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Synthesis of (–)-Cryptopleurine by Combining Gold(I) Catalysis with a Free Radical Cyclization

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(*R*)-(–)-Cryptopleurine, a highly cytotoxic alkaloid found in *Cryptocarya* and *Boehmeria* species, was synthesized in high optical purity using a gold(I)-NHC catalyzed cyclization of an unsymmetrical phenanthrene precursor combined with a free radical cyclization to achieve closure of the C-ring.

Introduction

Phenanthroquinolizidines are a small group of pentacyclic alkaloids well known for their strong biological effects. To date, only five members of this class (**1**–**5**, Figure 1) have been isolated from *Cryptocarya* (*Lauraceae*)[1] and *Boehmeria* (*Urticaceae*) species.[2] In addition to potent antiviral activities,[3] these agents exert potent anti-inflammatory[4] and anticancer effects.[4b,5] For instance, (–)-boehmeriasin A (**1**) has proven to be more potent than paclitaxel in vitro,[2e,6] although its detailed mode of action is still poorly understood.[5e,7] The anti-inflammatory effects of phenanthro-type alkaloids may be the result of complex interactions with the NF-κB signaling pathway[4b,8] whereas their anticancer activities may be related to induction of cell cycle arrest.[5a,5d,9]

Results and Discussion

Herein, we report the total synthesis of (*R*)-(–)-cryptopleurine (**3**) based on a gold(I)-NHC-catalyzed ring closure and a free radical cyclization. In the course of our previous investigations into radical cyclizations for construction of the pentacyclic skeleton of the phenanthro alkaloids,[10] we found radical ring closures of the D-ring to be critically dependent on the size of the E-ring building block; our earlier synthesis of (+)-**6** could not be extended to the phenanthroquinolizidine series. Moreover, the 2,3,6-trimethoxy-

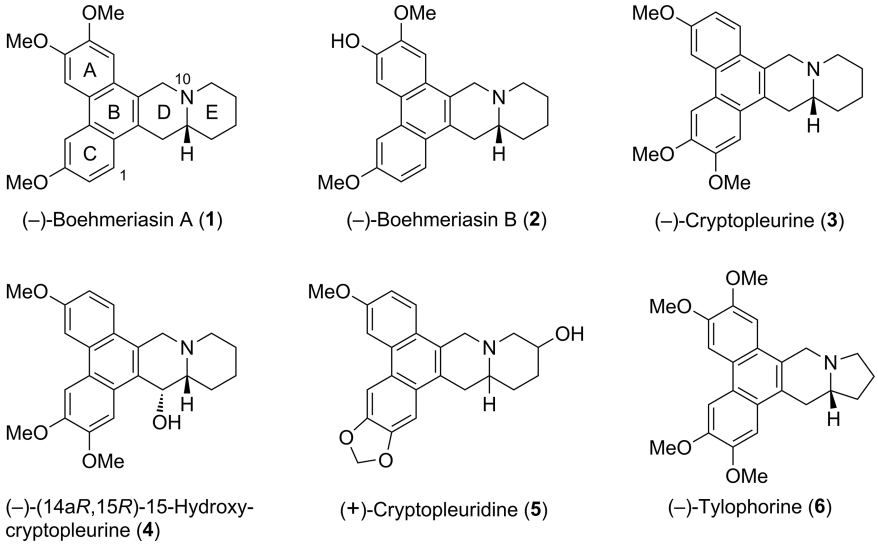

Figure 1. Selected phenanthro-type alkaloids.

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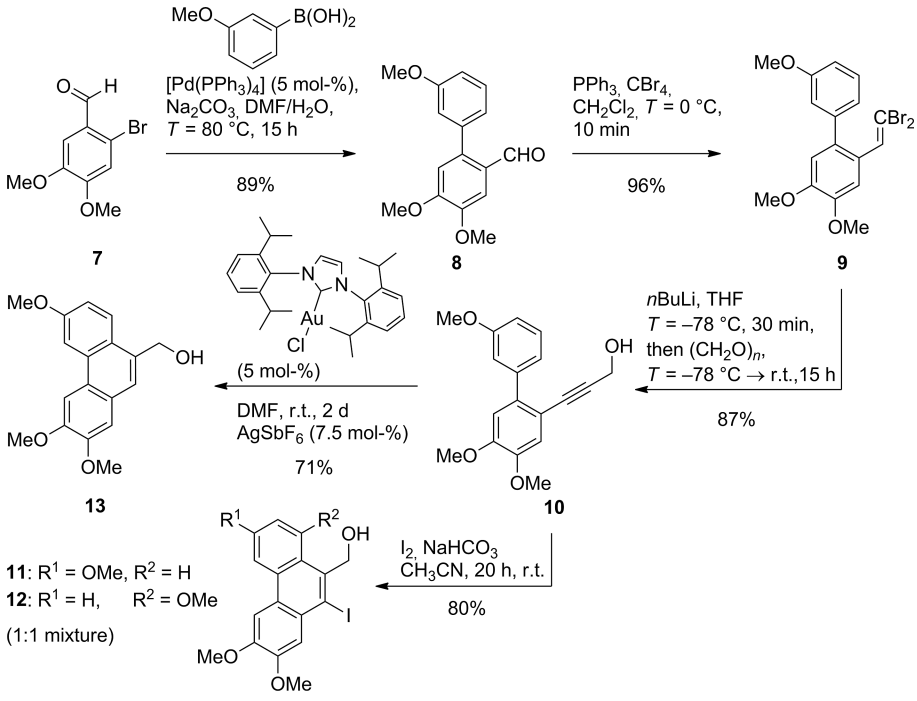


Scheme 1. Synthesis of phenanthrenes by gold(I) catalysis and iodocyclization.

substitution pattern of **3** proved more difficult to handle than the 2,3,6,7-tetramethoxy-substituted phenanthrene scaffold of **6**. With only three methoxy groups present, both the oxidative cyclization [3-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)acrylic acid → 2,3,6-trimethoxyphenanthrene-9-carboxylic acid] and the bromination [9-(hydroxymethyl)phenanthrene → 10-bromo-9-(bromomethyl)-2,3,6-trimethoxyphenanthrene] steps used to generate the starting point for a traceless radical cyclization according to Kim[11] failed, in our hands, to proceed with any useful regioselectivity.

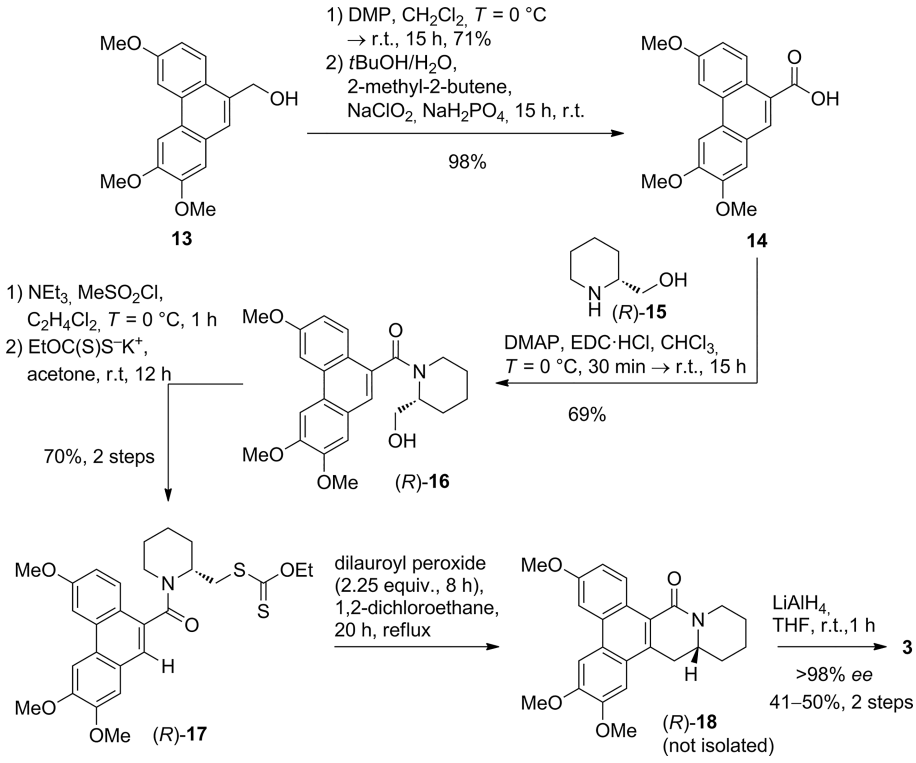
Thus, we sought to develop a new and more flexible total synthesis of the natural alkaloid (–)-cryptopleurine (**3**)[1b] based on a gold(I)-NHC catalyzed cyclization to establish the phenanthrene system (for selected syntheses of cryptopleurine, see ref.[12]; for selected syntheses of phenanthrenes using gold(I) catalysis, see ref.[13]). The current synthesis starts with Suzuki coupling[14] of 2-bromo-4,5-dimethoxybenzaldehyde (**7**, Scheme 1) and 3-methoxyphenyl boronic acid to generate biphenyl **8** which was then converted into the vinyl dibromide **9**.

Subsequent treatment with *n*-butyllithium gave the lithium acetylide[15] and quenching of this salt with paraformaldehyde furnished propargylic alcohol **10**. In contrast, our earlier attempts to obtain **10** by Sonogashira coupling[16] of a 2-iodobiphenyl intermediate with various alkynes were unsuccessful. Treatment of **10** (MeCN solution) with iodine in the presence of $NaHCO_3$ according to a method previously employed by Larock led to the desired iodocyclization in 80% combined yield.[17] Unfortunately, a nearly equimolar mixture of 2,3,6-(**11**) and 2,3,8-substituted phenanthrenes (**12**) was obtained. Although both regioisomers are separable by RP-HPLC, this route was ultimately deemed impractical. After a series of experiments with other electrophiles and catalysts such as $PtCl_2$ employed by Fürstner in his tylophorine synthesis,[12f] we found Echavarren's Au^I-NHC complex (Scheme 1) to be a superior inducer of cyclization. With this reagent,[18] the desired 6-*endo-dig* cyclization was effected at room temperature to furnish alcohol **13** as a single regioisomer (71%); conversely, the use of $PtCl_2$ produced a complex mixture.

After a two-step oxidation [Dess–Martin periodinane (DMP),[19] Pinnick-oxidation,[20] Scheme 2] carboxylic acid **14** was coupled to (*R*)-2-(hydroxymethyl)piperidine [(*R*)-**15**] using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl) and *N*,*N*-dimethyl-4-aminopyridine (cat.) (DMAP) to give amide (*R*)-**16** in 69% yield.[21] *O*-Mesylation followed by reaction with potassium *O*-ethyl xanthogenate afforded (*R*)-**17**, the open-chain precursor to radical cyclization product (*R*)-**18**.

The ring closure was achieved by a method of Zard[22] using stoichiometric amounts of dilauryol peroxide (Luperox® LP) to restore the aromatic system after intramolecular addition of the radical to the 9,10-double bond of the phenanthrene unit. Upon reduction of amide (*R*)-**18** with $LiAlH_4$, desired alkaloid **3** was obtained in high optical purity (≥ 98% *ee*) as determined by chiral HPLC (Supporting Information). Notably, previous examples of radical cyclizations in the synthesis of phenanthro alkaloids are known.[10,23]

It is noteworthy that purification of **3** was problematic due to its very high sensitivity to light which exceeds that of **6**. Also complicating the purification of **3** was the fact that this class of alkaloids is poorly soluble in most solvents; chloroform, and to a lesser extent dichloromethane, are exceptions to this rule. The sensitizing properties of the



Scheme 2. Synthesis of (*R*)-(–)-cryptopleurine.

phenanthrene scaffold led to rapid C-ring photo-oxidation in this environment.[24] Repeated preparative HPLC was required to remove impurities formed during analytical characterization and the isolated yield of (–)-**3** dropped from 50% (over 2 steps from **17** after two HPLC runs) to 41% after two further preparative HPLC runs. HPLC/MS analysis of the sample after ultimate purification verified the acquisition of analytically pure material (Figure 2). However, NMR analysis after evaporation of the solvent (amberized glassware) indicated extensive decomposition (see Supporting Information).

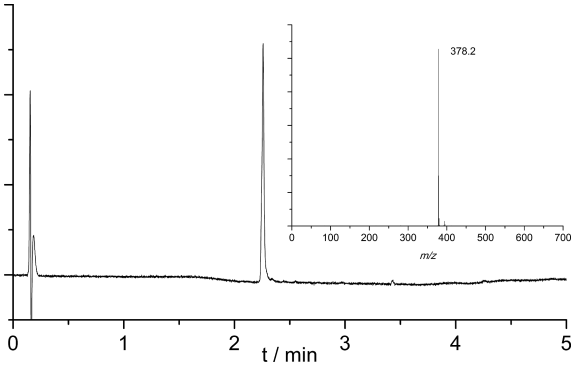


Figure 2. HPLC/MS of **3** immediately following purification. DAD: $\lambda = 286 \pm 4$ nm, $t_R = 2.3$ min, MeCN/H_2O (0.1% HCO_2H) = 10:90 (0.00–0.50 min)→90:10 (3.00 min), C_{18} (50 × 2.1 mm), core-shell, 1.00 mL·min^{-1}, $T = 50$ °C.

Conclusions

In summary, we present a new methodology for the synthesis of asymmetrically-substituted 9-phenanthryl methanol **13** and its conversion to (*R*)-(–)-cryptopleurine (**3**) which could be achieved without any detectable racemization (chiral HPLC, see Supporting Information).

Experimental Section

General Methods: All reactions were carried out in dried glassware under an inert atmosphere (argon) in anhydrous solvents using standard syringe and septa techniques.[25] Anhydrous THF was distilled from potassium/benzophenone under argon. Anhydrous dichloromethane was distilled from CaH_2 under argon. The solvents used for flash chromatography were distilled prior to use, the solvents used for analytical and preparative HPLC were of "gradient grade" quality and were degassed in an ultrasonic bath prior to use. Dry DMF (water ≤ 0.005%, over molecular sieves) was ordered from a commercial supplier and used as received. BF_3·OEt_2 was freshly distilled immediately prior to use. CCl_4 (water ≤ 0.005%, over molecular sieves) was degassed by multiple freeze-pump-thaw cycles. All other solvents and reagents were purchased from commercial suppliers and were used without further purification. TLC experiments were carried out with aluminum sheets or glass plates (Merck) coated with silica gel 60 F^{254} and spots were visualized with UV-light (254 nm, 366 nm) and developed with phosphomolybdic acid reagent, which was prepared by dissolving phosphomolybdic acid (25 g), $Ce(SO_4)_2$·$4H_2O$ (10 g) and H_2SO_4 (60 mL) in water (940 mL). Flash chromatography was carried out using unmodified silica gel (25–40 μm, 60 Å, Macherey–Nagel; or 32–63 μm, 60 Å, Acros Organics). Melting points were determined with a Krüss digital melting point apparatus or with a Büchi melting point apparatus according to Dr. Tottoli and are uncorrected. NMR spectra were recorded with Bruker 300, 400, or 600 MHz spectrometers using 5 mm probes and standard pulse sequences. The spectra were measured in $CDCl_3$, CD_3CN, CD_2Cl_2

or [D$_6$]DMSO and the chemical shifts were referenced to the residual solvent signal ($CDCl_3$: δ_H = 7.26, δ_C = 77.16. CD_2Cl_2: δ_H = 5.32, δ_C = 53.84. CD_3CN: δ_H = 1.94, δ_C = 118.26/1.32; [D$_6$]DMSO: δ_H = 2.50, δ_C = 39.52 ppm).[26] IR spectra were recorded with a Bruker Tensor 27 FTIR spectrometer using a diamond ATR unit, mass spectra were measured using an Agilent/Bruker XCT linear ion trap LC/MSD detector (ESI-MS). ESI-HRMS spectra were recorded with a Waters Q-TOF Ultima-III spectrometer with a dual source and a suitable external calibrant. LC/MS-solvents (Optima LC/MS®: water, MeOH and MeCN) were purchased from Fisher Scientific (Germany). Analytical HPLC was carried out on a Knauer Smartline HPLC system (Berlin, Germany) in high pressure gradient mode equipped with two pumps, a Knauer Smartline K 1050 (water) and a Knauer K 1001 (MeCN or MeOH), each pump equipped with a 10 mL pump head. The system was connected to a K-2800 diode array detector. The size of the injection loop was 20 µL, the total flow rate 1.0–2.0 mL·min^{-1}. An ACE3-C_{18} column (Advanced Chromatography Technologies, 125 × 4.6 mm, 3 µm particle size) or an ACE3-C_{18}PFP column (Advanced Chromatography Technologies, 150 × 4.6 mm, 3 µm particle size) was used. The elution was performed with a gradient of H_2O and MeCN or MeOH at T = 25–40 °C (MeCN), or T = 40–60 °C (MeOH). A manually controlled column oven (JETStream) was used for temperature adjustment during analytical scale HPLC analysis. Preparative NP- and RP-HPLC were carried out on a Knauer Smartline HPLC-system (high pressure gradient), equipped with two K-1800 pumps (pump head size: each 100 mL), a diode array detector (S-2600) and a 2.0–5.0 mL injection loop. Running the HPLC in reversed phase mode (RP), the elution was performed using an ACE5-C_{18} column (Advanced Chromatography Technologies, 125 × 21.2 mm, 5 µm particle size) or an ACE5-C_{18}PFP column (Advanced Chromatography Technologies, 150 × 30 mm, 5 µm particle size) with a gradient of H_2O [pure, or with 0.1% (v/v) formic acid] and MeCN or MeOH at T = 21 °C and total flow rates of 26.2–52.4 mL·min^{-1} for columns with 21.2 mm diameter, and 37.5–56.3 mL·min^{-1} for 30 mm-columns, respectively. For chiral HPLC analysis, a Daicel CHIRALPAK AD-H ("polar mode") was used. For running the HPLC in normal phase mode, a preparative HPLC column, packed with unmodified silica (125 × 21.2 mm, 3 µm, NUCLEODUR®, Macherey–Nagel), was used and the elution was performed using a combination of *n*-hexane and 2-propanol (isocratic mode) and a total flow rate of 21.2 mL·min^{-1} at T = 21 °C. HPLC/MS was carried out on an Agilent 1200 system (binary pump, column oven, auto sampler, DAD) using an Ascentis Express®-C_{18} column (50 × 2.1 mm, core-shell, particle size: 2.7 µm) or an Ascentis Express®-C_8 column (30 × 2.1 mm, core-shell, particle size: 2.7 µm) with a gradient of H_2O containing 0.1% formic acid for positive ionization or 15.0 mM ammonium hydrogen carbonate for negative ionization mode and MeCN at a temperature of T = 40–60 °C and a total flow rate of 0.50–1.00 mL·min^{-1}. The mass spectra were recorded using positive or negative electrospray ionization. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at wavelengths of 546 nm and 578 nm (Hg-lamp). The data were extrapolated to a wavelength of λ = 589 nm using the Drude equation.[27]

4,5-Dimethoxy-2-(3-methoxyphenyl)benzaldehyde (8): 2-Bromo-4,5-dimethoxybenzaldehyde (**7**, 9.80 g, 40.0 mmol), 3-methoxyphenylboronic acid (6.08 g, 40.0 mmol), [Pd(PPh_3)$_4$] (2.32 g, 2.00 mmol, 5.00 mol-%), and K_2CO_3 (11.1 g, 160 mmol. 4.0 equiv.) were placed in a round-bottom flask and dissolved in DMF (200 mL). After stirring at room temperature for 10 min, the reaction mixture was heated to T = 60 °C. Water was then added in three portions (80 mL) and stirring was continued for 15 h. After cooling to room temperature, saturated aqueous NH_4Cl (100 mL) and toluene (300 mL) were added. The solvent was removed in vacuo and the residue treated with fresh toluene (2 × 100 mL) followed by evaporation of the solvent. After H_2O (300 mL) and Et_2O (500 mL) had been added, the organic layer was separated and extracted with Et_2O (3 × 125 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and the solvent was evaporated in vacuo, giving a brown residue (oil) which was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 10:1) yielding **8** as a colorless solid (9.58 g, 89%). R_f = 0.20 (petroleum ether/EtOAc = 5:1); m.p. 98–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.83 (s, 1 H, C*H*O), 7.52 (s, 1 H, 6-*H*), 7.36 (t, J = 7.6 Hz, 1 H, 5′-*H*), 7.00–6.90 (m, 3 H, 2′,4′,6′-*H*), 6.86 (s, 1 H, 3-*H*), 3.98/3.97 (2 × s, 6 H, 2 × OCH_3), 3.85 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 191.2 (*C*HO), 159.5 (C_q-OMe), 153.4 (C_q-OMe), 148.9 (C_q-OMe), 141.4 (C1)*, 139.1 (C2)*, 129.4 (C6)*, 127.0 (C1′)*, 122.9 (*C*H), 116.0 (*C*H), 113.4 (*C*H), 112.6 (*C*H), 108.6 (*C*H), 56.3 (O*C*H$_3$), 56.2 (O*C*H$_3$), 55.4 (O*C*H$_3$) ppm (* assignments interchangeable). FTIR (ATR): $\tilde{\nu}$ = 3070, 2955, 2920, 2906, 2843, 2822, 1672, 1597, 1587, 1510, 1463, 1439, 1388, 1262, 1249, 1049, 1029, 864, 862, 797, 746 cm^{-1}. MS (ESI$^+$): *m*/*z* (%) = 295.0 (100) [*M* + Na]$^+$. HRMS (ESI$^+$): Calcd. for [$C_{16}H_{16}O_4$Na]: *m*/*z* = 295.0946; found 295.0952.

4,5-Dimethoxy-1-(2,2-dibromoethenyl)-2-(3-methoxyphenyl)benzene (9): For transformations of the type RC(H)=O→RC≡CR′ according to the method developed by Corey and Fuchs, see refs.[15,28] A solution of CBr_4 (9.75 g, 29.4 mmol, 2.00 equiv.) in CH_2Cl_2 (20 mL) was added to a stirred solution of PPh_3 (19.3 g, 73.5 mmol, 5.00 equiv.) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 20 min. Subsequently, the aldehyde (4.00 g, 14.7 mmol); dissolved in CH_2Cl_2 (20.0 mL), was added in one portion and the resulting reaction mixture was stirred at room temperature. The mixture was then treated with a mixture of *n*-hexane/EtOAc = 1:1 (80 mL). The precipitate was filtered off using a pad of Celite®, washed with fresh *n*-hexane/EtOAc = 1:1 (50 mL) before removing the solvent in vacuo. Finally, flash chromatography on silica gel (petroleum ether/EtOAc = 10:1) delivered **9** (6.01 g, 96%) as a colorless solid. R_f = 0.20 (petroleum ether/EtOAc = 10:1); m.p. 75–78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (t, J = 8.0 Hz, 1 H, 5′-*H*), 7.28 (s, 1 H, 6-*H*), 7.21 (s, 1 H, 3-*H*), 6.92 (m_c, 1 H, aryl-*H*), 6.90 (m_c, 1 H, aryl-*H*), 6.87 (m_c, 2 H, C*H*=CBr$_2$, aryl-*H*), 3.95 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 159.4 (C_q-OMe), 149.1 (C_q-OMe), 147.8 (C_q-OMe), 141.4 (C1′)*, 137.2 (*C*H=CBr$_2$)*, 134.4 (C_q), 129.3 (*C*H), 125.9 (C_q), 122.1 (*C*H), 115.1 (*C*H), 113.2 (*C*H), 112.5 (*C*H), 111.9 (*C*H), 89.3 (CH=*C*Br$_2$)*, 56.2 (O*C*H$_3$), 56.0 (O*C*H$_3$), 55.4 (O*C*H$_3$) ppm (* assignments interchangeable). FTIR (ATR): $\tilde{\nu}$ = 3070, 3014, 2948, 2920, 2822, 1605, 1514, 1444, 1388, 1252, 1203, 1047, 1028, 895, 868, 818, 790, 703 cm^{-1}. MS (ESI$^+$): *m*/*z* (%) = 448.9 (49) [*M*(^{79}Br) + Na]$^+$, 427.0 (100) [*M*(^{79}Br) + H]$^+$. HRMS (ESI$^+$): Calcd. for [$C_{17}H_{16}O_3{}^{79}Br_2$Na]: *m*/*z* = 448.9364, found 448.9368.

1,2-Dimethoxy-4-(3-methoxyphenyl)-5-(1-hydroxyprop-2-yn-3-yl)-benzene (10): *n*-Butyllithium (19.6 mL, 31.3 mmol, 2.5 equiv., 1.6 M in hexanes) was added dropwise to a stirred solution of the dibromoalkene **9** (5.35 g, 12.5 mmol) in THF (50.0 mL) at T = –78 °C. After the addition was completed, the mixture was stirred at this temperature for 45 min. Subsequently, paraformaldehyde (602 mg, 18.8 mmol, 1.50 equiv.) was added in one portion, then the cooling bath was removed and the mixture stirred at room temperature for 15 h. After aqueous NH_4Cl (75 mL) had been added, the mixture was extracted with EtOAc (4 × 200 mL), the combined organic extracts were dried with anhydrous Na_2SO_4 and the solvent

was removed in vacuo. Flash chromatography on silica gel (petroleum ether/EtOAc = 3:1) furnished desired propargylic alcohol **10** (3.27 g, 87%) as a colorless oil. R_f = 0.41 (petroleum ether/EtOAc = 2:1). RP-HPLC (i.d. 4.6 mm): t_R = 8.2 min, H_2O/MeCN = 55:45, ACE3-Phenyl, 1.00 mL·min^{-1}, T = 40 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (t, J = 7.8 Hz, 1 H, 5′-*H*), 7.16 (m_c, 1 H, 2′-*H*), 7.12 (td, J = 7.8, 0.9 Hz, 1 H, 6′-*H*), 7.01 (s, 1 H, 3-*H*), 6.87 (ddd, J = 0.9, 2.7, 7.8 Hz, 1 H, 4′-*H*), 6.85 (s, 1 H, 6-*H*), 4.34 (s, 2 H, 2′′-*H*), 3.89 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3) ppm. ^{13}C NMR, (100.6 MHz, $CDCl_3$): δ = 159.2 (C_q-OMe), 149.5 (C_q-OMe), 148.0 (C_q-OMe), 141.8 (C1′),* 137.4 (C4)*, 129.1 (*C*H), 121.7 (*C*H), 115.5 (*C*H), 115.1 (*C*H), 112.9 (*C*H), 112.7 (C5)*, 112.4 (*C*H), 88.7 (C2′′)*, 85.5 (C3′′)*, 56.13 (OCH_3), 56.06 (OCH_3), 55.4 (OCH_3), 51.7 (C1′′) ppm (*assignments interchangeable). FTIR (ATR): $\tilde{\nu}$ = 3485, 3082, 2969, 2954, 2923, 2840, 2223, 1601, 1514, 1464, 1441, 1392, 1213, 1202, 1053, 1024, 861, 776, 750, 707 cm^{-1}. MS (ESI$^+$): *m*/*z* = 321.1 [*M* + Na]$^+$, 299.1 [*M* + H]$^+$, 281.0 [*M* – (OH)]$^+$. HRMS (ESI$^+$): Calcd. for [$C_{18}H_{18}O_4$Na]: *m*/*z* = 321.1103, found 321.1107. In addition, the side product 5-ethynyl-1,2-dimethoxy-4-(3-methoxyphenyl)benzene (100 mg, 3%) was isolated as a colorless oil.

(2,3,6-Trimethoxyphenanthrene-9-yl)methanol (13): 1,2-Dimethoxy-4-(3-methoxyphenyl)-5-(1-hydroxyprop-2-yn-3-yl)benzene (**10**, 298 mg, 1.00 mmol) was dissolved in DMF (6.00 mL) and stirred at room temperature. Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I) (31.1 mg, 50.0 µmol 5.0 mol-%) and $AgSbF_6$ (25.8 mg, 75.0 µmol, 7.5 mol-%) were added and the mixture was stirred for 48 h. After complete consumption of the starting material (determined by HPLC, method: vide infra), the suspension was filtered by using a syringe tip filter (PTFE, i.d. 20.0 mm, 0.20 µm) and was directly injected into the HPLC injection valve (5.0 mL). Subsequently, purification was achieved by preparative RP-HPLC affording the desired phenanthrene **13** (212 mg, 71%) as a single regioisomer and as a colorless solid. R_f = 0.31 (toluene/EtOAc = 3:1); m.p. 179.5–180.3 °C, ref. 181–184 °C,[23e] 183–184 °C.[29] RP-HPLC (i.d. 4.6 mm; 30.0 mm): t_R = 7.5 min, ACE3-C_{18}PFP, MeCN/H_2O = 55:45, isocratic, 1.00 mL·min^{-1}, λ = 212 nm, T = 40 °C; t_R = 7.8 min, ACE5-C_{18}PFP, 37.5 mL·min^{-1}, T = 21 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, J = 9.0 Hz, 1 H, 8-*H*), 7.86 (d, J = 2.7 Hz, 1 H, 5-*H*), 7.80 (s, 1 H, 4-*H*), 7.49 (s, 1 H, 10-*H*), 7.23 (dd, J = 9.0, 2.7 Hz, 1 H, 7-*H*), 7.14 (s, 1 H, 1-*H*), 5.10 (s, 2 H, CH_2OH), 4.08 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3) ppm. ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ = 158.1 (C_q-OCH$_3$), 149.6 (C_q-OCH$_3$), 149.3 (C_q-OCH$_3$), 132.9 (C8a), 131.8 (C4b), 127.1 (C10a), 126.2 (C8), 124.5 (C4a), 124.3 (C9), 123.3 (C10), 115.3 (C7), 108.5 (C1), 104.8 (C5), 103.4 (C4), 64.4 (*C*H$_2$OH), 56.2 (OCH_3), 56.0 (OCH_3), 55.7 (OCH_3) ppm. FTIR (ATR): $\tilde{\nu}$ = 3210, 2925, 2874, 1675, 1611, 1511, 1468, 1429, 1377, 1343, 1230, 1068, 887, 830, 775 cm^{-1}. MS (ESI$^+$): *m*/*z* (%) = 299.1 (100) [*M* + H]$^+$, 281.1 (16) [*M* – (OH)]$^+$. HRMS (ESI$^+$): Calcd. for [$C_{18}H_{18}O_4$Na]: *m*/*z* = 321.1103, found 321.1102.

2,3,6-Trimethoxyphenanthrene-9-carbaldehyde: Dess–Martin periodinane (810 mg, 1.50 equiv.) was added in one portion to a stirred solution (T = 0 °C) of (2,3,6-trimethoxyphenanthrene-9-yl)-methanol (380 mg, 1.27 mmol) in CH_2Cl_2 (20 mL). Stirring was continued at this temperature for 1 h, then the cooling bath was removed, and the reaction mixture was stirred at room temperature for 15 h. Diethyl ether (50 mL) and aqueous NaOH (1.3 M, 15.4 mL) were added and the mixture was stirred for another 10 min. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 25 mL). After washing the combined organic extracts with aqueous NaOH (1.3 M, 15 mL) followed by drying over anhydrous Na_2SO_4, the solvent was removed in vacuo and the crude residue was purified by preparative RP-HPLC delivering the desired aledhyde (266 mg, 71%) as a slightly yellowish solid. R_f = 0.45 (toluene/EtOAc = 3:1); m.p. 162.1–162.9 °C, ref. 161 °C.[30] RP-HPLC (i.d. 4.6 mm; 30.0 mm): t_R = 8.1 min, ACE3-C_{18}PFP, H_2O/MeCN = 40:60, 1.00 mL·min^{-1}, T = 40 °C, λ = 212 nm; t_R = 10.5 min, ACE5-C_{18}PFP, 37.5 mL·min^{-1}, T = 21 °C. ^{1}H NMR, COSY (400 MHz, CD_2Cl_2): δ = 10.20 (s, 1 H, C*H*O), 9.25 (d, J = 9.1 Hz, 1 H, 8-*H*), 7.95 (s, 1 H, 10-*H*), 7.82 (d, J = 2.7 Hz, 1 H, 5-*H*), 7.78 (s, 1 H, 4-*H*), 7.29 (dd, J = 9.1, 2.7 Hz, 1 H, 7-*H*), 7.28 (s, 1 H, 1-*H*), 4.07 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3) ppm. ^{13}C NMR, HSQC, HMBC (100.6 MHz, CD_2Cl_2): δ = 193.4 (*C*HO), 158.6 (C_q-OMe), 152.1 (C_q-OMe), 150.0 (C_q-OMe), 138.3 (C10), 131.6 (C8a), 128.7 (C9), 127.5 (C10a) 127.4 (C8), 125.6 (C4b), 122.1 (C4a), 116.3 (C7), 109.5 (C1), 104.3 (C5), 103.4 (C4), 56.0 (OCH_3), 55.9 (OCH_3), 55.4 (OCH_3) ppm. FTIR (ATR): $\tilde{\nu}$ = 2893, 2831, 2714, 1672 (C=O), 1612, 1576, 1521, 1510, 1457, 1210, 1070, 829, 816, 707, 612 cm^{-1}. MS (ESI$^+$): *m*/*z* (%) = 319.0 (30) [*M* + Na]$^+$, 297.0 (100) [*M* + H]$^+$. HRMS (ESI$^+$): Calcd. for [$C_{18}H_{17}O_4$]: *m*/*z* = 297.1127, found 297.1126.

2,3,6-Trimethoxyphenanthrene-9-carboxylic Acid (14): For oxidations of the type (R-CHO → R-CO_2H) according to a method of Pinnick, see ref.[20] A solution containing sodium chlorite (518 mg, 5.73 mmol. 9.20 equiv.) and sodium dihydrogen phosphate (516 mg, 4.30 mmol, 6.90 equiv.) in water (6.75 mL) was added over 10 min (room temp.) to a stirred solution of 2,3,6-trimethoxyphenanthrene-9-carbaldehyde (185 mg, 623 µmol) in a mixture of *tert*-butanol (13.1 mL) and 2-methylbut-2-ene (4.10 mL). The reaction mixture was stirred for 15 h at room temperature. After complete consumption of the starting material (HPLC), the solvent was removed in vacuo and the residue dissolved in a mixture of HCl (1 M)/$CHCl_3$ = 1:1 (100 mL). The organic layer was separated, then the aequous layer was extracted with $CHCl_3$ (2 × 50 mL). After drying of the combined organic extracts over anhydrous Na_2SO_4, the solvent was removed in vacuo. Purification of the residue by preparative RP-HPLC afforded **14** (193 mg, 98%) as a colorless lyophilisate. R_f = 0.08 (toluene/EtOAc) = 3:1. RP-HPLC (i.d. 4.6 mm, 30.0 mm): t_R = 6.9 min, H_2O (0.1% HCO_2H)/MeCN = 50:50, ACE3-C_{18}PFP, 1.00 mL·min^{-1}, T = 40 °C; t_R = 7.0 min, ACE5-C_{18}PFP, 37.5 mL·min^{-1}; m.p. 148.1–148.4 °C (lyophilisate), ref. 222 °C (crystallized).[12l] ^{1}H NMR, COSY (400 MHz, [D_6]-DMSO): δ = 12.49 (s, 1 H, CO_2H), 8.88 (d, J = 9.3 Hz, 1 H, 8-*H*), 8.36 (s, 1 H, 10-*H*), 8.14 (d, J = 2.6 Hz, 1 H, 5-*H*), 8.10 (s, 1 H, 4-*H*), 7.61 (s, 1 H, 1-*H*), 7.30 (dd, J = 9.3, 2.6 Hz, 1 H, 7-*H*), 4.08 (s, 3 H, OCH_3), 4.02 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3) ppm. ^{13}C NMR, HSQC, HMBC (100.6 MHz, [D_6]DMSO): δ = 168.9 (*C*O_2H), 157.8 (C_q-OMe), 150.9 (C_q-OMe), 149.6 (C_q-OMe), 131.5 (C4b), 129.0 (C10), 127.9 (C8), 126.1 (C4a), 125.3 (C10a), 124.0 (C9), 122.7 (C8a), 116.2 (C7), 109.7 (C1), 104.5 (C5), 104.0 (C4), 56.0 (OCH_3), 55.6 (OCH_3), 55.5 (OCH_3) ppm. FTIR (ATR): $\tilde{\nu}$ = 2940, 2833, 2610, 1667, 1667, 1616, 1525, 1510, 1465, 1449, 1424, 1411, 1230, 1122, 811, 744 cm^{-1}. MS (ESI$^+$): *m*/*z* (%) = 313.1 (100) [*M* + H]$^+$, 295.0 (51) [*M* – (OH)]$^+$. HRMS (ESI$^+$): Calcd. for [$C_{18}H_{17}O_5$]: *m*/*z* = 313.1076, found 313.1071.

(*R*)-[2-(Hydroxymethyl)piperidine-1-yl]-(2,3,6-trimethoxyphenanthrene9-yl)methanone [(*R*)-16]: (*R*)-2-(hydroxymethyl)piperidine [(*R*)-**15**], (172 mg, 1.49 mmol, 1.50 equiv.), EDC·HCl (227 mg, 1.19 mmol, 1.20 equiv.) and 4-(dimethylamino)pyridine (DMAP, 24.2 mg, 198 µmol, 0.20 equiv.) were added to a cooled (T = 0 °C) and well-stirred solution of 2,3,6-trimethoxyphenanthrene-9-carboxylic acid (**14**, 310 mg, 992 µmol) in $CHCl_3$ (7.44 mL). The mixture was then stirred for 15 h at room temperature. After the addition of HCl (1 M, 7.50 mL) stirring was continued for another 5 min, then the organic layer was separated, washed with water

(10 mL), dried with anhydrous Na_2SO_4 and finally, the solvent was removed in vacuo. Purification of the residue by preparative RP-HPLC furnished amide (*R*)-**16** (279 mg, 69%) as a colorless oil. R_f = 0.77 (EtOAc/EtOH = 3:1). RP-HPLC/MS (i.d. 2.1 mm): = t_R = 2.6 min, MeCN/H_2O (0.1 HCO_2H) = 10:90 (0.0 min)→80:20 (3.0 min), C_{18} (50×2.1 mm), *T* = 50 °C, 1.00 mL·min^{-1}. RP-HPLC (i.D: 4.6 mm; 30.0 mm): t_R = 5.5 min, H_2O/MeCN = 55:45, ACE3-C_{18}PFP, 1.00 mL·min^{-1}, *T* = 25 °C; ACE5-C_{18}PFP, 37.5 mL·min^{-1}. $[\alpha]_D^{23}$ = +4.3 (*c* = 0.87, CH_2Cl_2). ^{1}H NMR, COSY (400 MHz, CD_3CN): (rotamers) δ = 8.04–7.98 (m, 2 H, aryl-*H*), 7.88–7.79 (m, 1 H, aryl-*H*), 7.50–7.40 (m, 1 H, aryl-*H*), 7.37–7.32 (m, 1 H, aryl-*H*), 7.26–7.16 (m, 1 H, aryl-*H*), 5.03–4.93/3.81–3.73/3.50–3.42 (m, 1 H, 2′-*H*), 4.77–4.61/3.26–3.19 (m, 2 H, 6′-*H*^{1}), 3.93–3.68/3.63–3.31 (m, 2 H, CH_2OH), 4.06 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 3.10–2.92/2.92–2.81 (m, 2 H, 6′-*H*^{2}), 1.91–1.30 (m, 6 H, 3′-*H*, 4′-*H*, 5′-*H*) ppm. ^{13}C NMR, HSQC, HMBC (100.6 MHz, CD_3CN): (rotamers) δ = 171.2/171.2/171.1/170.7 (*C*=O), 159.6/159.7/159.6/159.5 (C_q-OCH_3), 151.1/151.1/151.0/151.0 (C_q-OCH_3), 150.9/150.9/ 150.9/150.9 (C_q-OCH_3), 133.5/133.3/133.1/133.0 (C_q), 132.2/132.6/132.3/132.1 (C_q), 128.5/129.7/129.6/128.2 (*C*H), 127.9/127.6/127.6/127.3 (C_q), 125.1/125.2/125.1/124.9 (C_q), 123.1/123.8/123.2/122.9 (*C*H), 121.5/121.9/121.3/120.6 (*C*H), 117.3/117.3/ 116.7/116.1 (*C*H), 109.7/109.7/109.7/109.6 (*C*H), 105.2/105.1/104.8/104.7 (*C*H), 61.0/60.9/60.4/60.2 (CH_2OH), 56.7 (OCH_3), 56.4 (OCH_3), 56.3 (OCH_3), 51.1/57.6/56.8 (C2′), 44.7/44.0/37.9 (C6′), 27.1/26.6/26.6/26.4/26.4/26.2/25.8/25.8 (C5′,C3′), 20.4, 20.4, 20.3, 20.1 (C4′) ppm. FTIR (ATR): $\tilde{\nu}$ = 2936, 2856, 1613, 1510, 1347, 1252, 1159, 1042, 731 cm^{-1}. MS (ESI$^+$): *m*/*z* (%) = 410.2 (100) $[M + H]^+$. HRMS (ESI$^+$): calcd. for $[C_{24}H_{28}NO_5]$: *m*/*z* = 410.1962, found 410.1967.

(*R*)-*O*-Ethyl-*S*-[(1-(2,3,6-trimethoxyphenanthrene-9-carbonyl)piperidine-2-yl)methyl]xanthogenate [(*R*)-17]: At *T* = –30 °C methanesulfonyl chloride (12.3 µL, 18.2 mg, 159 µmol, 1.25 equiv.) and DIPEA (27.1 µL, 20.6 mg, 159 µmol, 1.25 equiv.) were added dropwise to a stirred solution of the alcohol (*R*)-**16** (52.0 mg, 127 µmol) in dichloroethane (2.50 mL) After complete addition the mixture was stirred at this temperature for another 20 min, then 1 h at room temperature (TLC). If the starting material had not been completely consumed, additional methanesulfonyl chloride (6.15 µL, 9.10 mg, 79.5 µmol, 0.63 equiv.) and DIPEA (13.5 µL, 10.3 mg, 79.5 µmol, 0.63 equiv.) were added and stirring was continued for another 1 h (*T* = 0 °C→25 °C). Subsequently, acetone (1.00 mL) and potassium *O*-ethyl xanthogenate (22.3 mg, 140 µmol, 1.10 equiv.) were added to the reaction mixture (suspension). After stirring for 15 h, the solvent was removed in vacuo. The crude residue was dissolved in DMF and purified by preparative RP-HPLC, affording the title compound (45.3 mg, 69%, 2 steps) as a colorless oil. R_f = 0.33 (toluene/EtOAc = 3:1). RP-HPLC/MS (i.d. 2.1 mm): t_R = 5.2 min, MeCN/H_2O (0.1% HCO_2H) = 5:95 (0.0 min)→85:15 (4.0 min), C_{18} (30×2.1 mm), 0.50 mL·min^{-1}, *T* = 40 °C. RP-HPLC (i.d. 4.6 mm; 30.0 mm): t_R = 7.8 min, H_2O/MeCN = 35:65, ACE3-C_{18}PFP, 1.00 mL·min^{-1}, *T* = 21 °C; ACE5-C_{18}PFP, 37.5 mL·min^{-1}. $[\alpha]_D^{23}$ = +59.9 (*c* = 0.43, CH_2Cl_2). ^{1}H NMR, COSY, NOESY (600 MHz, CD_3CN): (rotamers) δ = 8.04–7.94 (m, 2 H, aryl-*H*), 7.89–7.76 (m 1 H, aryl-*H*), 7.50–7.40 (m 1 H, aryl-*H*), 7.39–7.30 (m, 1 H, aryl-*H*), 7.16–7.09 (m, 1 H, aryl-*H*), 5.30 (m_c, 0.4 H, 2′-*H*), 4.80–4.68 (m_c; 1 H, OCH_2Me and 0.5 H, 6′-*H*), 4.46–4.39 (m_c, 0.3 H, 2′-*H*), 4.00–3.82 (3×m, 0.5 H, OCH_2Me), 4.07/4.06 (s_{br}, 3 H, OCH_3), 4.02/4.01 (s_{br}, 3 H, OCH_3), 3.95/3.94 (s_{br}, 3 H, OCH_3), 3.77–3.64 (m_c, 0.7 H, OCH_2Me, CH_2SCSOEt), 3.50 (dd, *J* = 12.8, 5.3 Hz, 0.4 H, CH_2SCSOEt), 3.46–3.40 (m_c, 0.5 H, CH_2SCSOEt), 3.28–3.22 (m, 0.5 H, 6′-*H*), 3.17 (dd, *J* = 14.7, 4.6 Hz, 0.3 H, CH_2SCSOEt), 3.09 (dd, *J* = 14.7, 4.6 Hz, 0.3 H, CH_2SCSOEt), 3.13–2.96 (m, 0.5 H, 6′-*H*), 2.91–2.81 (m, 0.5 H, 6′-*H*), 2.10–1.61 (m, 6 H, 3′-*H*, 4′-*H*, 5′-*H*), 1.44 (t, *J* = 7.3 Hz, 1.4 H, OCH_2CH_3), 0.98 (t, *J* = 7.3 Hz, 0.6 H, OCH_2CH_3), 0.89 (t, *J* = 7.3 Hz, 1 H, OCH_2CH_3) ppm. ^{13}C NMR, HSQC, HMBC (151 MHz, CD_3CN): (rotamers) δ = 215.7/215.4/214.5/214.2 (*C*=S), 170.7/170.6/170.6 (*C*=O), 159.7/159.6/159.6/159.4 (2×C_q-OMe), 151.1/151.0/151.0/150.8 (C_q-OMe), 133.0/132.5/132.5/132.2/131.9/131.7 (2×C_q), 129.6/128.9/128.4/128.2 (*C*H), 127.8/127.4/127.3/126.9 (C_q), 125.4/125.0/125.0/124.9 (C_q), 123.7/123.7/122.9/122.9 (C_q), 121.6/121.5/121.4 (*C*H), 117.2/117.2/117.1/117.0 (*C*H), 110.3/110.2/109.6/109.5 (*C*H), 105.1/105.0/104.7/104.7 (*C*H), 104.6/104.5/ 104.5/104.1 (*C*H), 71.6/71.5/71.0/71.0 [C(=S)O*C*H_2Me], 56.6/56.6 (OCH_3), 56.3/56.3 (OCH_3), 56.2/56.1 (OCH_3), 53.4/53.2/47.6/47.3 (C2′), 43.9/43.3/37.4/37.4 (C6′), 36.7/36.4/36.3/36.2 [*C*H_2SC(=S)OEt], 29.7/29.3/28.9/28.7 (C5′), 27.2/26.6/26.4/26.2 (C3′), 19.9/19.7 (C4′), 14.0/13.4/13.3 (OCH_2CH_3) ppm. FTIR (ATR): $\tilde{\nu}$ = 2935, 2714, 1671, 1614, 1521, 1509, 1427, 1377, 1294, 1207, 990, 793, 751 cm^{-1}. MS (ESI$^+$): *m*/*z* (%) = 514.1 (100) $[M + H]^+$, 295.1 (16) $[C_{18}H_{15}O_4]^{+}$. HRMS (ESI$^+$): calcd. for $[C_{27}H_{32}NO_5S_2]$: *m*/*z* = 514.1722, found 514.1718.

(*R*)-(–)-Cryptopleurine (3): For intramolecular cyclization reactions of xanthogenates attacking aromatic compounds according to a method developed by Zard, see ref.[22a] **Cyclization:** Dilauroyl peroxide (2.23 mL, 1.50 equiv., 0.05 M in $C_2H_4Cl_2$) was added dropwise, over a period of about 5 h (syringe pump, constant rate: 0.45 mL·h^{-1}) to a stirred solution of the xanthogenate [(*R*)-**17**, 38.0 mg, 74.1 µmol] in boiling 1,2-dichloroethane (2.50 mL). After the addition was completed, the reaction mixture was heated to reflux for 10 h. A second portion of dilauroyl peroxide (1.12 mL, 0.75 equiv., 0.05 M in $C_2H_4Cl_2$) was then added (syringe pump, 0.45 mL·h^{-1}, $t_{add.} \approx$ 2.5 h) and the mixture heated to reflux for another 3 h, after the addition had been completed. Evaporation of the solvent gave a crude residue which was used in the reduction step without further purification or characterization. **Reduction:** The crude residue from the cyclization step was dissolved in THF (6.00 mL) and the resulting solution was added dropwise to a stirred solution of $LiAlH_4$ (155 µL, 371 µmol, 5.00 equiv., 2.4 M in THF, diluted with dry THF to a final volume of 4.00 mL) at room temperature. After the addition had been completed the reaction mixture was slightly warmed (*T* < 50 °C) in a water bath and stirred for 20 min. The suspension was re-cooled to *T* = 0 °C and subsequently treated with EtOH (150 µL), water (150 µL) and aqueous NaOH (150 µL, 15% in H_2O). The precipitate was filtered off and after being washed with fresh THF (50 mL), it was discarded. Removing the solvent in vacuo furnished a crude residue which was purified by multiple preparative (**#**) HPLC runs (**#1**+**#2**: reversed phase, **#3**+**#4**: normal phase). **#1**: MeCN/H_2O = 40:60 (0.0 min)→80:20 (10.0 min), ACE3-C_{18}PFP, 1.00 mL·min^{-1}, *T* = 21 °C; ACE5-C_{18}PFP, 37.5 mL·min^{-1}. **#2**: MeCN/H_2O = 20:80 (0.0 min)→80:20 (10.0 min), ACE3-C_{18}, 1.50 mL·min^{-1}; ACE5-C_{18}, 26.2 mL·min^{-1}. 14.0 mg (50%), slightly yellowish solid, *er* > 99:1 (determined by HPLC on chiral phase). M.p. 186.1–189.4 °C, ref. 191–192 °C,[12g] 191–193 °C.[12b] UV/Vis: λ_{max} = 257, 286 nm (DAD, HPLC). RP-HPLC/MS (i.d. 2.1 mm): t_R= 2.3 min, MeCN/H_2O (0.1% HCO_2H) = 10:90 (0.00–0.50 min)→90:10 (3.00 min), C_{18} (50×2.1 mm), 1.00 mL·min^{-1}, *T* = 50 °C. HPLC (i.d. 4.6 mm; 21.2 mm): t_R = 8.5 min, $CHCl_3$/EtOH = 99:1, NUCLEODUR® 1.00 mL·min^{-1} (4.6 mm), *T* = 21 °C; 17.5 mL·min^{-1} (21.2 mm). Chiral HPLC (i.d. 4.6 mm): *rac*-**3**: t_R = 30.7 min [(*S*)-**3**], 39.4 min [(*R*)-**3**], ChiralPak® AD-H, 100% EtOH, 0.50 mL·min^{-1}, *T* = 40 °C, λ = 254 ±4 nm; ^{1}H NMR, COSY, NOESY (400 MHz, CD_2Cl_2): δ = 7.93–7.87 (m, 3 H, 1-*H*, 4-*H*, 5-*H*), 7.22 (dd, *J* = 9.3, 2.4 Hz, 1 H, 7-*H*), 7.13 (m_c, 1 H, 8-*H*), 4.44 (d, *J* = 15.5 Hz, 1 H,

9-H^1), 4.05 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 3.69 (d, J = 15.5 Hz, 1 H, 9-H^2), 3.37 (d, J = 11.3 Hz, 1 H, 11-H^1) 3.21 (dd, J = 16.7, 3.7 Hz, 1 H, 15-H^1), 3.01 (dd, J = 16.7, 10.4 Hz, 1 H, 15-H^2), 2.57 (m_c, 1 H, 14a-H), 2.41 (m_c, 1 H, 11-H^2), 2.05 (dd, J = 13.0, 3.2 Hz, 1 H, CH_2), {1.94–1.79 (m, 3 H), 1.70–1.58 (m, 1 H), 1.54–1.42 (m, 1 H), 12-H, 13-H, 14-H} ppm. ^{13}C NMR, HSQC, HMBC (100.6 MHz, CD_2Cl_2): δ = 158.2 (C_q-OMe), 150.1 (C_q-OMe), 149.0 (C_q-OMe), 130.7 (C_q), 129.7 (C_q), 126.2 (C_q), 126.0 (C_q), 125.2 (*C*H), 125.0 (C_q), 123.6 (C_q), 115.4 (C-7), 104.8 (*C*H), 104.6 (*C*H), 103.6 (*C*H), 58.0 (C-14a), 56.3 (O*C*H$_3$), 56.2 (O*C*H$_3$), 56.1 (C-11) 55.8 (O*C*H$_3$), 55.8 (C-9), 34.1 (C-15), 33.1(C-14), 26.2 (C-12), 24.3 (C-13) ppm. FTIR (ATR): $\tilde{\nu}$ = 2931, 1612, 1514, 1470, 1426, 1246, 1125, 731 cm^{-1}. MS (ESI+): *m/z* (%) = 378.2 (100) $[M + H]^+$. MS^2 (ESI+, MS → MS^2): *m/z* (%) = 378.2 (100) $[M + H]^+$ → 295.1 (100). HRMS (ESI+): calcd. for $[C_{24}H_{28}NO_3]$: *m/z* = 378.2069, found: 378.2070. The analytical data are in accordance with the literature.[12b,31] A third preparative HPLC run was performed prior to the measurement of the optical rotation as decomposition had occurred during acquisition of the analytical data. **#3**: CH_2Cl_2/ethanol = 95:5, NUCLEODUR®, 1.50 mL·min^{-1} (4.6 mm), T = 21 °C; 26.2 mL·min^{-1} (21.2 mm). (*R*)-**3**: >98% *ee*. $[\alpha]_D^{21}$ = −97.1 (c = 0.20, $CDCl_3$); ref. $[\alpha]_D^{20}$ = −108.7 (c = 1.03, $CHCl_3$),[12g] $[\alpha]_D^{20}$ = −103 (c = 2.13, $CHCl_3$).[12b] A fourth preparative HPLC run was performed as decomposition had occurred during acquisition of the analytical data. **#4**: t_R = 8.5 min, $CHCl_3$/EtOH = 99:1, NUCLEODUR® 1.00 mL·min^{-1} (4.6 mm), T = 21 °C; 17.5 mL·min^{-1} (21.2 mm); 11.5 mg (41% over 2 steps), slightly yellowish solid. The analytical HPLC of this material is shown in Figure 2<xfig2>.

Supporting Information (see footnote on the first page of this article): 1D and 2D NMR spectra of all synthesized compounds, HPLC- and HPLC/MS data.

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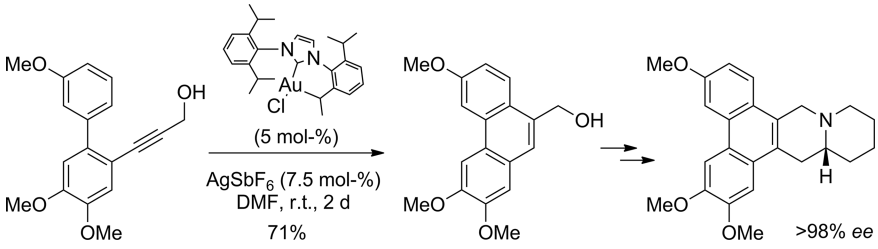
Alkaloid Synthesis



(*R*)-(–)-Cryptopleurine, a highly bioactive phenanthroquinolizidine alkaloid, was synthesized in high optical purity using a combination of gold(I)-NHC catalyzed regioselective ring closure of an unsymmetrical phenanthrene precursor and free radical cyclization chemistry to install ring C in the penultimate step.

Keywords: Total synthesis / Natural products / Alkaloids / Nitrogen heterocycles / Radical reactions / Gold

