (br d, *J* = 12.3 Hz, 1H, R-$CH_2CH_2CH_2$-R), 1.85-1.72 (m, 2H, R-$CH_2CH_2CH_2$-R), 1.65-1.37 (m, 2H, R-$CH_2CH_2CH_2$-R); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.4, 149.3, 148.3, 130.1, 126.4, 125.3, 124.3, 124.0, 123.6, 123.4, 114.8, 104.7, 103.82, 103.80, 57.5, 56.2, 56.0, 55.9, 55.5, 34.5, 33.6, 25.8, 24.2; IR (neat): 2930, 1611, 1470, 1124 cm^{-1}; HRMS: calcd for $C_{24}H_{28}NO_3$ $[MH]^+$ 378.2064, found 378.2061. The spectral data were in agreement with those previously reported for this compound.[21a]

Preparation of alkyne-ketone 16a through Sonogashira coupling of bromo-ketone-carbamate 12a with optically pure alkyne 15 – ee assessment of 12a

A procedure analogous to that for **5a** was employed using bromo-ketone **12a** (1 eq, 151 mg, 0.391 mmol), (*R*)-(but-3-yn-2-yloxy)(tert-butyl)diphenylsilane **15**[41] (4 eq, 482 mg, 1.563 mmol), bis(triphenylphosphine)palladium(II) chloride (0.1 eq, 27 mg, 0.0391 mmol), copper(I) iodide (0.04 eq, 3 mg, 0.0156 mmol), and triphenylphosphine (0.2 equiv, 21 mg, 0.0782 mmol). A pale yellow semisolid (222 mg, 93%) was obtained after chromatographic purification. The ^{1}H NMR shows only one diastereomer when using 100% ee **12a** from entry 9 of Table 1 ($[\alpha]_D^{20}$ = -42.7 ($CHCl_3$, c = 3.91). When using scalemic bromide **12a** from entry 2 of Table 1, two diastereomers of **16a** were observed in both ^{1}H NMR and ^{13}C NMR. Natural proline-derived diastereomer. ^{1}H NMR (300 MHz, 65 °C, benzene-d_6): δ 8.00-7.90 (m, 2H, Ar-*H*), 7.88-7.76 (m, 2H, Ar-*H*), 7.48 (br s, 1H, Ar-*H*, *o* to C=O), 7.30-7.16 (m, 6H, Ar-*H*), 6.71 (s, 1H, Ar-*H*, *o* to alkyne), 4.93 (q, *J* = 6.6 Hz, 1H, R_2CH-O), 4.54-4.38 (m, 1H, R_2CH_2-N), 3.92 (br s, 1H, RCH_2-N), 3.48 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 3.32-2.97 (m, 3H, $COCH_2$-R + one RCH_2-N), 1.97-1.80 (m, 1H, R-CH_2CH_2-R), 1.72 -1.25 (m, 3H, R-CH_2CH_2-R), 1.59 (d, *J* = 6.6 Hz, 3H, R-CH_3), 1.20 [s, 9H, $C(CH_3)_3$]; ^{13}C NMR (75 MHz, 65 °C, benzene-d_6, rotamer data in parenthesis): δ 198.39, 155.5, 152.72, 150.7, 136.6 (136.8), 134.9, 134.77, 130.3 (130.4), 128.4 (128.3), 117.45, 115.88, 113.3, 96.7, 84.95, 61.8, 56.1, 55.6, 52.14, 47.1, 31.9, 27.63, 25.50, 24.0, 19.9. Unnatural proline derived diastereomer. ^{1}H NMR (300 MHz, 65 °C, benzene-d6): δ 8.00-7.90 (m, 2H, Ar-*H*), 7.88-7.76 (m, 2H, Ar-*H*), 7.49 (br s, 1H, Ar-*H*, *o* to C=O), 7.30-7.16 (m, 6H, Ar-*H*), 6.70 (s, 1H, Ar-*H*, *o* to alkyne), 4.93 (q, *J* = 6.6 Hz, 1H, R_2CH-O),

4.54-4.38 (m, 1H, R_2CH-N), 3.93 (br s, 1H, RCH_2-N), 3.48 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 3.32-2.97 (m, 3H, $COCH_2$-R + one RCH_2-N), 1.97-1.80 (m, 1H, R-CH_2CH_2-R), 1.72 -1.25 (m, 3H, R-CH_2CH_2-R), 1.58 (d, J = 6.6 Hz, 3H, R-CH_3), 1.20 [s, 9H, $C(CH_3)_3$]; ^{13}C NMR (75 MHz, 65 °C, benzene-d_6, rotamer data in parenthesis): δ 198.37, 155.5, 152.75, 150.7, 136.6 (136.8), 134.9, 134.75, 130.3 (130.4), 128.4 (128.3), 117.42, 115.90, 113.3, 96.7, 84.97, 61.8, 56.1, 55.6, 52.13, 47.1, 31.9, 27.62, 25.40, 24.0, 19.9; IR (neat): 3071, 2957, 2933, 2858, 1698, 1593, 1512, 1451, 1386, 1271, 1111, 1094 cm^{-1}; HRMS: calcd for $C_{36}H_{43}NO_6NaSi$ $[M+Na]^+$ 636.2752, found 636.2752.

Preparation of alkyne-ketone 16d through Sonogashira coupling of bromo-ketone-carbamate 12d with optically pure alkyne 15 – ee assessment of 12d

A procedure analogous to that for **5a** was employed using bromo-ketone **12d** (1 eq, 85 mg, 0.150 mmol), (*R*)-(but-3-yn-2-yloxy)(tert-butyl)diphenylsilane **15**[41] (4 eq, 185 mg, 0.599 mmol), bis(triphenylphosphine)palladium(II) chloride (0.1 eq, 11 mg, 0.015 mmol), copper(I) iodide (0.04 eq, 1.1 mg, 0.006 mmol), and triphenylphosphine (0.2 equiv, 8 mg, 0.030 mmol). A pale yellow semisolid (98 mg, 82%) identified as **16d** was obtained after chromatographic purification. The ^{1}H NMR shows only one diastereomer when using 100% ee **12d** from entry 15 of Table 1 $[\alpha]_D^{20}$ = + 63.0 ($CHCl_3$, c = 0.81). When mixed with (-) **12d** (from enantiomer of **10d**), two diastereomers were shown in both ^{1}H NMR and ^{13}C NMR, although they are very similar. Subtle differences in the ^{13}C NMR spectra were used to assess diastereomeric purity. ^{1}H NMR (300 MHz, $CDCl_3$, diasteromer data in parenthesis, rotamer data in brackets): δ 7.79 (dd, J = 1.8, 7.5 Hz, 2H, Ar-*H*), 7.71 (dd, J = 1.5, 7.8 Hz, 2H, Ar-*H*), 7.57 (dd, J = 1.5, 8.1 Hz, 2H, Ptz-*H*, *o* to S), 7.45-7.28 (m, 7H, Ar-*H*), 7.22 (dd, J = 1.8, 7.8 Hz, 2H, Ptz-*H*, *o* to N), 7.11 (dt, J = 1.5, 7.8 Hz, 2H, Ptz-*H*, *m* to N), 7.00 (dt, J = 1.2, 7.5 Hz, 2H, Ptz-*H*, *m* to S), 6.651(s, 1H, Ar-*H*, *o* to alkyne), (6.657 (s, 1H, Ar-*H*, *o* to alkyne)), 5.00-4.86 (m, 1H, R_2CH-N), 4.72 (q, J = 6.6 Hz, 1H, R_2CH-O), 3.90 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), [3.77 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3)], 3.50 (dd, J = 7.8, 16.5 Hz, 1H, RCH_2-N), 3.47 (dd, J = 7.2, 16.2 Hz, 1H, RCH_2-N), 3.23 (dd, J = 6.6, 16.5 Hz, 1H, $COCH_2$-R), 3.17 (dd, J = 6.0, 16.5 Hz, 1H, $COCH_2$-R), 2.79 (dt, J = 2.4, 13.5 Hz, 1H, R-$CH_2CH_2CH_2$-R), 1.70-1.10 (m, 7H, R-$CH_2CH_2CH_2$-R), 1.46 (d, J = 6.6 Hz, 3H, RCH_3), 1.07 [s, 9H, $C(CH_3)_3$]; ^{13}C NMR (75 MHz, $CDCl_3$, diasteromer data in parenthesis, rotamer data in brackets): δ 197.83 (197.84), 157.08 (157.05), 151.21 (151.21), 148.84 (148.84), 141.46 (141.44), [135.81 (135.81)], 135.63 (135.63), 133.56 (133.48), 133.38 (133.37), 132.83 (132.77), [129.75 (129.75)], 129.61 (129.61), 128.21 (128.14), [127.63 (127.59)], 127.44 (127.44), [127.36 (127.33)], 127.14 (127.14), 124.67 (124.64), 121.42 (121.37), 115.66 (115.66), 115.13 (115.17), 111.30 (111.30), 96.52 (96.49), 83.54 (83.52), 60.44 (60.44), 56.05 (56.05), 55.91 (55.91), 49.68 (49.76), 42.20 (42.07), 41.55 (41.60), 28.15 (28.15), 26.77 (26.74), 24.92 (24.96), 24.75 (24.80), 19.17 (19.14), 19.10 (19.13); IR (neat): 3070, 2933, 2858, 1726, 1668, 1661, 1591, 1513, 1513, 1462, 1428, 1367, 1268, 1254, 1232, 1151, 1106 cm^{-1}; HRMS: calcd for $C_{48}H_{50}N_2O_5NaSiS$ $[M+Na]^+$ 817.3102, found 817.3106.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

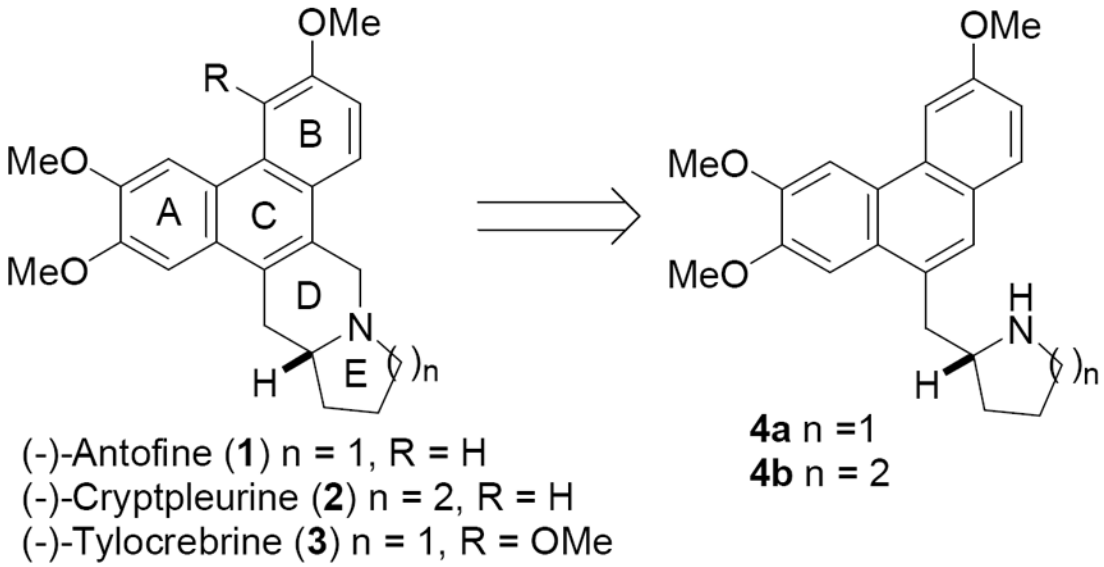
Acknowledgments

This work was supported by the SCORE program of National Institutes of Health (SC1GM083693). We thank Dr. Paul Wiget for helpful discussions.

References

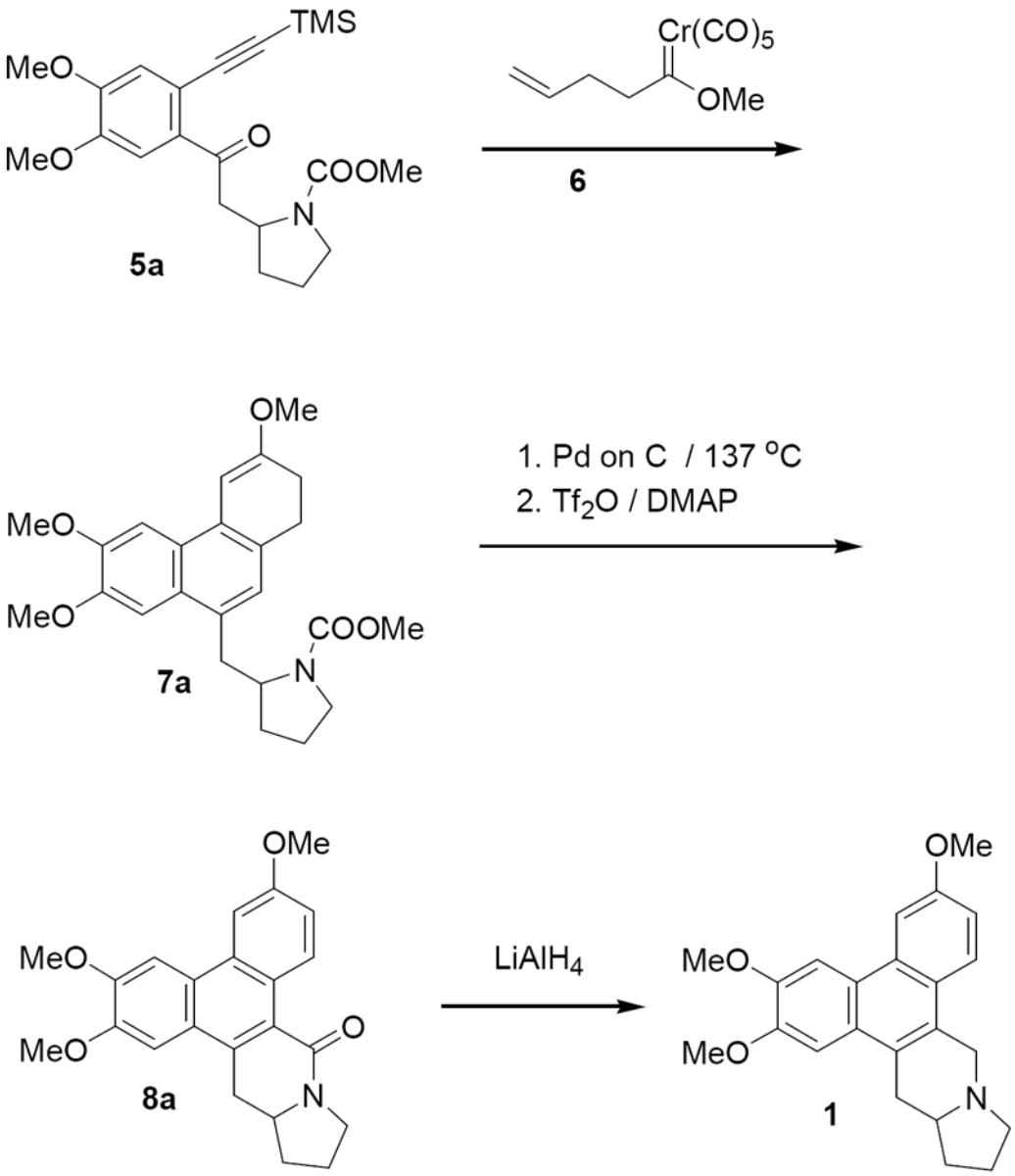
1. Gao W, Chen APC, Leung CH, Gullen EA, Fürstner A, Shi Q, Wei L, Lee KH, Cheng YC. Bioorg Med Chem Lett. 2008; 18:704–709. [PubMed: 18077159]
2. Wang K, Su B, Wang Z, Wu M, Li Z, Hu Y, Fan Z, Mi N, Wang Q. J Agr Food Chem. 2010; 58:2703–2709. [PubMed: 20000413]
3. Baumgartner B, Erdelmeier CAJ, Wright AD, Rali T, Sticher O. Phytochemistry. 1990; 29:3327–3330.
4. Min HY, Song SH, Lee B, Kim S, Lee SK. Chem Biodiver. 2010; 7:409–414.
5. Major review articles focused on synthesis: Li Z, Jin Z, Huang R. Synthesis. 2001:2365–2378.. Chemler S. Curr Bioact Cmpds. 2009; 5:2–19.
6. One member of the compound class, tylocrebrine, showed neurotoxicity during phase I clinical trials in 1965 (ataxia and disorientation). Suffness M, Douros J. Anticancer Agents Based on Natural Product Models. Cassady JM, Douros JD. Med Chem. 16Academic PressLondon1980; :465–487.
7. Govindachari TR, Ragade IS, Viswanathan N. J Chem Soc. 1962:1357–1360.
8. Wang KL, Lü MY, Wang QM, Huang RQ. Tetrahedron. 2008; 64:7504–7510.
9. a Chauncy B, Gellert E. Aust J Chem. 1970; 23:2503–2513.b Faber L, Wiegerebe W. Helv Chim Acta. 1976; 59:2201–2212. [PubMed: 1017959]
10. Yamashita S, Kurono N, Senboku H, Tokuda M, Orito K. Eur J Org Chem. 2009:1173–1180.
11. a Lebrun S, Couture A, Deniau E, Grandcauldon P. Tetrahedron. 1999; 55:2659–2670.b Su CR, Damu AG, Chiang PC, Bastow KF, Morris-Natschke SL, Lee KH, Wu TS. Bioorg Med Chem. 2008; 16:6233–6241. [PubMed: 18456501]
12. Iwao M, Mahalanabis KK, Watanabe M, De Silva SO, Snieckus V. Tetrahedron. 1983; 39:1955–1962.
13. Ambrosini LM, Cernak TA, Lambert TH. Tetrahedron. 2010; 66:4882–4887.
14. Ciufolini MA, Roschangar F. J Am Chem Soc. 1996; 118:12082–12089.
15. Bhakuni DS, Gupta PK. Indian J Chem B. 1982; 21B:393–395.
16. Wang Z, Li Z, Wang K, Wang Q. Eur J Org Chem. 2010:292–299.
17. Fürstner A, Kennedy JWJ. Chem Eur J. 2006; 12:7398–7410. [PubMed: 16881031]
18. a Niphakis MJ, Georg GI. J Org Chem. 2011; 75:6019–6022. [PubMed: 20704319] b Pansare SV, Lingampally R, Dyapa R. Eur J Org Chem. 2011:2235–2238.c Xu X, Liu Y, Park CM. Angew Chem Int Ed. 2012; 51:9372–9376.
19. Kim S, Lee J, Lee T, Park HG, Kim HD. Org Lett. 2005; 5:2703–2706. [PubMed: 12868894] . Kim S, Lee T, Lee E, Lee J, Fan G, Lee SK, Kim D. J Org Chem. 2004; 69:3144–3149. [PubMed: 15104454] . c. For synthesis of the enantiomer, see reference 9b Yang X, Shi Q, Bastow KF, Lee KH. Org Lett. 2010; 12:1416–1419. [PubMed: 20196574]
20. Kim S, Lee YM, Lee J, Lee T, Fu Y, Song Y, Cho J, Kim D. J Org Chem. 2007; 72:4886–4891. [PubMed: 17523674]
21. a Cui M, Wang Q. Eur J Org Chem. 2009:5445–5451.b Grieco PA, Parker DT. J Org Chem. 1988; 53:3325–3330.c Bremmer ML, Khatri NA, Weinreb SM. J Org Chem. 1983; 48:3661–3666.d Trigo GG, Gálvez E, Söllhuber MM. J Heterocyclic Chem. 1980; 17:69–72.e Bradsher CK, Berger H. J Am Chem Soc. 1957; 79:3287–3288.f Marchini P, Belleau B. Can J Chem. 1958; 36:581–588.f Kotani E, Kitazawa M, Tobinga S. Tetrahedron. 1974; 30:3027–3030.
22. Buckley TF III, Rapoport H. J Org Chem. 1983; 48:4222–4232.
23. Suzuki H, Aoyagi S, Kibayashi C. J Org Chem. 1995; 60:6114–6122.
24. a Iida H, Watanabe Y, Tanaka M, Kibayashi C. J Org Chem. 1984; 49:2412–2418.b Iida H, Kibayashi C. Tetrahedron Lett. 1981; 22:1913–1914.c Cragg JE, Herbert RB. J Chem Soc Perkin Trans. 1982; 1:2487–2490.d Paton JM, Pauson PL, Stevens TS. J Chem Soc C. 1969:1309–1314.e Pansare SV, Dyapa R. Org Biomol Chem. 2012; 10:6776–6784. [PubMed: 22821193] f Zeng C, Liu H, Zhang M, Guo J, Jiang S, Yu S. Synlett. 2012:2251–2254.
25. Camacho-Davila A, Herndon JW. J Org Chem. 2006; 71:6682–6685. [PubMed: 16901172]
26. For the most recent example of this reaction, see: Kumar Patti R, Duan S, Herndon JW. Tetrahedron Lett. 2011; 52:4182–4185. [PubMed: 21857755] and references therein

27. For significant variation of the alkyne group, see: Li R, Camacho-Davila A, Herndon JW. Tetrahedron Lett. 2005; 46:5117–5120.. For significant variation in the γ,δ-unsaturated carbene complex, see: Ghorai BK, Menon S, Johnson DL, Herndon JW. Org Lett. 2002; 4:2121–2124. [PubMed: 12074647]
28. a Cambeiro XC, Pericas MA. Adv Synth Catal. 2011; 353:113–124.b Chung JYL, Wasicak JT. Tetrahedron Lett. 1990; 31:3957–3960.c Dickson HD, Smith SC, Hinkle KW. Tetrahedron Lett. 2004; 45:5597–5599.d Barrett AGM, Hopkins BT, Love AC, Tedeschi L. Org Lett. 2004; 6:835–837. [PubMed: 14986987] e Miwa K, Aoyama T, Shioiri T. Synlett. 1994:107–108.
29. Moldvai I, Dornyei G, Temesvari-Major E, Szantay C. Org Prep Proc Int. 2007; 39:503–508.
30. Colombo F, Benaglia M, Orlandi S, Usuelli F, Celentano G. J Org Chem. 2006; 71:2064–2070. [PubMed: 16496994] . In the one example conducted, the rotation value for the pure enantiomer had never been reported
31. a Hakimelahi GH, Moosavi-Movahedi AA, Saboury AA, Osetrov V, Khodarahmi GA, Shia KS. Int J Sci Res. 2005; 14:59–70.b Hakimelahi GH, Moosavi-Movahedi AA, Saboury AA, Osetrov V, Khodarahmi GA, Shia KS. Eur J Med Chem. 2005; 40:339–349. [PubMed: 15804533] c Ogawa M, Natsume M. Heterocycles. 1985; 23:831–834.
32. Harrison JR, O'Brien P, Porter DW, Smith NM. J Chem Soc Perkin Trans. 1999; 1:3623–3631.
33. Grotjahn DB. Chem Eur J. 2005; 11:7146–7153. [PubMed: 16086334] . This method is however more appropriate for the conversion of terminal alkynes to aldehydes
34. Marion N, Ramón RS, Nolan SP. J Am Chem Soc. 2009; 131:448–449. [PubMed: 19140786]
35. For a recent review comparing the relative merits of platinum, gold, and mercury catalysts, see: Leyva-Perez A, Corma A. Angew Chem Int Ed. 2012; 51:614–635.. An additional consideration is cost. As of the writing of this manuscript, $Hg(OTFA)_2$ is $2.38/mmol, while (IPr)AuCl is $130.41/mmol.
36. a Gante, J. German Patent Application DE. 1986-3607194. Chem Abstr. 1988; 108:167972.c Greene, TW.; Wuts, PGM., editors. Protective Groups In Organic Synthesis. 3. John Wiley & Sons; New York, USA: 1999. p. 547d Weinstock J, Gaitanopoulous DE, Sutton BM. J Org Chem. 1975; 40:1914–1917. [PubMed: 1133607]
37. Matoba K, Imai T, Nishino Y, Takahata H, Hirai Y, Yamazaki T. Chem Pharm Bull. 1980; 28:1810–1813.. Yamasaki T, Nagata M. J Pharm Soc Jpn. 1962; 82:352–355.. Very recently this transformation was reported using super acid catalysis. Raja EK, Nilsson Lill SO, Klumpp DA. Chem Commun. 2012; 48:8141–8143.
38. This assignment was based on the different appearance of the 200 MHz and 400 MHz proton NMR spectra. The two peaks are much sharper in the 400 MHz spectra.
39. The ^{1}H NMR spectrum of this material revealed the presence of a trimethylsilyl group. In the racemic synthesis complete desilylation occurred under the reaction conditions. We attribute the observed difference to a difference in the activity of the silica gel used in the filtration process.
40. The spectral data are not in agreement with those previously reported. In the previous manuscript[25] the ^{1}H NMR and ^{13}C NMR spectra for cyclic compound **8a** were erroneously presented instead of the spectra for **17a**.
41. Kiyotsuka Y, Kobayashi Y. J Org Chem. 2009; 74:7489–7495. [PubMed: 19787857]

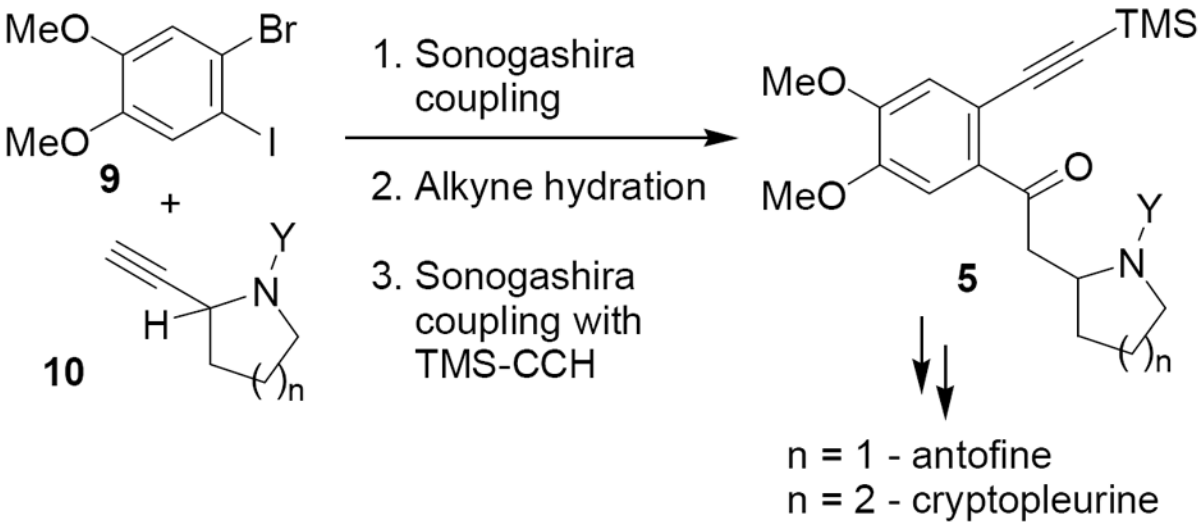


(-)-Antofine (**1**) n = 1, R = H
(-)-Cryptpleurine (**2**) n = 2, R = H
(-)-Tylocrebrine (**3**) n = 1, R = OMe

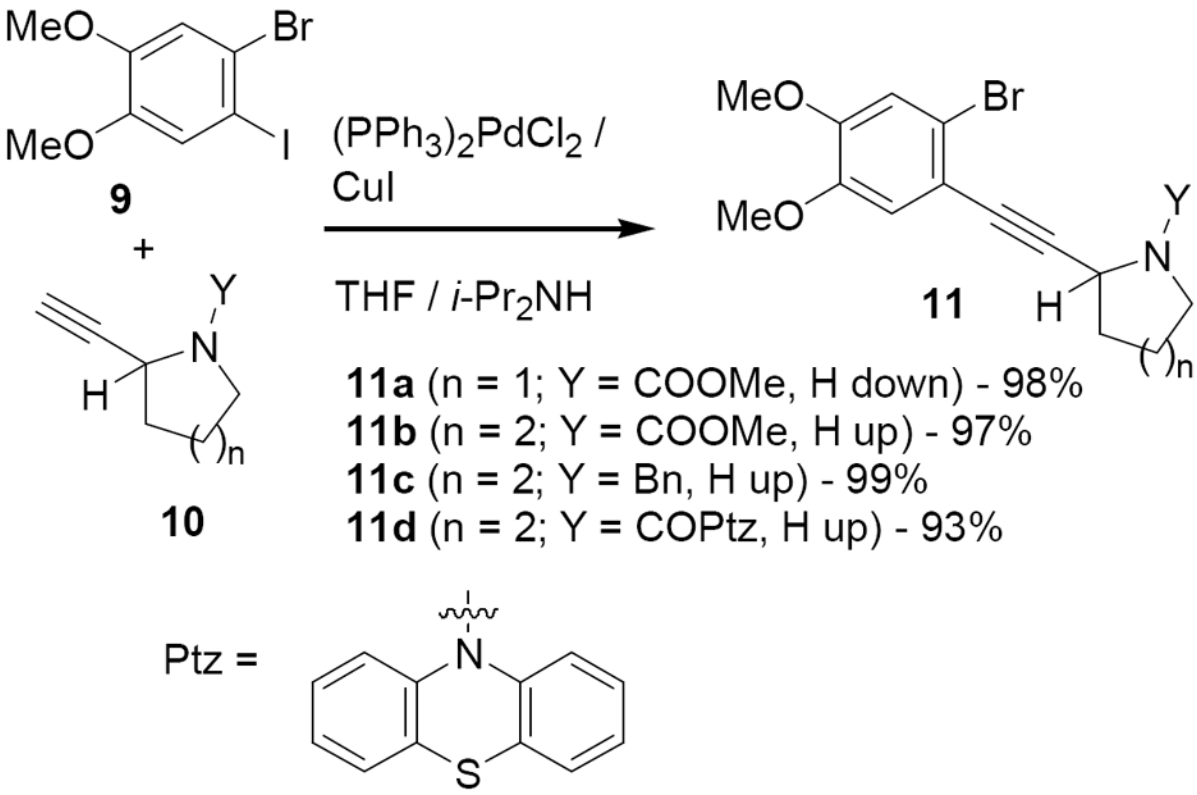
Scheme 1.



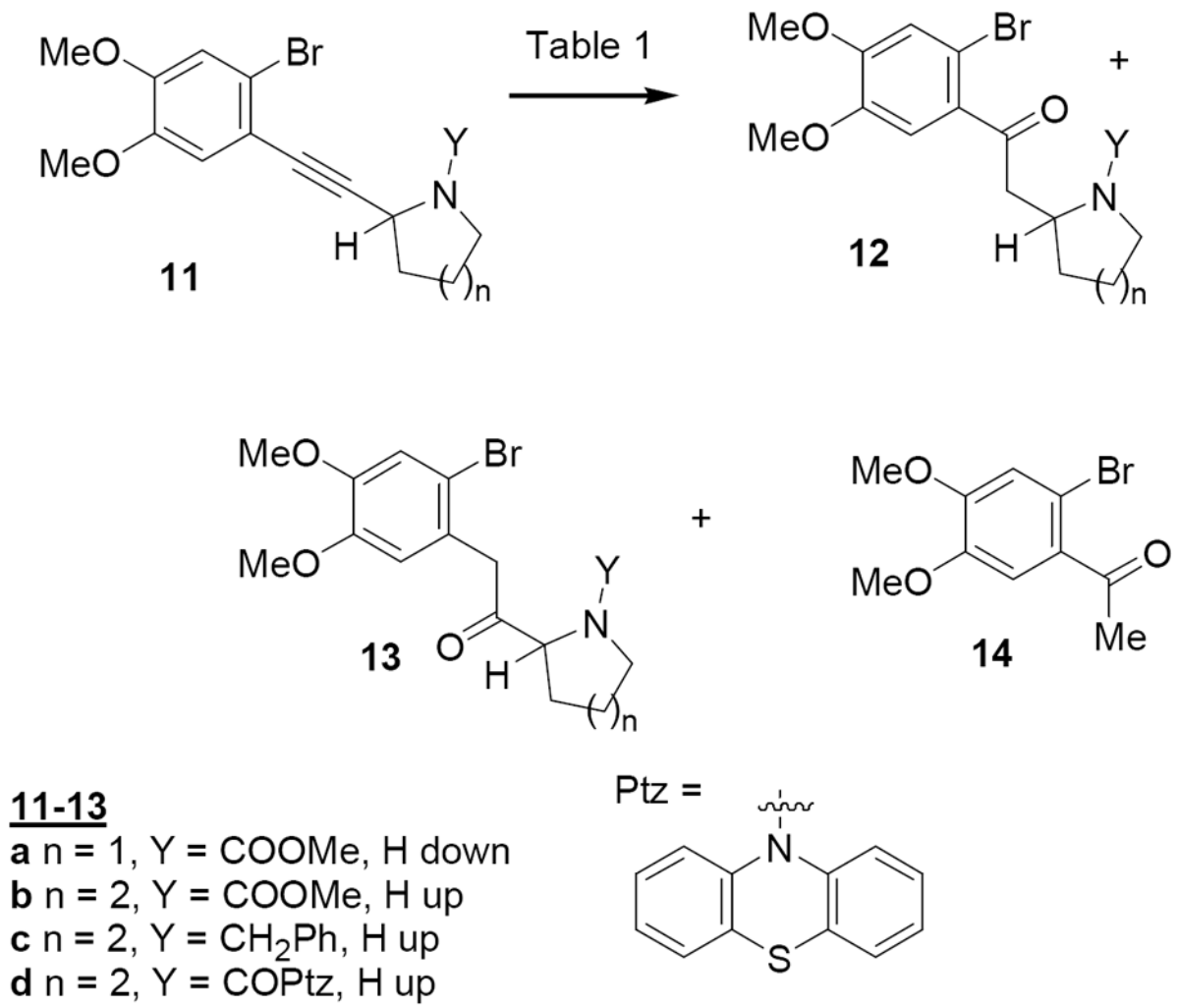
Scheme 2.



Scheme 3.



Scheme 4.

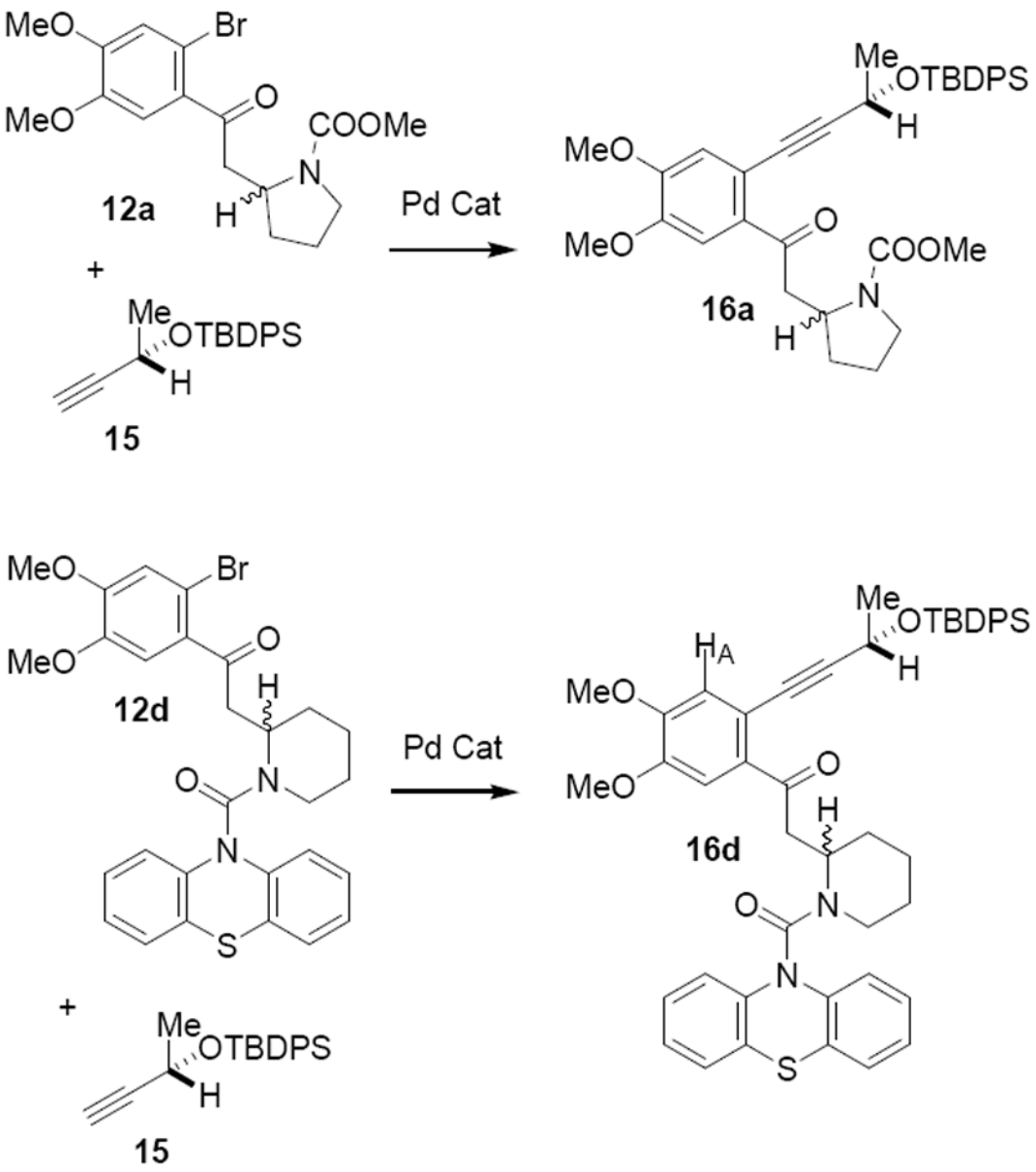


11-13

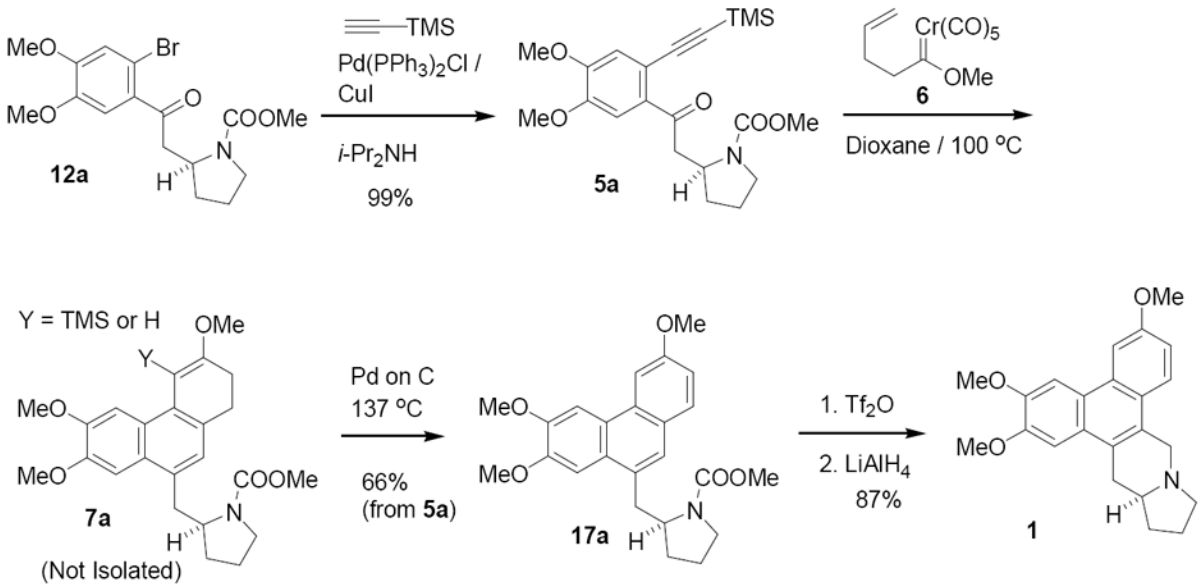
a n = 1, Y = COOMe, H down
b n = 2, Y = COOMe, H up
c n = 2, Y = CH_2Ph, H up
d n = 2, Y = COPtz, H up

Ptz =

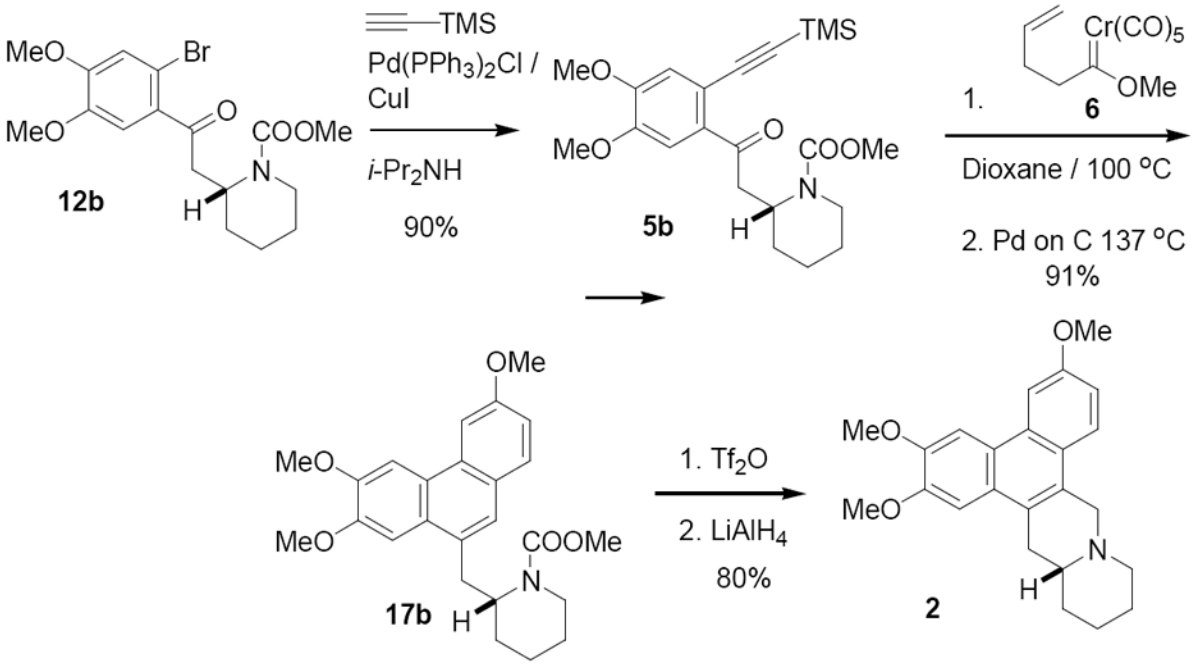
Scheme 5.



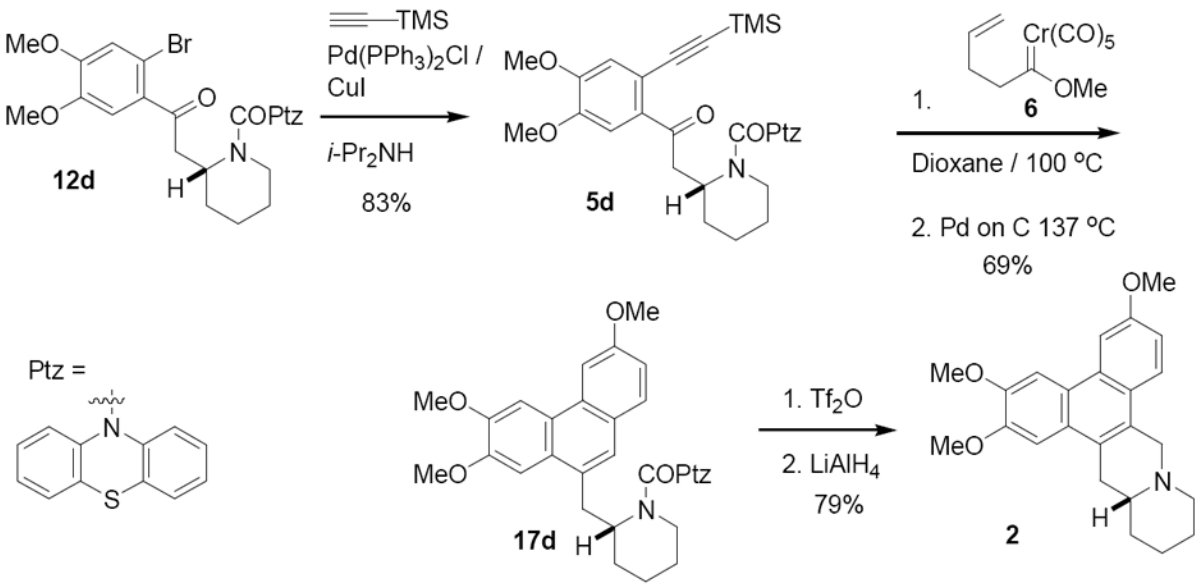
Scheme 6.



Scheme 7.



Scheme 8.



Scheme 9.

Table 1

Alkyne hydration of propargylamines **11a-d.** (See also Scheme 5)

Entry	n	Y	Conditions	12:13	Yield 12	ee of 12[a]
1	1	COOMe	0.05 equiv $Hg(OAc)_2$, $AcOH/HCO_2H/H_2O$ (20:10:1) r.t., 15 h	67:33	33	12
2	1	COOMe	0.05 equiv $Hg(OAc)_2$, $AcOH/HCO_2H/H_2O$ (2:1:1) r.t., 56 h	**12** only	96	13
3	1	COOMe	2.1 equiv HgO, 2.1 equiv $Hg(OTFA)_2$, $EtOAc/H_2O$ (40:1), r.t., 3 h, H_2S[b]	92:8	60	86
4	1	COOMe	2.5 equiv HgO, 2.5 equiv $Hg(OTFA)_2$, $MeCN/H_2O$ (40:1), r.t., 3 h, H_2S[b]	78:22	70	68
5	1	COOMe	2.5 equiv HgO, 2.5 equiv $Hg(OTFA)_2$, $MeOH/H_2O$ (40:1), r.t., 3 h, H_2S[b]	87:13	24	50
6	1	COOMe	3.2 equiv HgO, 1.6 equiv $Hg(OTFA)_2$, THF/H_2O (40:1), r.t., 5 h, H_2S, then $NaHCO_3$[c]	**12** only	98	100
7	1	COOMe	5% [Cl(indenyl)(PPh_3)Ru], Wet Acetone, reflux, 18 h	-	0	-
8	1	COOMe	5% [Au(PPh_3)NTf_2], MeOH, r.t. to reflux, 12 h	-	0	-
9	2	COOMe	3.2 equiv HgO, 1.6 equiv $Hg(OTFA)_2$, THF/H_2O (40:1), r.t., 1.5 h, H_2S, then $NaHCO_3$[c]	92:8	87	68
10	2	COOMe	3.2 equiv HgO, 1.6 equiv $Hg(OTFA)_2$, NaH_2PO_4-NaOH buffer (pH 7) (THF /buffer = 4:1), r.t., 2 d, H_2S, then $NaHCO_3$[c]	**12** only	49	63
11	2	COOMe	5% [(IPr)AuCl], 5% AgSbF6, THF/H_2O (2:1) 0 °C, 2h, r.t., 12 h[d]		0	
12	2	COOMe	10% [(IPr)AuCl], 10% AgSbF6, $Dioxane/H_2O$ (2:1) Reflux, 1 h[d]	**12** only	90	23
13	2	Bn	3.2 equiv HgO, 1.6 equiv $Hg(OTFA)_2$, NaH_2PO_4-NaOH buffer (pH = 7) (THF /buffer = 4:1), r.t., 2 d, H_2S, then $NaHCO_3$[c]	**14** (20%) + **12c** (13%)		
14	2	COPtz[f]	2.4 equiv HgO, 1.2 equiv $Hg(OTFA)_2$, THF/H_2O (20:1), r.t., 3h, H_2S, then $NaHCO_3$[c]	83:17	70	84
15	2	COPtz[f]	2.4 equiv HgO, 1.2 equiv $Hg(OTFA)_2$, THF/H_2O (20:1), 0 °C, 1 h, H_2S, then $NaHCO_3$[c]	86:14	70	>95%
16	2	COPtz[f]	2.4 equiv HgO, 1.2 equiv $Hg(OTFA)_2$, THF/H_2O (20:1), 0 °C, 1 h, aqueous Na_2S[e]	86:14	71	>95%
17	2	COPtz[f]	10% [(IPr)AuCl], 10% $AgSbF_6$, $Dioxane/H_2O$ (2:1) Reflux, 1 h[e]	**12** only	28	75

[a] The ee was determined through optical rotation values.

[b] H_2S gas workup: pre-cool the reaction mixture to 0 °C and bubble H_2S gas (from HCl and FeS) for 10 min before filtration (Celite) and extraction.

[c] H_2S gas then $NaHCO_3$ workup: pre-cool the reaction mixture to 0 °C and bubble H_2S gas (from HCl and FeS) for 10 min before addition of $NaHCO_3$ (saturated aqueous) followed by filtration (Celite) and extraction.

[d] IPr = (2,6-di-i-propylphenyl)imidazol-2-ylidene.

[e] Aqueous Na_2S workup: pre-cool the reaction mixture to 0 °C before addition of Na_2S (15 eq, aqueous), followed by filtration and extraction (EtOAc).

[f] Ptz = 10*H*-phenothiazine.