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Divergent Total Synthesis of Triptolide, Triptonide, Tripdiolide, 16-Hydroxytriptolide, and Their Analogues

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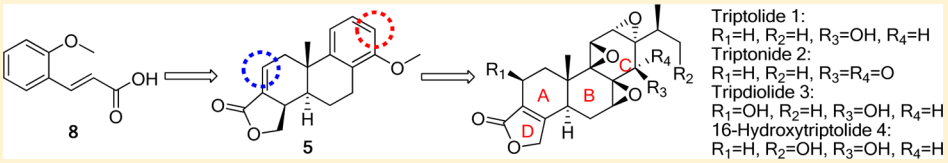
Supporting Information

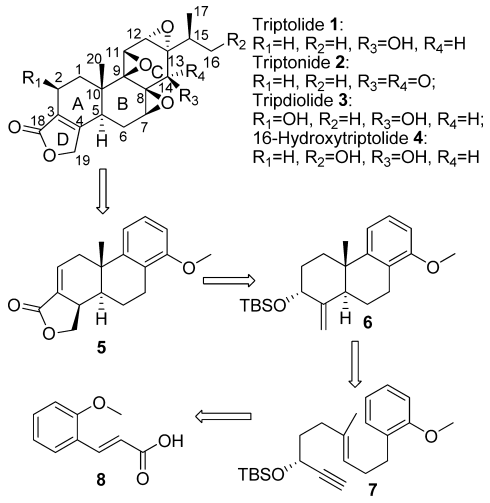


ABSTRACT: A divergent route was developed for the formal total synthesis of triptolide, triptonide, and tripdiolide, as well as a total synthesis of 16-hydroxytriptolide and their analogues in an enantioselective form. Common advanced intermediate **5** was concisely assembled by employing an indium(III)-catalyzed cationic polycyclization reaction and a palladium-catalyzed carbonylation−lactone formation reaction as key steps. This advanced intermediate was readily converted to the above natural products by using palladium-catalyzed cross-coupling or the Claisen rearrangement reaction as key steps. Additionally, preliminary structure−cytotoxic activity relationship studies of C13 suggested that it might be a new modification site that could still retain the cytotoxicity.

INTRODUCTION

Triptolide **1**, triptonide **2**, tripdiolide **3**, and 16-hydroxytriptolide **4** are structurally related bioactive diterpene natural products isolated from *Tripterygium wilfordii* Hook. f. (TWHF) (Scheme 1),[1] a vinelike plant indigenous to many southern provinces of China, whose crude extracts have been widely used in treatment of cancer and autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus.[2] Key structural features of these compounds include three successive epoxide groups on the B/C ring, a *trans*-decalin A/B-ring system, and an unsaturated five-membered lactone D-ring. All these compounds possess potent antitumor, anti-inflammatory, and immunosuppressive activities.[3] Their fascinating structure and distinguished biological activity led to considerable interest in their total synthesis and structure modifications in the past few decades and yielded important structure−activity relationship information.[4] Triptolide and its derivatives have already entered human clinical trials for rheumatoid arthritis and cancer.[5] In view of the common structural feature of these natural products, it is highly desirable to develop a synthesis, in which a readily accessible fragment bearing suitable functionality would serve as a common intermediate for the convergent and efficient synthesis of these natural products as well as a small library of triptolide analogues to fully understand their structure−cytotoxic activity relationship. Herein we describe a divergent route toward the total synthesis of these natural products from readily available 2-methoxycinnamic acid **8** (Scheme 1).

Scheme 1. Structures of Triptolide, Triptonide, Tripdiolide, and 16-Hydroxytriptolide and Retrosynthetic Analysis



RESULTS AND DISCUSSION

As shown in Scheme 1, triptolide, triptonide, tripdiolide, and 16-hydroxytriptolide could potentially be synthesized from common advanced tetracyclic intermediate **5**, a key intermediate bearing suitable functionality for the convergent and efficient synthesis of these natural products. We envisioned that the construction of lactone **5** would be achieved via palladium-catalyzed carbonylation reaction using alkene **6** as the precursor.[6] The *trans*-decalin A/B ring framework of **6** could

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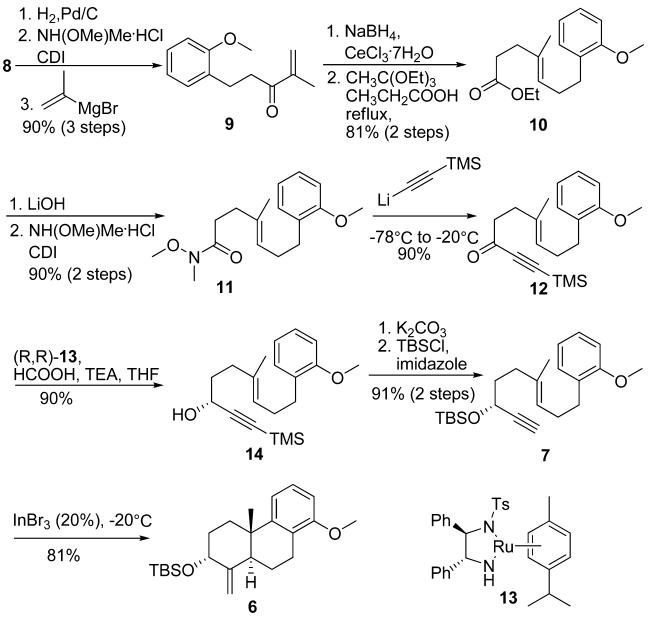
be synthesized by indium(III)-catalyzed cationic polyene cyclization reaction from chiral propargylic silyl ether **7**.[7] The acyclic chiral ether **7** could be synthesized from commercially available 2-methoxycinnamic acid **8**.

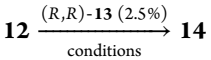
Our synthetic work began with the hydrogenation of commercially available acid **8** (Scheme 2), which was converted

Scheme 2. Synthesis of Intermediate 6



to the corresponding Weinreb amide followed by reaction with isopropenylmagnesium bromide to afford enone **9**. Luche reduction of **9**[8] followed by Johnson–Claisen rearrangement produced ester **10**.[9] Hydrolysis of **10** followed by Weinreb amide formation produced amide **11**, which was reacted with lithium trimethylsilyl acetylide to give alkynone **12**. For the preparation of optically active propargylic alcohol (*R*)-**14**, we initially subjected **12** to an enantioselective transfer hydrogenation reaction using Noyori's Ru-catalyst (*R*,*R*)-**13** in 2-propanol at room temperature,[10] but unfortunately, upon stirring for 24 h, no reaction occurred (Table 1). After several

Table 1. Conditions for Asymmetric Transfer Hydrogenation



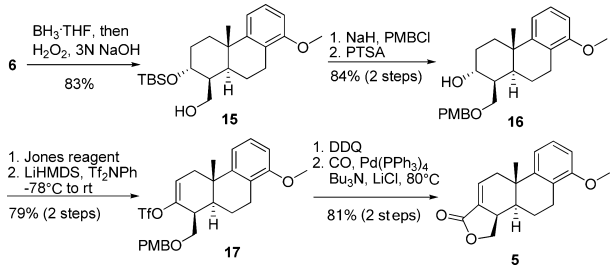
		14	
entry	conditions	yield (%)	ee (%)[a]
1	iPrOH, rt, 24 h	n.r.	n.r.
2	HCOOH, Et_3N, 1.5 h	15	98
3	HCOOH, Et_3N, THF, rt, 2.5 h	90	96

[a]Determined by HPLC analysis.

attempts, we found that treatment of **12** with 2.5 mol % of (*R*,*R*)-**13** in triethylamine and formic acid for 1.5 h provided the desired alcohol **14** in only 15% yield with 98% ee.[11] This was probably due to the instability of the trimethylsilyl group in the reaction system. When the reaction was conducted with 2.5 mol % of **13** in the presence of triethylamine and formic acid in tetrahydrofuran at room temperature for 2.5 h,[12] alcohol **14** was obtained in 90% yield with comparable enantioselectivity (96% ee) (see Supporting Information). During workup with potassium carbonate/methanol, the acetylenic trimethylsilyl group was cleaved and the hydroxyl group was protected as a *tert*-butyldimethylsilyl ether to give chiral silyl ether **7**. The key indium(III)-catalyzed cationic cascade reaction of **7** was then achieved by slow addition of **7** to an intensely stirred suspension of $InBr_3$ in dichloromethane at −20 °C.[7a] Under this condition, key intermediate **6** was obtained in 81% yield, as a single isomer. More importantly this reaction can routinely be carried out on a 10 g scale without loss of yield.

With the *trans*-decalin A/B ring framework alkene **6** in hand, our attention was turned to the construction of the lactone D-ring (Scheme 3). Hydroboration of **6** with BH_3·THF complex

Scheme 3. Synthesis of Intermediate 5



and subsequent oxidation with alkaline hydrogen peroxide yielded alcohol **15** as the single isomer. Protection of the free hydroxyl group as the PMB ether followed by treatment with *p*-TsOH resulted in removal of the silyl protecting group to afford alcohol **16**. Oxidation of **16** with Jones reagent followed by conversion of the resulting carbonyl group to the corresponding vinyl triflate afforded compound **17**. Finally, oxidative PMB ether cleavage of **17** followed by palladium-catalyzed carbonylation[6] and in situ lactonization gave tetracyclic lactone **5**, whose structure was secured by X-ray single-crystal analysis[13] (see Supporting Information).

With the advanced intermediate **5** secured, we then moved forward to investigate its conversion to triptolide, triptonide, tripdiolide, and 16-hydroxytriptolide in a divergent manner (Schemes 4 and 5). After investigation of a variety of reported double bond migration conditions (Table 2), such as $RhCl_3 \cdot 3H_2O$,[14] Grubbs II catalyst,[15] $Rh(PPh_3)_3Cl$,[16] $Pd(OAc)_2$, and DBU,[17] we were glad to find that reaction of **5** with a catalytic amount of tris(triphenylphosphine)rhodium and triethylsilane in refluxing toluene afforded **18** in high yield. Ortho-iodination of **18** gave intermediate **19** in quantitative yield, which was subjected to palladium-catalyzed cross-coupling with 1-methyl-1-(prop-2-enyl)silacyclobutane **20**[18] followed by hydrogenation to produce triptophenolide methyl ether **21** ($[\alpha]^{25}_D$ +39.5 (*c* 0.42, CH_2Cl_2); lit.,[4e] $[\alpha]^{25}_D$ +40.3 (*c* 0.37, CH_2Cl_2)), a key advanced intermediate which was previously used for the synthesis of triptolide **1** and triptonide **2**.[4e,i]

Next, dihydroxylation of **5** at room temperature with OsO_4(cat.)/NMO and subsequent Parikh–Doering oxidation provided ketone **22** (Scheme 4),[19] whose structure was secured by X-ray single-crystal analysis (see Supporting Information).[13] Dehydration of **22** using the Burgess reagent in refluxing benzene followed by Luche reduction produced 2-*β*-alcohol **23**.[8,20] Ortho-iodination of **23** gave the C13-iodine intermediate, which was not isolable because of poor solubility and was subjected to palladium-catalyzed cross-coupling reaction with 1-methyl-1-(prop-2-enyl)silacyclobutane **20**[18] followed by

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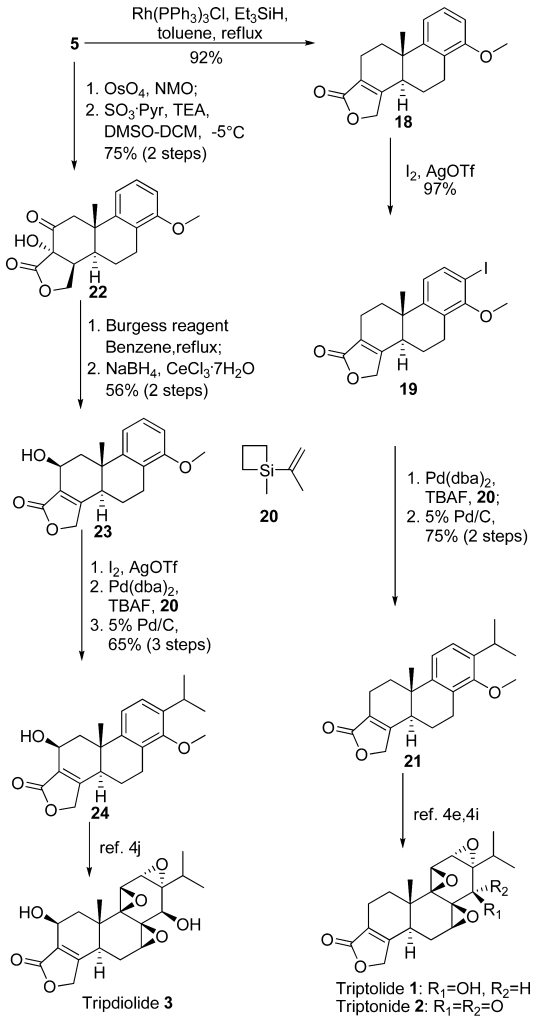
Scheme 4. Synthesis of Key Intermediates 21 and 24



dehydrogenation to afford 2-β-hydroxytriptophenolide methyl ether **24** ($[\alpha]^{25}_D$ +32.1 (*c* 0.09, CH_2Cl_2); lit.[4j] $[\alpha]^{25}_D$ +30 (*c* 0.06, CH_2Cl_2)), a key advanced intermediate which was previously used for the synthesis of tripdiolide **3**.[4j]

The synthesis of 16-hydroxytriptolide **4** commenced with benzylic oxidation of compound **18** with ceric nitrate and subsequent Jones oxidation to give ketone **25** (Scheme 5).[21] Subsequent treatment of **25** with BBr_3 resulted in removal of the methyl protecting group to afford phenol **26**. Alkylation of the phenol group of **26** with crotyl bromide produced allylic ether **27**, which was subjected to Claisen rearrangement to produce a 1:1 mixture of C15 epimers **28a** and **28b**. Oxidative cleavage of the terminal alkene of **28a**/**28b** using OsO_4(cat.)/$NaIO_4$ afforded aldehyde **29a** and **29b**. Treatment of **29a** and **29b** with $NaBH_4$ produced the corresponding triol intermediate, which was directly subjected to periodate oxidation to give **30a** and **30b**.[22] Note that compounds **28a** and **28b**, **29a** and **29b**, and the triol intermediates could not be separated by flash chromatography or preparative HPLC, but the monoepoxide intermediates **30a** and **30b** could be separated by flash chromatography. Subsequently, epoxidation of **30a** and **30b** by in situ-generated methyl(trifluoromethyl)dioxirane[4e] and further epoxidation with alkaline hydrogen peroxide successfully introduced the C9,C11 and C12,C13 epoxides, respectively, to give compounds **31** and **32**. After careful analysis of ^{1}H NMR spectra of compounds **31** and **32**, we found that the C16 methylene group of compound **32** showed two dd peaks (δ 3.64, dd, 1H and 3.55, dd, 1H), which was similar to that of natural 16-hydroxytriptolide (δ 3.26, dd, 1H and 3.15, dd, 1H), while the methylene group of compound **31** showed two s peaks (δ 3.58, s, 1H and 3.56, s, 1H). We therefore speculated that the configuration of C15 in compound **32** was of the *S*-configuration. Reduction of **32** with sodium borohydride produced a 2:1 mixture of compounds **4** and **33**. ^{1}H NMR and ^{13}C NMR of compound **4** were identical to that of natural 16-hydroxytriptolide,[1b] which confirmed our hypothesis.

In the previous structure−cytotoxic activity relationship studies of triptolide **1** and its analogues in several cancer cell lines, little information was reported regarding the role of the C13 substituent in cytostatic activity. Therefore, we planned to synthesize some C13 isopropyl group modified analogues to further unravel the structure−cytotoxic activity relationship on this postition (Scheme 6).

The synthesis of analogues **38**−**44** followed a sequence similar to that was previously developed for the synthesis of 16-hydroxytriptolide in Scheme 5. Alkylation of the phenol group of **26** with allyl bromide provided allylic ether **34**, which was subjected to Claisen rearrangement to give compound **35**. Oxidative cleavage of the terminal alkene of **35** using OsO_4 (cat.)/$NaIO_4$ afforded aldehyde **36**. Treatment of **36** with $NaBH_4$ produced the corresponding triol intermediate, which was directly subjected to periodate oxidation to give **37**.[22] Further epoxidation of **37** with in situ-generated methyl(trifluoromethyl)dioxirane[4e] and alkaline hydrogen peroxide successfully introduced C9,C11 and C12,C13 epoxides, affording C13-hydroxyethyl-substituted analogues **38**. Reaction of **38** with a variety of acyl chlorides yielded analogues **39**−**44**.

The synthetic analogues **31**, **32**, **38**−**44**, and 16-hydroxytriptolide **4** were tested for their effects on the proliferation of two tumor cell lines, SKOV-3 (human ovarian cancer cells) and PC-3 (human prostate cancer cells). Triptolide **1** and triptonide **2** (two synthetic samples that were previously prepared by our group from L-abietic acid[4i]) were used as positive controls, and the screening results are shown in Table 3. The result revealed that by introduction of the C16 hydroxyl group, compounds **4**, **31**, and **32** still retained cytotoxic activity, albeit a little less potent than triptolide **1** and/or triptonide **2**. However, C13 hydroxyethyl-substituted analogue **38** was shown to be only weakly cytotoxic (SKOV-3, IC_{50} = 1.509 μM) or nontoxic (PC-3, IC_{50} > 10 μM). It indicated that the C15 methyl group was crucial to its potent cytotoxic activity (e.g., compare compound **38** to **32**), but the stereochemistry at C15 was not so important (e.g., compare compound **31** to **32**). More interestingly, by esterification of the terminal hydroxyl group of compound **38**, analogues **39**−**44** still had potent cytotoxicity against these two cell lines. Among them, compound **43** exhibited the highest potency, with the lowest IC_{50} value (42 nM for SKOV-3 cells). On the basis of the above results, we might presume that the modification on C13 could still retain the cytotoxic activity.

■ CONCLUSIONS

We established a divergent route for the formal total synthesis of triptolide, triptonide, and tripdiolide, as well as a total synthesis of 16-hydroxytriptolide, and their C13 analogues in an enantioselective form. The common advanced intermediate **5** possessing a trans-fused A/B-ring system and a lactone D-ring was synthesized on a large scale by using an $InBr_3$-mediated cationic polyene cyclization reaction and palladium-catalyzed carbonylation−lactone formation. This intermediate was

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Scheme 5. Synthesis of 16-Hydroxytriptolide 4

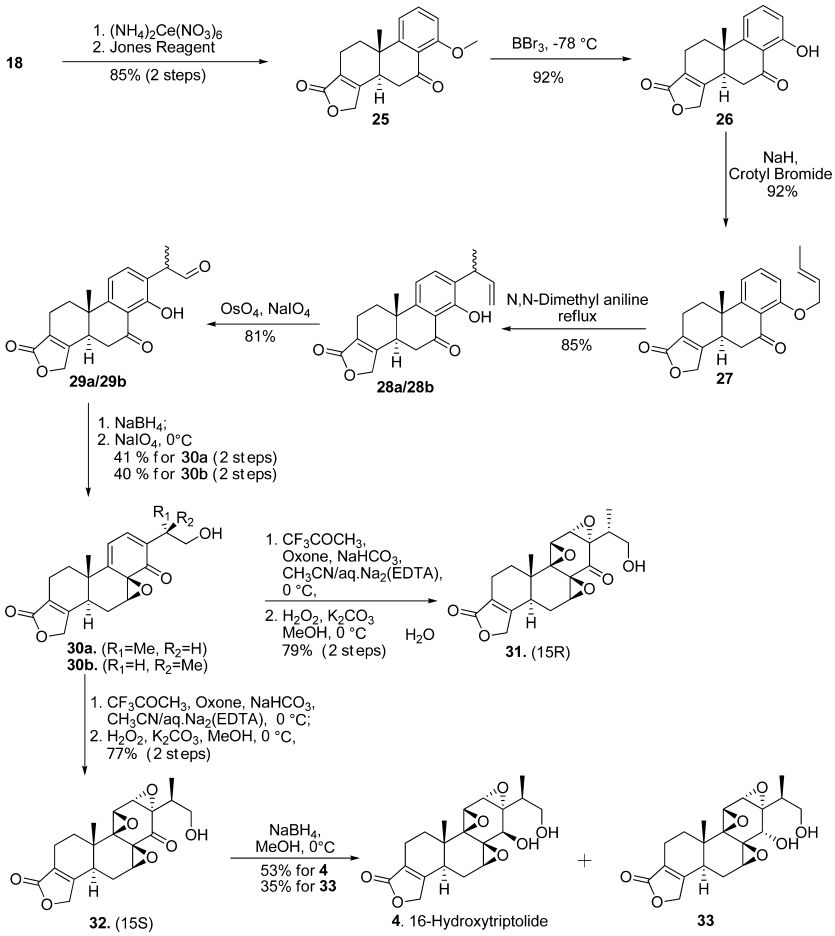


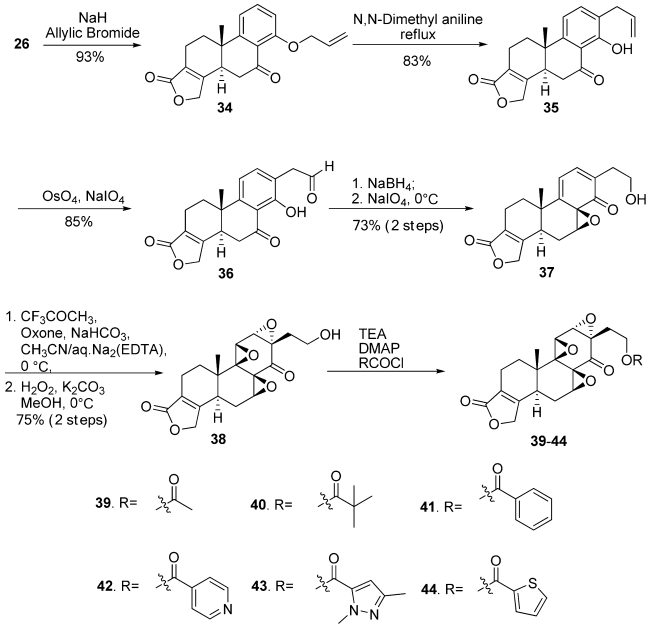
Table 2. Conditions for Double Bond Migration

5 $\xrightarrow{\text{conditions}}$ 18

entry	conditions	% yield 18[a]
1	DBU, $Pd(OAc)_2$, toluene, reflux	n.r.
2	Grubbs II catalysis, CH_2Cl_2, reflux, 12 h	35
3	$RhCl_3 \cdot 3H_2O$, 95% EtOH, reflux, 15 h	21
4	$Rh(PPh_3)_3Cl$, Et_3SiH, toluene, reflux, 8 h	92

[a]Isolated yield.

Scheme 6. Synthesis of C13-Modified Analogues of Triptolide



further converted to the above natural products and analogues by using palladium-catalyzed cross-coupling reaction or Claisen rearrangement reaction as the key step. Preliminary structure–cytotoxic activity relationship studies of position C13 revealed that it might be a new modification site that could still retain cytotoxicity.

EXPERIMENTAL SECTION

General. Commercially available anhydrous *n*-butanol (*n*-BuOH), dichloromethane (DCM), diethyl ether, 1,2-dimethoxyethane (DME), methanol (MeOH), tetrahydrofuran (THF), toluene, and reagents were used to perform the reactions without further purification, unless otherwise stated. Mass spectra were obtained on an HR-ESI-MS spectrometer (sector analyzer). Melting points were determined in an open glass capillary and are uncorrected. IR spectra were recorded on a FT-IR spectrophotometer using KBr pellets. Optical rotations were recorded on a polarimeter. HPLC analysis used a chiral column (Daicel Chiralcel OJ-H, 5 μm, 4.6 mm × 250 mm), 2-propanol and *n*-hexane was the eluent, and the detection wavelength was 254 nm; ^{1}H and ^{13}C NMR spectra were determined on 300, 400, 500, and 600 MHz spectrometers using tetramethylsilane as internal reference. Data are presented as follows: chemical shift, multiplicity (s = singlet, br s =

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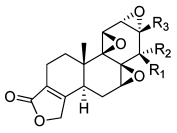
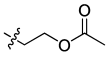
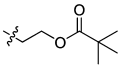
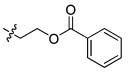
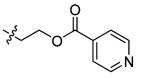
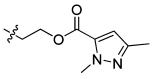
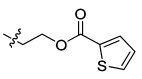
Table 3. Cytotoxic Activity (IC_{50} value)[a]



Compounds	R_1, R_2	R_3	$IC_{50}(\mu M)$[a]	
			SKOV-3	PC-3
1	R_1=OH, R_2=H		0.006	0.020
2	R_1=R_2=O		0.026	0.035
4	R_1=OH, R_2=H		0.215	0.867
31	R_1=R_2=O		0.126	0.456
32	R_1=R_2=O		0.113	0.228
38	R_1=R_2=O		1.509	>10
39	R_1=R_2=O		0.382	0.909
40	R_1=R_2=O		0.576	0.891
41	R_1=R_2=O		0.262	0.131
42	R_1=R_2=O		0.339	0.559
43	R_1=R_2=O		0.042	0.099
44	R_1=R_2=O		0.109	0.080

[a]The drug concentration required for 50% inhibition of cell proliferation; the maximum concentration used here was 100 μM.

broad singlet, d = doublet, br d = broad doublet, t = triplet, m = moultiple), and *J* (coupling constant in hertz (Hz)).

*5-(2-Methoxyphenyl)-2-methylpent-1-en-3-one (**9**).* A mixture of compound **8** (20.0 g, 112.25 mmol) and 5% Pd/C (0.8 g) in MeOH (500 mL) was stirred under H_2 at room temperature for 8 h. Then the solid was removed by filtration through a pad of Celite, dried over anhydrous Na_2SO_4, filtered, and concentrated to afford a crude product, which was dissolved in dry methylene chloride (400 mL). Then carbonyl diimidazole (21.6 g, 134.7 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (13.0 g, 134.7 mmol) were added at room temperature. After stirring for 3 h, brine (150 mL) was added and the biphasic mixture was extracted with ethyl acetate (400 mL), washed with water, dried over anhydrous Na_2SO_4, filtered through a short pad of silica gel, and concentrated to afford a crude product. To the resulting crude product in dry tetrahydrofuran (250 mL) under argon protection at 0 °C was added isopropenylmagnesium bromide solution (0.5 M in tetrahydrofuran, 270 mL, 134.7 mmol). The reaction was slowly warmed to 23 °C and stirred for another 3 h before saturated aqueous ammonium chloride (100 mL) and ethyl acetate (200 mL) were added. The layers were separated, and the

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organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash chromatography on silica gel (20:1 PE/EtOAc) to provide **9** (20.6 g, 101.0 mmol, 90%) as a colorless oil. R_f = 0.40, (silica gel, PE/EtOAc = 10:1); IR (KBr) 3057, 2956, 2837, 1676, 1630, 1600, 1587, 1495, 1464, 1441, 1367, 1242, 1086, 1030, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29−7.09 (m, 2H), 6.91−6.84 (m, 2H), 5.97 (s, 1H), 5.75 (s, 1H), 3.83 (s, 3H), 3.05−2.85 (m, 4H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3, 157.0, 143.9, 129.6, 129.2, 127.0, 124.1, 120.0, 109.8, 54.7, 37.4, 25.5, 17.2; ESIMS m/z 205.3 $[M + H]^+$; HRMS (ESI) calcd for $C_{13}H_{17}O_2$ $[M + H]^+$ 205.1229, found 205.1235.

*(E)-Ethyl 7-(2-Methoxyphenyl)-4-methylhept-4-enoate (**10**).* To a stirred solution of compound **9** (20.0 g, 97.9 mmol) in methanol (250 mL) at −5 °C was added $CeCl_3·7H_2O$ (43.8 g, 117.5 mmol). After stirring at −5 °C for 15 min, sodium borohydride (4.4 g, 117.5 mmol) was added, stirring was continued for a further 30 min, 10% HCl (50 mL) was added to quench the reaction, and the mixture was extracted with ethyl acetate (400 mL), washed successively with brine and water, dried over anhydrous Na_2SO_4, filtered through a short pad of silica gel, and concentrated to give a white solid as the crude product, which was dissolved in distilled triethyl orthoacetate (179 mL, 979 mmol). Propionic acid (0.74 mL, 9.8 mmol) was added, and the resulting reaction mixture was stirred under reflux for 24 h. Then the mixture was cooled, poured into water, extracted with EtOAc, washed with 1 N hydrochloric acid, concentrated, and purified by flash chromatography on silica gel (50:1 PE/EtOAc) to provide **10** (21.9 g, 79.3 mmol, 81%) as a colorless oil. R_f = 0.39 (silica gel, PE/EtOAc = 30:1); IR (KBr) 2979, 2937, 2837, 1736, 1601, 1587, 1495, 1463, 1290, 1242, 1176, 1157, 1034, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21−7.08 (m, 2H), 6.90−6.82 (m, 2H), 5.25 (dd, J = 7.2, 6.1 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 2.65−2.55 (m, 2H), 2.42−2.34 (m, 2H), 2.32−2.21 (m, 4H), 1.56 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 157.4, 133.8, 130.5, 129.8, 126.9, 124.9, 120.2, 110.1, 60.2, 55.2, 34.7, 33.2, 30.4, 28.1, 15.8, 14.2; ESIMS m/z 277.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{17}H_{25}O_3$ $[M + H]^+$ 277.1804, found 277.1805.

*(E)-N-Methoxy-7-(2-methoxyphenyl)-N,4-dimethylhept-4-enamide (**11**).* To a stirred solution of compound **10** (19.5 g, 70.6 mmol) in MeOH (200 mL) and water (50 mL) was added LiOH (5.0 g, 212 mmol). After stirring at room temperature for 3 h, the solvent was evaporated under reduced pressure, ethyl acetate (300 mL) was added, and the mixture was washed successively with brine and water, dried over anhydrous Na_2SO_4, filtered, and concentrated to give a white solid as the crude product, which was dissolved in dry methylene chloride (250 mL). Carbonyl diimidazole (13.7 g, 84.7 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride were added (8.3 g, 84.7 mmol) at room temperature. After stirring for 3 h, brine (100 mL) was added, the biphasic mixture was extracted with ethyl acetate, and the organic phase was dried over anhydrous sodium sulfate, filtered, concentrated, and purified by flash column chromatography on silica gel (10:1 PE/EtOAc) to provide **11** (18.4 g, 63.5 mmol, 90%) as a white solid. R_f = 0.26, (silica gel, PE/EtOAc = 10:1); mp 81−83 °C; IR (KBr) 2937, 2856, 2837, 1664, 1600, 1587, 1493, 1383, 1242, 1176, 1111, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (td, J = 7.8, 1.7 Hz, 1H), 7.11 (dd, J = 7.4, 1.6 Hz, 1H), 6.89−6.82 (m, 2H), 5.26 (t, J = 6.7 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 3H), 3.18 (s, 3H), 2.63 (dd, J = 8.9, 6.7 Hz, 2H), 2.54−2.44 (m, 2H), 2.34−2.20 (m, 4H), 1.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 157.5, 134.5, 130.6, 129.9, 126.9, 124.6, 120.3, 110.2, 61.2, 55.2 × 2, 34.3, 30.9, 30.4, 28.2, 16.0; ESIMS m/z 292.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{17}H_{26}NO_3$ $[M + H]^+$ 292.1913, found 292.1920.

*(E)-9-(2-Methoxyphenyl)-6-methyl-1-(trimethylsilyl)non-6-en-1-yn-3-one (**12**).* To a stirred solution of TMS-acetylene (11.3 mL, 80.3 mmol) in anhydrous THF (150 mL) was slowly added a solution of *n*-BuLi (40.2 mL, 80.3 mmol, 2.0 M in THF) under argon at −78 °C. After 30 min, the resulting solution was warmed to −20 °C and then cooled back to −78 °C. The lithium acetylide solution obtained was added dropwise through a canula to a solution of Weinreb amide **11** (18.0 g, 61.8 mmol) in anhydrous THF (150 mL) at −78 °C. The resulting solution was warmed to −20 °C over 1 h, and after 60 min, cooled to −40 °C. The solution was then added to a mixture of ice and phosphate buffer (pH 7, 100 mL). After extraction with CH_2Cl_2, the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash chromatography on silica gel (30:1 PE/EtOAc) to provide **12** (18.3 g, 55.6 mmol, 90%) as a colorless oil. R_f = 0.50 (silica gel, PE/EtOAc = 20:1); IR (KBr) 2958, 2837, 2150, 1714, 1676, 1600, 1587, 1495, 1464, 1244, 1111, 847, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (td, J = 7.8, 1.8 Hz, 1H), 7.10 (dd, J = 7.4, 1.5 Hz, 1H), 6.90−6.82 (m, 2H), 5.25 (td, J = 7.1, 1.2 Hz, 1H), 3.82 (s, 3H), 2.70−2.60 (m, 4H), 2.37−2.22 (m, 4H), 1.56 (s, 3H), 0.25 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.7, 157.5, 133.4, 130.5, 129.9, 127.0, 125.3, 120.3, 110.2, 102.0, 97.9, 55.2, 44.0, 33.6, 30.4, 28.2, 15.9, −0.7 × 3; ESIMS m/z 329.5 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{29}O_2Si$ $[M + H]^+$ 329.1937, found 329.1944.

*(R,E)-9-(2-Methoxyphenyl)-6-methyl-1-(trimethylsilyl)non-6-en-1-yn-3-ol (**14**).* To a stirred solution of compound **12** (9.0 g, 27.4 mmol) in anhydrous THF (250 mL) under argon protection was added TEA (15.2 mL, 109.6 mmol), HCOOH (10.3 mL, 274 mmol), and (*R*,*R*)-ruthenium catalyst **13** (439 mg, 0.69 mmol) at room temperature. After stirring for 2.5 h, The mixture was extracted with ethyl acetate, washed successively with brine and water, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography on silica gel (20:1 PE/EtOAc) to provide **14** (8.16 g, 24.7 mmol, 90%) as a colorless oil. R_f = 0.50 (silica gel, PE/EtOAc = 10:1); $[\alpha]^{25}_D$ −16.1 (c 0.13, CH_2Cl_2); IR (KBr) 3361, 2956, 2858, 2835, 2171, 1600, 1587, 1495, 1464, 1244, 1052, 1032, 843, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21−7.09 (m, 2H), 6.91−6.81 (m, 2H), 5.27 (dd, J = 7.7, 6.6 Hz, 1H), 4.29 (dd, J = 12.0, 6.3 Hz, 1H), 3.83 (s, 3H), 2.68−2.59 (m, 2H), 2.28 (dd, J = 15.2, 7.4 Hz, 2H), 2.14 (t, J = 7.5 Hz, 2H), 1.86−1.72 (m, 2H), 1.57 (s, 3H), 1.25 (s, 1H), 0.18 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 134.6, 130.6, 129.9, 127.0, 125.1, 120.3, 110.2, 106.8, 89.5, 62.6, 55.3, 35.8, 35.2, 30.5, 28.2, 15.8, −0.1 × 3; ESIMS m/z 331.5 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{31}O_2Si$ $[M + H]^+$ 331.2093, found 331.2099.

*(R,E)-tert-Butyl(9-(2-methoxyphenyl)-6-methylnon-6-en-1-yn-3-yloxy)dimethylsilane (**7**).* To a stirred solution of compound **12** (12.0 g, 36.3 mmol) in MeOH (150 mL) was added K_2CO_3 (7.1 g, 72.6 mmol) at room temperature. After stirring for 2.5 h, the solid was removed by filtration through a pad of Celite, and the filtrate was condensed and dissolved in ethyl acetate (200 mL), washed successively with brine and water, dried over anhydrous Na_2SO_4, filtered, and concentrated to give a crude product, which was dissolved in anhydrous DMF (60 mL). Imidazole (3.7 g, 54.5 mmol) and TBSCl (6.6 g, 43.6 mmol) were added at 0 °C, and after stirring at room temperature overnight, H_2O (200 mL) was added and the resulting mixture extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine and water, dried over Na_2SO_4, filtered, and concentrated to give a crude product, which was purified by flash chromatography on silica gel (100:1 PE/EtOAc) to provide **7** (12.3 g, 33.0 mmol, 91%) as a colorless oil. R_f = 0.50 (silica gel, PE/EtOAc = 50:1); $[\alpha]^{25}_D$ +19.4 (c 0.11, CH_2Cl_2); IR (KBr) 3309, 2952, 2929, 2856, 1600, 1587, 1495, 1463, 1439, 1244, 1097, 1034, 837, 777, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22−7.10 (m, 2H), 6.92−6.82 (m, 2H), 5.26 (t, J = 7.1 Hz, 1H), 4.33 (td, J = 6.5, 2.1 Hz, 1H), 3.83 (s, 3H), 2.69−2.60 (m, 2H), 2.39 (d, J = 2.1 Hz, 1H), 2.27 (dd, J = 15.4, 7.4 Hz, 2H), 2.11 (dd, J = 10.1, 5.7 Hz, 2H), 1.81−1.74 (m, 2H), 1.58 (s, 3H), 0.92 (s, 9H), 0.13 (d, J = 8.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 134.6, 130.7, 129.8, 126.9, 124.6, 120.3, 110.1, 85.7, 72.1, 62.4, 55.2, 37.0, 35.0, 30.5, 28.2, 25.8 × 3, 18.2, 15.9, −4.5, −5.0; ESIMS m/z 373.6 $[M + H]^+$; HRMS (ESI) calcd for $C_{23}H_{37}O_2Si$ $[M + H]^+$ 373.2563, found 373.2566.

*tert-Butyl((2R,4aS,10aR)-8-methoxy-4a-methyl-1-methylene-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yloxy)dimethylsilane (**6**).* To a stirred solution of anhydrous CH_2Cl_2 (300 mL) under argon protection at −20 °C was added $InBr_3$ (2.5 g, 8.0 mmol), and after stirring for 30 min, a solution of alkyne **7** (13.5 g, 36.2 mmol) in dry CH_2Cl_2 (60 mL) was added via cannula at −20 °C. The reaction mixture was stirred at −20 °C for 4 h. Then the reaction was quenched with saturated $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried

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over anhydrous Na_2SO_4, and concentrated to give a crude product, which was purified by flash column chromatography on silica gel (50:1 PE/EtOAc) to provide **6** (10.9 g, 29.3 mmol, 81%) as a colorless oil. R_f = 0.30 (silica gel, PE/EtOAc = 50:1); $[\alpha]^{25}_D$ +124.1 (*c* 0.09, CH_2Cl_2); IR (KBr) 3076, 2931, 2883, 2856, 1650, 1600, 1581, 1433, 1255, 1061, 1043, 1003, 835, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (t, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 4.97 (t, *J* = 1.3 Hz, 1H), 4.68 (t, *J* = 1.7 Hz, 1H), 4.30 (t, *J* = 2.7 Hz, 1H), 3.85 (s, 3H), 3.00 (dd, *J* = 18.1, 5.3 Hz, 1H), 2.76 (dd, *J* = 12.4, 1.2 Hz, 1H), 2.71−2.54 (m, 1H), 2.05−1.98 (m, 2H), 1.88−1.66 (m, 4H), 1.00 (s, 3H), 0.85 (s, 9H), 0.03 (d, *J* = 16.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 152.6, 148.7, 126.0, 124.3, 117.6, 108.1, 106.6, 73.4, 55.2, 40.9, 39.2, 32.6, 31.9, 25.8 × 3, 23.7, 22.0, 20.1, 18.1, −4.7, −5.1; ESIMS *m*/*z* 373.6 $[M + H]^+$; HRMS (ESI) calcd for $C_{23}H_{37}O_2Si$ $[M + H]^+$ 373.2563, found 373.2569.

*((1S,2R,4aS,10aS)-2-(tert-Butyldimethylsilyloxy)-8-methoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)methanol (**15**).* To a stirred solution of compound **6** (10.5 g, 28.2 mmol) in anhydrous THF (200 mL) was added BH_3·THF (0.5 M in THF, 141 mL, 70.5 mmol) at 0 °C. After stirring at room temperature for 4 h, the reaction mixture was cooled to 0 °C, and then NaOH (3 M, 28.2 mL, 84.6 mmol) and H_2O_2 (30% aq solution, 16.0 mL, 141 mmol) were added. After stirring at room temperature for 3 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$, extracted with EtOAc, washed with brine and water, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product which was purified by flash chromatography on silica gel (10:1 PE/EtOAc) to provide **15** (9.1 g, 23.4 mmol, 83%) as a colorless oil. R_f = 0.50, (silica gel, PE/EtOAc = 5:1); $[\alpha]^{25}_D$ +87.3 (*c* 0.22, CH_2Cl_2); IR (KBr) 3369, 2929, 2883, 2858, 1581, 1471, 1460, 1435, 1255, 1080, 1059, 837, 775, 717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 7.9 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 4.15 (s, 1H), 3.83−3.74 (m, 4H), 3.57 (t, *J* = 10.0 Hz, 1H), 2.91 (dd, *J* = 17.9, 6.1 Hz, 1H), 2.68−2.53 (m, 1H), 2.33−2.22 (m, 1H), 1.97−1.74 (m, 5H), 1.67−1.54 (m, 3H), 1.00 (s, 3H), 0.84 (s, 9H), 0.04 (d, *J* = 2.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 150.0, 126.0, 124.3, 116.9, 106.5, 67.5, 61.8, 55.2, 52.7, 36.9, 36.8, 31.9, 26.2, 25.9 × 3, 24.5, 24.4, 23.0, 18.1, −4.8 × 2; ESIMS *m*/*z* 391.6 $[M + H]^+$; HRMS (ESI) calcd for $C_{23}H_{39}O_3Si$ $[M + H]^+$ 391.2668, found 391.2669.

*(1S,2R,4aS,10aS)-8-Methoxy-1-((4-methoxybenzyloxy)methyl)-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-ol (**16**).* To a stirred solution of compound **15** (10.2 g, 26.1 mmol) in anhydrous DMF (80 mL) were added NaH (60% dispersion in mineral oil, 2.1 g, 52.2 mmol) and TBAI (0.48 g, 1.3 mmol) at 0 °C, and after stirring at room temperature for 30 min, PMBCl (7.1 mL, 52.2 mmol) was added. After stirring overnight at room temperature, the reaction mixture was extracted with EtOAc, washed successively with saturated NH_4Cl, brine, and water, dried over anhydrous Na_2SO_4, filtered, and concentrated to give a crude product, which was dissolved in MeOH (150 mL). Then PTSA (9.0 g, 52.2 mmol) was added at room temperature. After stirring for 3 h, the reaction mixture was extracted with ethyl acetate, washed successively with brine and water, dried over anhydrous Na_2SO_4, filtered, and concentrated to give a crude product which was purified by flash chromatography on silica gel (4:1 PE/EtOAc) to provide **16** (8.7 g, 21.9 mmol, 84%) as a white solid. R_f = 0.25 (silica gel, PE/EtOAc = 4:1); mp 79−81 °C; $[\alpha]^{25}_D$ +93.2 (*c* 0.33, CH_2Cl_2); IR (KBr) 3423, 2927, 1612, 1579, 1512, 1458, 1365, 1250, 819, 717 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.6 Hz, 2H), 7.16 (t, *J* = 8.0 Hz, 1H), 6.96−6.89 (m, 3H), 6.68 (d, *J* = 7.9 Hz, 1H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.43 (d, *J* = 11.6 Hz, 1H), 4.20 (d, *J* = 1.8 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.60 (dd, *J* = 9.6, 2.5 Hz, 1H), 3.46 (t, *J* = 9.9 Hz, 1H), 2.94 (dd, *J* = 17.9, 6.1 Hz, 1H), 2.74−2.58 (m, 1H), 2.27 (ddd, *J* = 13.0, 5.3, 2.0 Hz, 1H), 2.12−2.06 (m, 1H), 2.04−1.98 (m, 1H), 1.96−1.79 (m, 3H), 1.76 (dd, *J* = 12.5, 1.4 Hz, 1H), 1.69−1.60 (m, 1H), 1.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 157.8, 150.4, 131.2, 129.9 × 2, 126.8, 124.9, 117.6, 114.5 × 2, 107.3, 73.4, 69.6, 68.4, 56.0, 55.9, 49.2, 37.6, 37.5, 32.6, 26.3, 25.1, 23.6; ESIMS *m*/*z* 397.5 $[M + H]^+$; HRMS (ESI) calcd for $C_{25}H_{33}O_4$ $[M + H]^+$ 397.2379, found 397.2375.

*(1S,4aS,10aS)-8-Methoxy-1-((4-methoxybenzyloxy)methyl)-4a-methyl-1,4,4a,9,10,10a-hexahydrophenanthren-2-yl Trifluoromethanesulfonate (**17**).* Jones reagent (8 N) was prepared by dissolving 2.67 g of chromic trioxide in 2.3 mL of concentrated sulfuric acid and diluting this solution with water to 10 mL at 0 °C. To a stirred solution of compound **16** (10.1 g, 25.5 mmol) in acetone (200 mL) at 0 °C was added Jones reagent (8 N, 6.4 mL, 51 mmol). After stirring for an additional 20 min at 0 °C, the reaction was quenched by adding 2-propanol, concentrated in vacuo, extracted with EtOAc, washed successively with saturated NH_4Cl, brine, and water, dried over anhydrous Na_2SO_4, filtered through a short pad of silica gel, and concentrated to provide a crude product. To a stirred solution of the resulting crude product in dry THF (100 mL) under argon protection at −78 °C was added KHMDS (0.5 M solution in toluene, 61.2 mL, 30.6 mmol), and the resultant solution was stirred at −78 °C for 30 min. Then a solution of *N*-phenyl-bis(trifluoromethanesulfonimide) (10.9 g, 30.6 mmol) in THF (20 mL) was added dropwise. The resultant solution was stirred at −78 °C for 30 min and warmed to room temperature overnight. Then the reaction was extracted with EtOAc, washed with brine and water, dried over anhydrous Na_2SO_4, filtered, and concentrated to give a crude product, which was purified by flash chromatography on silica gel (30:1 PE/EtOAc) to provide **17** (10.6 g, 20.1 mmol, 79%) as a colorless oil. R_f = 0.62 (silica gel, PE/EtOAc = 10:1); $[\alpha]^{25}_D$ +219.5 (*c* 0.13, CH_2Cl_2); IR (KBr) 2939, 2839, 1612, 1581, 1512, 1460, 1414, 1246, 1209, 1142, 1034, 893 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.6 Hz, 2H), 7.17 (t, *J* = 8.0 Hz, 1H), 6.92−6.84 (m, 3H), 6.68 (d, *J* = 8.0 Hz, 1H), 5.81 (d, *J* = 5.3 Hz, 1H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 3.85−3.76 (m, 7H), 3.64 (dd, *J* = 9.8, 5.2 Hz, 1H), 3.02−2.95 (m, 2H), 2.69 (dd, *J* = 17.5, 6.2 Hz, 1H), 2.59−2.43 (m, 1H), 2.30 (d, *J* = 17.2 Hz, 1H), 2.26−2.18 (m, 1H), 1.94 (dd, *J* = 13.2, 6.6 Hz, 1H), 1.75 (qd, *J* = 12.9, 5.7 Hz, 1H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 156.9, 150.4, 146.6, 130.1 × 2, 129.3, 126.6, 124.3, 117.9, 117.5, 113.7 × 2, 106.8, 72.6, 67.3, 55.2, 43.4, 41.8, 39.1, 35.5, 24.8, 24.2, 22.0; ESIMS *m*/*z* 527.6 $[M + H]^+$; HRMS (ESI) calcd for $C_{26}H_{30}F_3O_6S$ $[M + H]^+$ 527.1715, found 527.1722.

*(3aR,3bS,9bS)-6-Methoxy-9b-methyl-3,3a,4,5,9b,10-hexahydrophenanthro[2,1-c]furan-1(3bH)-one (**5**).* To a stirred solution of compound **17** (12.0 g, 22.8 mmol) in CH_2Cl_2−H_2O (2:1, v/v, 100 mL) at room temperature was added DDQ (6.2 g, 27.4 mmol). After stirring at room temperature for 0.5 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was extracted with EtOAc, washed successively with brine and water, dried over anhydrous Na_2SO_4, filtered through a short pad of silica gel, and concentrated to provide a crude product which was used for the next step without purification. To a stirred solution of the resulting crude product in dry CH_3CN (150 mL) under CO were added $Pd(PPh_3)_4$ (2.7 g, 2.3 mmol), *n*-Bu_3N (10.9 mL, 45.6 mmol), and LiCl (1.0 g, 23.9 mmol). After stirring at room temperature for 8 h, the solid was removed by filtration through a pad of Celite, and the filtrate was condensed and purified by flash column chromatography on silica gel (8:1, PE/EtOAc) to provide **5** (5.3 g, 18.5 mmol, 81%) as a white solid. R_f = 0.40 (silica gel, PE/EtOAc = 5:1); mp 222−224 °C; $[\alpha]^{25}_D$ −47 (*c* 0.07, CH_2Cl_2); IR (KBr) 2933, 2897, 2860, 1665, 1577, 1552, 1513, 1473, 1328, 1224, 1096, 879 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (t, *J* = 8.1 Hz, 1H), 6.97−6.90 (m, 2H), 6.71 (d, *J* = 8.1 Hz, 1H), 4.40 (t, *J* = 8.5 Hz, 1H), 4.10 (dd, *J* = 11.3, 8.1 Hz, 1H), 3.82 (s, 3H), 3.49−3.32 (m, 1H), 3.07−2.89 (m, 2H), 2.76−2.61 (m, 1H), 2.35−2.25 (m, 2H), 1.96−1.74 (m, 2H), 1.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 157.3, 146.5, 133.8, 130.9, 126.5, 123.9, 116.7, 107.2, 68.5, 55.2, 40.7, 38.25, 38.21, 37.0, 23.7, 23.6, 20.2; ESIMS *m*/*z* 285.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{18}H_{21}O_3$ $[M + H]^+$ 285.1491, found 285.1495.

*(3bR,9bS)-6-Methoxy-9b-methyl-3b,4,5,9b,10,11-hexahydrophenanthro[2,1-c]furan-1(3H)-one (**18**).* To a stirred solution of compound **5** (5.2 g, 18.3 mmol) in anhydrous toluene (100 mL) under argon protection were added $Rh(PPh_3)_3Cl$ (4.3 g, 4.6 mmol) and Et_3SiH (0.22 mL, 1.4 mmol) at room temperature. After stirring at reflux for 8 h, the solvent was concentrated and the residue was purified by flash chromatography on silica gel (5:1, PE/EtOAc) to

provide **18** (4.8 g, 16.8 mmol, 92%) as a white solid. R_f = 0.30 (silica gel, PE/EtOAc = 5:1), mp 244−246 °C; $[\alpha]^{25}_D$ +66.9 (*c* 0.07, CH_2Cl_2); IR (KBr) 2924, 2891, 2848, 1743, 1677, 1599, 1578, 1473, 1461, 1442, 1431, 1259, 1068, 1047, 1024, 988, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 7.9 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 4.87−4.70 (m, 2H), 3.83 (s, 3H), 2.94 (dd, *J* = 18.4, 7.2 Hz, 1H), 2.79 (ddd, *J* = 18.7, 10.4, 8.7 Hz, 1H), 2.72−2.64 (m, 1H), 2.58−2.46 (m, 2H), 2.44−2.32 (m, 1H), 1.99−1.81 (m, 2H), 1.69 (td, *J* = 12.3, 6.6 Hz, 1H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 163.1, 157.4, 146.3, 126.4, 124.9, 123.4, 116.3, 107.4, 70.5, 55.3, 40.9, 36.4, 32.6, 22.4, 22.3, 19.6, 18.2; ESIMS *m*/*z* 285.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{18}H_{21}O_3$ $[M + H]^+$ 285.1491, found 285.1499.

(3bR,9bS)-7-Iodo-6-methoxy-9b-methyl-3b,4,5,9b,10,11-hexahydrophenanthro[2,1-c]furan-1(3H)-one (**19**). To a stirred solution of compound **18** (100 mg, 0.35 mmol) in chloroform (3 mL) at 0 °C were added silver triflate (108 mg, 0.42 mmol) and iodine (54 mg, 0.42 mmol). After stirring for 0.5 h at 0 °C, the mixture was filtered through Celite and washed with saturated aq $Na_2S_2O_3$ solution. The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography on silica gel (2:1 PE/EtOAc) to provide **19** (139.5 mg, 0.34 mmol, 97%) as a white solid. R_f = 0.25 (silica gel, PE/EtOAc = 3:1); mp 230−233 °C; $[\alpha]^{25}_D$ −59.3 (*c* 0.22, CH_2Cl_2); IR (KBr) 2933, 2899, 1741, 1674, 1460, 1429, 1393, 1344, 1061, 1028, 1017 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 4.90−4.69 (m, 2H), 3.79 (s, 3H), 3.16−2.91 (m, 2H), 2.67 (br d, *J* = 15.3 Hz, 1H), 2.59−2.27 (m, 3H), 2.05−1.81 (m, 2H), 1.76−1.65 (m, 1H), 1.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.2, 165.9, 157.7, 147.4, 136.6, 130.1, 124.7, 122.3, 89.0, 72.3, 59.9, 40.9, 36.5, 32.4, 23.3, 22.2, 19.6, 17.9; ESIMS *m*/*z* 411.3 $[M + H]^+$; HRMS (ESI) calcd for $C_{18}H_{20}IO_3$ $[M + H]^+$ 411.0457, found 411.0455.

(3bR,9bS)-7-Isopropyl-6-methoxy-9b-methyl-3b,4,5,9b,10,11-hexahydrophenanthro[2,1-c]furan-1(3H)-one (**21**). To a stirred solution of compound **20** (73 mg, 0.58 mmol) in anhydrous THF (5 mL) at 0 °C was added a solution of TBAF (303 mg, 1.16 mmol) in anhydrous THF (5 mL). The ice-bath was removed after completing the addition of TBAF. The reaction mixture was allowed to warm to room temperature and stirred for 10 min. Then compound **19** (120 mg, 0.29 mmol) and $Pd(dba)_2$ (3.4 mg, 0.015 mmol) were sequentially added to the mixture. The mixture was stirred at room temperature for 2 h, and EtOAc (10 mL) was added and stirred for another 5 min. The mixture was filtered through a short column of silica gel, washed with brine and water, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product. A solution of the resulting crude product and 5% Pd/C (6 mg) in MeOH (5 mL) was stirred at gentle reflux for 10 h. Then the mixture was filtered through Celite, concentrated, and purified by flash chromatography on silica gel (5:1 PE/EtOAc) to provide **21** (71 mg, 0.22 mmol, 75%) as a white solid. R_f = 0.41 (silica gel, PE/EtOAc = 2:1); mp 175−177 °C; $[\alpha]^{25}_D$ +39.5 (*c* 0.42, CH_2Cl_2); IR (KBr) 2961, 2932, 2870, 2826, 1751, 1677, 1485, 1447, 1340, 1266, 1067, 1029, 988, 813 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (s, 2H), 4.86−4.71 (m, 2H), 3.74 (s, 3H), 3.30 (sept, *J* = 6.9 Hz, 1H), 3.06 (ddd, *J* = 18.1, 7.4, 1.7 Hz, 1H), 2.95 (ddd, *J* = 18.3, 10.3, 8.3 Hz, 1H), 2.69 (dd, *J* = 13.3, 1.9 Hz, 1H), 2.54−2.47 (m, 2H), 2.38 (tdd, *J* = 14.4, 6.8, 3.3 Hz, 1H), 2.01−1.93 (m, 1H), 1.92−1.82 (m, 1H), 1.75−1.66 (td, *J* = 12.7, 6.5 Hz, 1H), 1.23 (d, *J* = 4.7 Hz, 3H), 1.22 (d, *J* = 4.7 Hz, 3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 163.0, 155.4, 144.0, 139.2, 128.0, 124.9, 124.1, 120.2, 70.5, 60.5, 41.0, 36.3, 32.6, 26.1, 23.9, 23.8, 22.7, 22.3, 19.7, 18.1; ESIMS *m*/*z* 327.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{21}H_{27}O_3$ $[M + H]^+$ 327.1960, found 327.1966.

(3aS,3bS,9bS,11aS)-11a-Hydroxy-6-methoxy-9b-methyl-3,3a,4,5,9b,10-hexahydrophenanthro[2,1-c]furan-1,11(3bH,11aH)-dione (**22**). To a stirred solution of compound **5** (200 mg, 0.70 mmol) and NMO (165 mg, 1.4 mmol) in a 9:1 mixture of acetone/water (10 mL) was added OsO_4 (0.45 mL, 0.035 mmol, 2% aq solution) at room temperature. After stirring at room temperature for 6 h, the reaction was quenched with saturated aq $Na_2S_2O_3$. After stirring for another 20 min, the mixture was extracted with EtOAc, and the combined organic layer was washed with brine and water, dried over anhydrous Na_2SO_4, filtered through a short column of silica gel, and concentrated under vacuum to give a crude product. SO_3·pyridine complex (336 mg, 2.1 mmol) was added to a stirring solution of the resulting crude product in CH_2Cl_2 (10 mL), DMSO (3 mL), and Et_3N (0.1 mL) at −5 °C. After stirring at the same temperature for 2 h, the reaction mixture was extracted with EtOAc, washed successively with saturated $NaHCO_3$, brine, and water, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography on silica gel (50:1 $CHCl_3$/MeOH) to provide **22** (166 mg, 0.525 mmol, 75%) as a white solid. R_f = 0.32 (silica gel, $CHCl_3$/MeOH = 50:1); mp 187−190 °C; $[\alpha]^{25}_D$ −19.3 (*c* 0.18, CH_2Cl_2); IR (KBr) 3338, 2970, 2943, 1771, 1705, 1580, 1458, 1429, 1266, 1245, 1125, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 8.1 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 8.1 Hz, 1H), 4.50 (t, *J* = 9.5 Hz, 1H), 4.43 (t, *J* = 9.3 Hz, 1H), 3.82 (s, 3H), 3.21−3.02 (m, 3H), 2.96 (ddd, *J* = 18.2, 6.1, 1.8 Hz, 1H), 2.79−2.67 (m, 1H), 2.52−2.43 (m, 1H), 1.92−1.78 (m, 2H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6, 174.2, 157.2, 146.8, 126.9, 123.1, 115.9, 107.4, 78.8, 66.3, 55.3, 49.1, 48.8, 42.2, 37.5, 25.6, 23.1, 20.9; ESIMS *m*/*z* 317.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{18}H_{21}O_5$ $[M + H]^+$ 317.1389, found 317.1390.

(3bR,9bS,11S)-11-Hydroxy-6-methoxy-9b-methyl-3b,4,5,9b,10,11-hexahydrophenanthro[2,1-c]furan-1(3H)-one (**23**). Burgess reagent (181 mg, 0.76 mmol) was added to a stirring solution of compound **22** (120 mg, 0.38 mmol) in benzene (5 mL) at room temperature. After stirring at reflux for 30 min, the reaction mixture was cooled to room temperature and extracted with EtOAc. The combined organic layer was washed with brine and water, dried over anhydrous Na_2SO_4, filtered through a short column of silica gel, and concentrated under vacuum to give a crude product. $NaBH_4$ (29 mg, 0.76 mmol) was added to a stirring solution of the resulting crude product and $CeCl_3·7H_2O$ (312 mg, 0.84 mmol) in methanol (10 mL) at −20 °C. After stirring at −20 °C for 30 min, the reaction was quenched with saturated aq NH_4Cl. The mixture was extracted with EtOAc, and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography on silica gel (30:1 $CHCl_3$/MeOH) to provide **23** (63 mg, 0.21 mmol, 56%) as a white solid. R_f = 0.25 (silica gel, $CHCl_3$/MeOH = 50:1); mp 232−235 °C; $[\alpha]^{25}_D$ −27.4 (*c* 0.08, CH_2Cl_2); IR (KBr) 3467, 2960, 2944, 1892, 1751, 1582, 1533, 1411, 1372, 1140, 1075, 878 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (t, *J* = 8.1 Hz, 1H), 7.02 (d, *J* = 7.9 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 4.98−4.81 (m, 2H), 4.76 (d, *J* = 5.9 Hz, 1H), 3.83 (s, 3H), 2.97 (dd, *J* = 18.1, 6.7 Hz, 1H), 2.86−2.69 (m, 2H), 2.64 (d, *J* = 11.6 Hz, 1H), 2.06−1.86 (m, 3H), 1.20 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$−CD_3OD) δ 174.2, 166.5, 157.1, 145.9, 126.1, 125.8, 122.6, 116.1, 107.0, 70.5, 59.2, 54.8, 42.2, 41.2, 35.4, 23.5, 22.1, 18.9; ESIMS *m*/*z* 301.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{18}H_{21}O_4$ $[M + H]^+$ 301.1440, found 301.1442.

(3bR,9bS,11S)-11-Hydroxy-7-isopropyl-6-methoxy-9b-methyl-3b,4,5,9b,10,11-hexahydrophenanthro[2,1-c]furan-1(3H)-one (**24**). To a stirred solution of compound **23** (70 mg, 0.23 mmol) in chloroform (10 mL) at 0 °C were added silver triflate (72 mg, 0.28 mmol) and iodine (35 mg, 0.28 mmol). After stirring at 0 °C for 0.5 h, the mixture was filtered through Celite and washed with saturated aq $Na_2S_2O_3$ solution. The organic layer was dried over anhydrous Na_2SO_4, filtered through a short column of silica gel, and evaporated under vacuum to give a crude product. To a stirred solution of compound **20** (58 mg, 0.46 mmol) in anhydrous THF (4 mL) at 0 °C was added a solution of TBAF (241 mg, 0.92 mmol) in anhydrous THF (3 mL). The ice-bath was removed after completing the addition of TBAF. The reaction mixture was allowed to warm to room temperature and stirred for 10 min. Then the above resulting crude product and $Pd(dba)_2$ (2.8 mg, 0.012 mmol) were added to the mixture. The mixture was stirred at room temperature for 4 h, and then EtOAc (10 mL) was added and stirred for another 5 min. Then the mixture was filtered through a short column of silica gel, washed with brine and water, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product. A

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solution of the above resulting crude product and 5% Pd/C (5 mg) in MeOH (5 mL) was stirred at gentle reflux for 8 h. The mixture was filtered through Celite, concentrated, and purified by flash column chromatography on silica gel (30:1, $CHCl_3$/MeOH) to provide **24** (51 mg, 0.15 mmol, 65%) as a white solid. R_f = 0.30 (silica gel, $CHCl_3$/MeOH = 50:1); mp 190−193 °C; $[\alpha]^{25}_D$ +32.1 (*c* 0.09, CH_2Cl_2); IR (KBr) 3482, 2966, 2937, 1896, 1750, 1592, 1537, 1433, 1309, 1145, 1088, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18−7.10 (m, 2H), 4.97−4.80 (m, 2H), 4.75 (d, *J* = 5.7 Hz, 1H), 3.73 (s, 3H), 3.30 (dt, *J* = 13.7, 6.9 Hz, 1H), 3.09 (ddd, *J* = 18.1, 6.7, 1.6 Hz, 1H), 2.99−2.84 (m, 1H), 2.73 (d, *J* = 14.6 Hz, 1H), 2.64 (br d, *J* = 12.7 Hz, 1H), 2.08−1.87 (m, 3H), 1.24 (d, *J* = 4.0 Hz, 3H), 1.22 (d, *J* = 4.0 Hz, 3H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 165.2, 155.3, 143.9, 139.2, 127.5, 126.6, 124.3, 120.7, 70.7, 60.6, 60.3, 42.0, 41.5, 36.1, 26.1, 24.1, 23.9, 23.8, 22.9, 19.6; ESIMS *m*/*z* 343.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{21}H_{27}O_4$ $[M + H]^+$ 343.1909, found 343.1904.

(3bR,9bS)-6-Methoxy-9b-methyl-3b,4,10,11-tetrahydrophenanthro[2,1-c]furan-1,5(3H,9bH)-dione (**25**). To a stirred solution of compound **18** (85 mg, 0.3 mmol) in acetonitrile (3 mL) and water (3 mL) was added ammonium ceric nitrate (493 mg, 0.9 mmol), and the mixture was stirred at room temperature for 1.5 h. Then the reaction mixture was extracted with CH_2Cl_2 and washed with brine and water. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product which, without purification, was dissolved in acetone (5 mL) and cooled to 0 °C followed by addition of 8 N Jones reagent (75 μL, 0.6 mmol). The mixture was stirred at 0 °C for 30 min, 2-propanol was added to quench the reaction, and the reaction mixture was diluted with ethyl acetate and filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by flash chromatograph on silica gel (5:1, PE/EtOAc) to give **25** (76 mg, 0.255 mmol, 85%) as a white solid; R_f = 0.30 (silica gel, PE/EtOAc = 5:1). mp 279−281 °C; $[\alpha]^{25}_D$ −47.7 (*c* 0.15, CH_2Cl_2); IR (KBr) 2928, 1751, 1677, 1590, 1573, 1472, 1431, 1276, 1238, 1045, 1017, 798 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (t, *J* = 8.2 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 4.81−4.66 (m, 2H), 3.91 (s, 3H), 3.17−3.06 (m, 1H), 2.79 (dd, *J* = 18.3, 6.0 Hz, 1H), 2.68−2.47 (m, 3H), 2.46−2.32 (m, 1H), 1.82 (td, *J* = 12.5, 6.4 Hz, 1H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.7, 173.4, 160.5, 160.2, 153.5, 134.8, 125.7, 121.0, 115.2, 111.0, 70.1, 56.2, 39.6, 37.8, 36.9, 32.0, 21.4, 17.8; ESIMS *m*/*z* 299.3 $[M + H]^+$; HRMS (ESI) calcd for $C_{18}H_{19}O_4$ $[M + H]^+$ 299.1283, found 299.1287.

(3bR,9bS)-6-Hydroxy-9b-methyl-3b,4,10,11-tetrahydrophenanthro[2,1-c]furan-1,5(3H,9bH)-dione (**26**). To a stirred solution of compound **25** (597 mg, 2.0 mmol) in dichloromethane (20 mL), under argon protection at −78 °C, was added BBr_3 (372 μL, 4.0 mmol). After stirring at −78 °C for 1 h, the reaction mixture was warmed to room temperature. An aqueous $NaHCO_3$ solution (10%) was added, extracted with dichloromethane, washed with brine, dried over Na_2SO_4, and concentrated to give a crude product, which was purified by flash chromatograph on silica gel (25:1, $CHCl_3$/MeOH) to provide **26** (523 mg, 1.84 mmol, 92%) as a white solid. R_f = 0.28 (silica gel, $CHCl_3$/MeOH = 25:1); mp 263−265 °C; $[\alpha]^{25}_D$ −47.3 (*c* 0.09, CH_2Cl_2); IR (KBr) 3466, 2961, 2922, 1750, 1681, 1636, 1452, 1433, 1345, 1248, 1227, 1212, 1163, 1060, 1020, 982, 811, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.63 (s, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 4.87−4.74 (m, 2H), 3.28−3.20 (m, 1H), 2.88−2.80 (m, 2H), 2.63−2.55 (m, 2H), 2.49−2.40 (m, 1H), 1.85 (td, *J* = 12.5, 6.4 Hz, 1H), 1.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 173.3, 164.0, 159.5, 152.1, 137.4, 126.2, 117.0, 115.3, 114.2, 70.0, 40.3, 36.7, 36.3, 31.7, 21.8, 17.8; ESIMS *m*/*z* 285.3 $[M + H]^+$; HRMS (ESI) calcd for $C_{17}H_{17}O_4$ $[M + H]^+$ 285.1127, found 285.1123.

(3bR,9bS)-6-((E)-But-2-enyloxy)-9b-methyl-3b,4,10,11-tetrahydrophenanthro[2,1-c]furan-1,5(3H,9bH)-dione (**27**). To a stirred solution of compound **26** (380 mg, 1.34 mmol) in anhydrous DMF (6 mL) was added NaH (60% dispersion in mineral oil, 59 mg, 1.47 mmol) at 0 °C. After stirring at room temperature for 30 min, crotyl bromide (276 μL, 2.68 mmol) was added. After stirring for 2 h, the reaction mixture was extracted with EtOAc, washed successively with saturated NH_4Cl, brinec and water, dried over anhydrous Na_2SO_4, filtered, and concentrated to give a crude product, which was purified by flash chromatography on silica gel (50:1, $CHCl_3$/MeOH) to provide **27** (416 mg, 1.23 mmol, 92%) as a white solid. R_f = 0.27 (silica gel, $CHCl_3$/MeOH) = 50:1); mp 136−138 °C; $[\alpha]^{25}_D$ −36.2 (*c* 0.07, CH_2Cl_2); IR (KBr) 2926, 2857, 1752, 1679, 1590, 1573, 1470, 1435, 1272, 1238, 1065, 1015, 798 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (t, *J* = 8.1 Hz, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 5.94 (dq, *J* = 13.0, 6.4 Hz, 1H), 5.78−5.66 (m, 1H), 4.76 (d, *J* = 17.0 Hz, 2H), 4.71−4.45 (m, 2H), 3.16−3.05 (m, 1H), 2.79 (dd, *J* = 18.2, 5.9 Hz, 1H), 2.67−2.45 (m, 3H), 2.44−2.30 (m, 1H), 1.85−1.68 (m, 4H), 1.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 173.4, 160.2, 159.5, 153.4, 134.5, 130.3, 125.6, 125.3, 121.3, 115.1, 112.3, 70.0, 69.5, 39.6, 37.8, 36.8, 32.0, 21.3, 17.9, 17.7; ESIMS *m*/*z* 339.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{21}H_{23}O_4$ $[M + H]^+$ 339.1596, found 339.1599.

(3bR,9bS)-7-(But-3-en-2-yl)-6-hydroxy-9b-methyl-3b,4,10,11-tetrahydrophenanthro[2,1-c]furan-1,5(3H,9bH)-dione (**28a/28b**). A stirred solution of compound **27** (455 mg, 1.34 mmol) in *N*,*N*-dimethylaniline (10 mL) under argon protection was heated at reflux for 8 h, cooled to room temperature, extracted with EtOAc, washed successively with 8 N HCl, brine, and water, dried over anhydrous Na_2SO_4, filtered, and concentrated to give a crude product, which was purified by flash chromatography on silica gel (80:1, $CHCl_3$/MeOH) to provide a 1:1 mixture of **28a**/**28b** (386 mg, 1.14 mmol, 85%) as a white solid. R_f = 0.50 (silica gel, $CHCl_3$/MeOH) = 50:1); mp 197−204 °C; $[\alpha]^{25}_D$ +39.7 (*c* 0.15, CH_2Cl_2); IR (KBr) 3471, 2962, 2939, 1761, 1684, 1636, 1446, 1414, 1317, 1250, 1225, 1016, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 13.05 (s, 1H), 13.04 (s, 1H), 7.35 (d, *J* = 7.9 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.06−5.92 (m, 2H), 5.14−4.96 (m, 4H), 4.87−4.64 (m, 4H), 3.95−3.86 (m, 2H), 3.20−3.15 (m, 2H), 2.81−2.76 (m, 4H), 2.54−2.47 (m, 4H), 2.45−2.27 (m, 2H), 1.77 (td, *J* = 12.6, 6.8 Hz, 2H), 1.33−1.25 (m, 6H), 1.11 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2, 173.2, 161.3, 159.7, 149.6, 141.6, 141.5, 134.92, 134.89, 132.85, 132.77, 125.8, 114.7, 113.6, 113.5, 113.4, 69.9, 40.1, 36.3, 36.2, 34.8, 34.7, 31.4, 21.6, 18.79, 18.76, 17.6; ESIMS *m*/*z* 339.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{21}H_{23}O_4$ $[M + H]^+$ 339.1596, found 339.1594.

2-((3bR,9bS)-6-Hydroxy-9b-methyl-1,5-dioxo-1,3,3b,4,5,9b,10,11-octahydrophenanthro[2,1-c]furan-7-yl)propanal (**29a/29b**). To a stirred solution of compound **28a**/**28b** (200 mg, 0.59 mmol) in tBuOH (20 mL) and H_2O (4 mL) were added $NaHCO_3$ (496 mg, 5.9 mmol), $NaIO_4$ (749 mg, 3.5 mmol), and OsO_4 (2% aq solution, 0.37 mL, 0.030 mmol) at room temperature. After stirring at room temperature for 12 h, the reaction was quenched with saturated aq $Na_2S_2O_3$. After stirring for another 30 min, the mixture was extracted with EtOAc, and the combined organic layer was washed with brine and water, dried over anhydrous Na_2SO_4, filtered, and concentrated to give a crude product which was purified by flash column chromatography on silica gel (50:1, $CHCl_3$/MeOH)) to provide a mixture of **29a**/**29b** (163 mg, 0.48 mmol, 81%) as a white solid. R_f = 0.30 (silica gel, $CHCl_3$/MeOH) = 50:1); mp 190−197 °C; $[\alpha]^{25}_D$ −44.4 (*c* 0.09, CH_2Cl_2); IR (KBr) 3487, 2952, 2937, 2827, 2725, 1769, 1735, 1565, 1522, 1322, 1244, 1011, 898 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 13.07 (s, 1H), 13.06 (s, 1H), 9.72 (s, 1H), 9.71 (s, 1H), 7.35−7.33 (m, 2H), 6.96 (d, *J* = 7.9 Hz, 2H), 4.81 (d, *J* = 17.2 Hz, 2H), 4.75 (d, *J* = 17.2 Hz, 2H), 3.96 (d, *J* = 7.3 Hz, 2H), 3.22 (d, *J* = 5.5 Hz, 2H), 2.89−2.76 (m, 4H), 2.61−2.50 (m, 4H), 2.47−2.35 (m, 2H), 1.82 (td, *J* = 12.3, 6.7 Hz, 2H), 1.43 (d, *J* = 3.1 Hz, 3H), 1.41 (d, *J* = 3.1 Hz, 3H), 1.16 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.8, 202.6, 202.5, 174.7, 163.13, 163.11, 161.0, 152.7, 137.9, 137.8, 127.6, 127.5, 116.6, 115.7, 71.4, 47.6, 47.5, 41.7, 38.1, 37.7, 33.01, 32.97, 23.2, 23.1, 19.2, 14.5, 14.4; ESIMS *m*/*z* 341.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{21}O_5$ $[M + H]^+$ 341.1389, found 341.1393.

Preparation of Compounds **30a** *and* **30b**. To a stirred solution of compound **29a**/**29b** (120 mg, 0.35 mmol) in methanol (5 mL) at 0 °C was added sodium borohydride (40 mg, 1.05 mmol). After stirring at 0 °C for 30 min, the mixture was quenched with aqueous saturated NH_4Cl, extracted with *n*-BuOH-EtOAc (1:2), washed with brine, dried

over anhydrous Na_2SO_4, and concentrated to give a crude product, which was dissolved in MeOH (12 mL). A solution of $NaIO_4$ (90 mg, 0.42 mmol) in water (3 mL) was added at 0 °C. After stirring at 0 °C for 50 min, the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give a crude product, which was purified by flash chromatography on silica gel (50:1, $CHCl_3$/MeOH) to provide **30a** and **30b**.

*Compound **30a**.* White solid (48.6 mg, 0.142 mmol, 41%); R_f = 0.26 (silica gel, $CHCl_3$/MeOH) = 25:1), mp 160−162 °C; $[\alpha]^{25}_D$ −191.3 (*c* 0.10, CH_2Cl_2); IR (KBr) 3457, 2924, 2911, 2864, 1752, 1689, 1609, 1566, 1529, 1411, 1298, 1162, 1009 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.05 (d, *J* = 6.7 Hz, 1H), 6.42 (d, *J* = 6.8 Hz, 1H), 4.74−4.64 (m, 2H), 4.06 (d, *J* = 5.4 Hz, 1H), 3.63−3.53 (m, 2H), 3.00 (dd, *J* = 12.5, 6.3 Hz, 1H), 2.60 (d, *J* = 15.3 Hz, 1H), 2.44 (dd, *J* = 17.6, 3.3 Hz, 1H), 2.32−2.22 (m, 2H), 2.13−2.03 (m, 2H), 1.63 (td, *J* = 12.2, 6.2 Hz, 1H), 1.13 (s, 3H), 1.12 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.1, 173.4, 160.1, 151.2, 137.9, 137.8, 125.3, 120.9, 70.0, 67.2, 66.7, 57.3, 43.5, 38.3, 34.6, 32.7, 24.1, 17.4, 16.8, 15.4; ESIMS *m*/*z* 343.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{23}O_5$ $[M + H]^+$ 343.1545, found 343.1542.

*Compound **30b**.* White solid (47.6 mg, 0.139 mmol, 40%); R_f = 0.30 (silica gel, $CHCl_3$/MeOH) = 25:1), mp 163−165 °C; $[\alpha]^{25}_D$ −195.2 (*c* 0.11, CH_2Cl_2); IR (KBr) 3434, 2928, 2907, 2857, 1756, 1693, 1583, 1562, 1433, 1375, 1269, 1024 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.05 (d, *J* = 6.7 Hz, 1H), 6.41 (d, *J* = 6.8 Hz, 1H), 4.72−4.64 (m, 2H), 4.02 (d, *J* = 5.4 Hz, 1H), 3.62 (dd, *J* = 10.6, 6.2 Hz, 1H), 3.56 (dd, *J* = 10.6, 5.3 Hz, 1H), 2.97 (dq, *J* = 12.9, 6.6 Hz, 1H), 2.62−2.55 (m, 1H), 2.44 (dd, *J* = 18.4, 2.4 Hz, 1H), 2.31−2.22 (m, 2H), 2.17−2.05 (m, 2H), 1.64 (ddd, *J* = 18.6, 12.2, 6.1 Hz, 1H), 1.16−1.12 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.8, 173.3, 160.1, 151.2, 137.9, 137.8, 125.3, 120.9, 69.9, 67.3, 66.2, 57.3, 43.7, 38.3, 34.9, 32.7, 24.2, 17.4, 16.7, 15.6; ESIMS *m*/*z* 343.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{23}O_5$ $[M + H]^+$ 343.1545, found 343.1544.

*(15R)-16-Hydroxytriptonide (**31**).* To a stirred solution of compound **30a** (80 mg, 0.23 mmol) in acetonitrile (5 mL) was added an aqueous Na_2(EDTA) solution (4×10^{-4} M, 5 mL). The resulting homogeneous solution was cooled to 0 °C followed by addition of 1,1,1-trifluoroacetone (0.5 mL). To this homogeneous solution was added in portions a mixture of sodium bicarbonate (59 mg, 0.69 mmol) and Oxone (300 mg, 0.46 mmol). After stirring at 0 °C for 5 h, the mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give a crude product. To a solution of the resulting crude product and K_2CO_3 (65 mg, 0.46 mmol) in MeOH (10 mL) was added H_2O_2 (1 mL, 30% aq solution) at 0 °C. After stirring for 2 h, the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give a crude product which was purified by flash chromatograph on silica gel (30:1, $CHCl_3$/MeOH) to give **31** (68 mg, 0.182 mmol, 79%) as a white solid. R_f = 0.24 (silica gel, $CHCl_3$/MeOH) = 25:1); mp 222−224 °C; $[\alpha]^{25}_D$ −243.0 (*c* 0.13, CH_2Cl_2); IR (KBr) 3393, 2923, 2851, 1766, 1737, 1723, 1678, 1434, 1392, 1034, 1018, 1004, 936 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.70 (s, 2H), 4.07 (d, *J* = 2.8 Hz, 1H), 4.03 (d, *J* = 2.7 Hz, 1H), 3.58 (s, 1H), 3.56 (s, 1H), 3.44 (d, *J* = 5.4 Hz, 1H), 2.90 (s, 1H), 2.87−2.72 (m, 1H), 2.52−2.47 (m, 1H), 2.46−2.37 (m, 1H), 2.24−2.16 (m, 1H), 1.97 (td, *J* = 14.8, 7.3 Hz, 1H), 1.63−1.60 (m, 1H), 1.40−1.28 (m, 1H), 1.14 (s, 3H), 1.00 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 173.0, 159.4, 125.6, 69.9, 65.3, 65.1, 63.3, 61.0, 60.5, 60.2, 55.9, 40.5, 35.2, 34.1, 30.4, 23.1, 17.0, 13.7, 12.6; ESIMS *m*/*z* 375.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{23}O_7$ $[M + H]^+$ 375.1444, found 375.1447.

*(15S)-16-Hydroxytriptonide (**32**).* To a stirred solution of compound **30b** (75 mg, 0.22 mmol) in acetonitrile (5 mL) was added an aqueous Na_2(EDTA) solution (4×10^{-4} M, 5 mL). The resulting homogeneous solution was cooled to 0 °C followed by addition of 1,1,1-trifluoroacetone (0.5 mL). To this homogeneous solution was added in portions a mixture of sodium bicarbonate (55 mg, 0.66 mmol) and Oxone (282 mg, 0.44 mmol). After stirring at 0 °C for 5 h, the mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give a crude product. To a solution of the resulting crude product and K_2CO_3 (61 mg, 0.44 mmol) in MeOH (10 mL) was added H_2O_2 (1 mL, 30% aq solution) at 0 °C. After stirring for 2 h, the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give a crude product which was purified by flash chromatograph on silica gel (30:1, $CHCl_3$/MeOH) to give **32** (63 mg, 0.169 mmol, 77%) as a white solid. R_f = 0.30 (silica gel, $CHCl_3$/MeOH) = 25:1); mp 230−232 °C; $[\alpha]^{25}_D$ −161.8 (*c* 0.11, CH_2Cl_2); IR (KBr) 3448, 2923, 2852, 1736, 1674, 1440, 1395, 1100, 1075, 1056, 1035, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.77−4.60 (m, 2H), 4.05 (d, *J* = 2.6 Hz, 1H), 4.01 (d, *J* = 2.7 Hz, 1H), 3.63 (dd, *J* = 10.9, 4.7 Hz, 1H), 3.53 (dd, *J* = 10.6, 6.9 Hz, 1H), 3.40 (d, *J* = 5.3 Hz, 1H), 2.80 (br d, *J* = 13.0 Hz, 1H), 2.46−2.37 (m, 1H), 2.32 (m, 1H), 2.26−2.12 (m, 2H), 1.96 (t, *J* = 14.0 Hz, 1H), 1.57 (dd, *J* = 12.3, 5.2 Hz, 1H), 1.34−1.23 (m, 1H), 1.04 (s, 3H), 0.90 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 173.1, 159.5, 125.6, 69.9, 65.0, 64.3, 63.4, 60.9, 60.6, 59.5, 56.0, 40.4, 35.2, 34.1, 30.4, 23.1, 17.0, 13.7, 11.3; ESIMS *m*/*z* 375.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{23}O_7$ $[M + H]^+$ 375.1444, found 375.1445.

*(15S)-16-Hydroxytriptolide (**4**) and (15S)-16-Hydroxyepitriptolide (**33**).* To a stirred solution of compound **32** (30 mg, 0.08 mmol) in MeOH (5 mL) at 0 °C was added $NaBH_4$ (6 mg, 0.16 mmol). After stirring at 0 °C for 1 h, the reaction was quenched with saturated aq NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give a crude product, which was purified by HPLC to give **4** and **33**.

*Compound **4**.* White solid, 16 mg, 0.042 mmol, 53%; $[\alpha]^{25}_D$ −77.7 (*c* 0.02, CH_2Cl_2); mp: 231−233; IR: (KBr) 3363, 2923, 2851, 1748, 1662, 1633, 1469, 1441, 1117, 1019, 911 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 4.81 (q, *J* = 18.7 Hz, 2H), 4.68 (br d, *J* = 6.1 Hz, 1H), 4.55 (s, 1H), 3.90 (d, *J* = 3.1 Hz, 1H), 3.65 (d, *J* = 2.8 Hz, 1H), 3.25 (dd, *J* = 11.2, 8.1 Hz, 1H), 3.13 (dd, *J* = 11.1, 6.3 Hz, 1H), 2.59 (br d, J = 17.5 Hz, 1H), 2.29−2.17 (m, 1H), 2.15−2.06 (m, 2 H), 2.04−1.92 (m, 3 H), 1.82 (dd, *J* = 14.8, 13.6 Hz, 1H), 1.32−1.27 (m, 2H), 0.95 (s, 3 H), 0.83 (d, *J* = 7.1 Hz, 3 H); ^1H NMR (300 MHz, $CDCl_3$) δ 4.68 (s, 2H), 3.93 (d, *J* = 3.2 Hz, 1H), 3.68 (d, *J* = 3.0 Hz, 1H), 3.61 (dd, *J* = 11.4, 4.0 Hz, 1H), 3.46 (dd, *J* = 11.3, 7.9 Hz, 1H), 3.45 (br s, 1H), 3.40 (d, *J* = 5.4 Hz, 1H), 3.11 (br s, 1H), 2.70 (br d, *J* = 13.2 Hz, 1H), 2.36−2.28 (m, 1H), 2.27−2.22 (m, 1H), 2.21−2.11 (m, 2H), 2.06−1.91 (m, 1H),1.65−1.51 (m, 1H), 1.24−1.16 (m, 1H), 1.11 (s, 3H), 0.96 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-*d6*) δ 173.2, 162.5, 123.1, 71.5, 70.3, 64.3, 63.0, 61.7, 60.8, 59.8, 55.3, 54.6, 40.1, 35.7, 35.2, 29.0, 22.7, 16.6, 13.7, 12.5; ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.2, 159.9, 125.5, 74.0, 70.0, 66.3, 63.90, 63.86, 60.5, 60.1, 56.7, 54.3, 40.4, 37.1, 35.7, 29.7, 23.6, 17.0, 13.6, 12.3; ESIMS *m*/*z* 377.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{25}O_7$ $[M + H]^+$ 377.1600, found 377.1603

*Compound **33**.* White solid (11 mg, 0.028 mmol, 35%); $[\alpha]^{25}_D$ −82.2 (*c* 0.03, CH_2Cl_2); mp: 241−242 °C; IR: (KBr) 3530, 3361, 2922, 2851, 1736, 1668, 1633, 1443, 1071, 1034, 1014, 923 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.69 (s, 2H), 4.53 (d, *J* = 3.1 Hz, 1H), 3.85−3.72 (m, 3H), 3.68 (dd, *J* = 11.2, 5.9 Hz, 1H), 3.37 (d, *J* = 3.1 Hz, 1H), 2.83−2.63 (m, 2 H), 2.33 (dd, *J* = 10.0, 3.9 Hz, 1H), 2.26−2.14 (m, 3H), 2.06−1.88 (m, 2H), 1.57 (dd, *J* = 12.2, 5.1 Hz, 1H), 1.27−1.17 (m, 1H), 1.11 (s, 3H), 1.05 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 Hz, $CDCl_3$) δ 173.4, 160.3, 125.4, 70.0, 66.1, 65.1, 64.4, 64.2, 61.7, 55.8, 55.7, 55.1, 40.5, 39.5, 35.8, 29.9, 23.5, 17.1, 13.5, 11.8; ESIMS *m*/*z* 377.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{25}O_7$ $[M + H]^+$ 377.1600, found 377.1604.

*(3bR,9bS)-6-(Allyloxy)-9b-methyl-3b,4,10,11-tetrahydrophenanthro[2,1-c]furan-1,5(3H,9bH)-dione (**34**).* To a stirred solution of compound **26** (381 mg, 1.34 mmol) in anhydrous DMF (5 mL) was added NaH (60% dispersion in mineral oil, 59 mg, 1.47 mmol) at 0 °C. After stirring at room temperature for 30 min, allylic bromide (232 μL, 2.68 mmol) was added. After stirring for 5 h, the reaction mixture was extracted with EtOAc, washed successively with saturated NH_4Cl, brine, and water, dried over anhydrous Na_2SO_4, filtered, and concentrated to give a crude product, which was purified by flash chromatography on silica gel (50:1, $CHCl_3$/MeOH) to

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provide **34** (405 mg, 1.25 mmol, 93%) as a white solid. R_f = 0.25 (silica gel, $CHCl_3$/MeOH) = 50:1); mp 150−152 °C; $[\alpha]^{25}_D$ −39.9 (*c* 0.09, CH_2Cl_2); IR (KBr) 2933, 2927, 2887, 1753, 1682, 1566, 1549, 1433, 1230, 1063, 1011, 797 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (td, *J* = 6.0 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.12−5.98 (m, 1H), 5.57 (ddd, *J* = 17.2, 3.3, 1.7 Hz, 1H), 5.31 (ddd, *J* = 10.6, 3.0, 1.5 Hz, 1H), 4.80−4.72 (m, 2H), 4.68 (ddt, *J* = 13.2, 4.6, 1.6 Hz, 1H), 4.57 (ddt, *J* = 13.2, 4.9, 1.6 Hz, 1H), 3.18−3.08 (m, 1H), 2.80 (dd, *J* = 18.2, 5.9 Hz, 1H), 2.68−2.47 (m, 3H), 2.45−2.33 (m, 1H), 1.81 (td, *J* = 12.2, 6.3 Hz, 1H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 173.3, 160.1, 159.3, 153.4, 134.4, 132.4, 125.6, 121.3, 117.6, 115.2, 112.3, 70.0, 69.4, 39.6, 37.7, 36.8, 31.9, 21.3, 17.7; ESIMS *m*/*z* 325.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{21}O_4$ $[M + H]^+$ 325.1440, found 325.1442.

(3bR,9bS)-7-Allyl-6-hydroxy-9b-methyl-3b,4,10,11-tetrahydrophenanthro[2,1-c]furan-1,5(3H,9bH)-dione (**35**). A stirred solution of compound **34** (435 mg, 1.34 mmol) in *N*,*N*-dimethylaniline (10 mL) under argon protection was heated at reflux for 8 h, cooled to room temperature, extracted with EtOAc, washed successively with 8 N HCl, brine, and water, dried over anhydrous Na_2SO_4, filtered, and concentrated to give a crude product, which was purified by flash chromatography on silica gel (80:1, $CHCl_3$/MeOH) to provide **35** (360 mg, 1.11 mmol, 83%) as a white solid. R_f = 0.45 (silica gel, $CHCl_3$/MeOH) = 50:1); mp 198−200 °C; $[\alpha]^{25}_D$ +35.6 (*c* 0.11, CH_2Cl_2); IR (KBr) 3066, 2987, 1753, 1688, 1656, 1467, 1400, 1264, 1221, 1010, 819 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.95 (s, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.03−5.89 (m, 1H), 5.13−5.01 (m, 2H), 4.83−4.69 (m, 2H), 3.40−3.34 (m, 2H), 3.17 (s, 1H), 2.81−2.76 (m, 2H), 2.58−2.46 (m, 2H), 2.45−2.33 (m, 1H), 1.78 (td, *J* = 12.3, 6.5 Hz, 1H), 1.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.1, 173.2, 161.7, 159.6, 149.9, 137.0, 135.7, 127.6, 125.8, 116.1, 114.7, 113.5, 69.9, 40.2, 36.4, 36.2, 33.1, 31.5, 21.6, 17.6; ESIMS *m*/*z* 325.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{21}O_4$ $[M + H]^+$ 325.1440, found 325.1439.

2-((3bR,9bS)-6-Hydroxy-9b-methyl-1,5-dioxo-1,3,3b,4,5,9b,10,11-octahydrophenanthro[2,1-c]furan-7-yl)acetaldehyde (**36**). To a stirred solution of compound **35** (191 mg, 0.59 mmol) in tBuOH (20 mL) and H_2O (4 mL) were added $NaHCO_3$ (496 mg, 5.9 mmol), $NaIO_4$ (749 mg, 3.5 mmol), and OsO_4 (2% aq solution, 0.37 mL, 0.030 mmol) at room temperature. After stirring at room temperature for 12 h, the reaction was quenched with saturated aq $Na_2S_2O_3$. After stirring for another 30 min, the mixture was extracted with EtOAc, and the combined organic layer was washed with brine and water, dried over anhydrous Na_2SO_4, filtered, and concentrated to give a crude product which was purified by flash column chromatography on silica gel (50:1, $CHCl_3$/MeOH)) to provide **36** (163.2 mg, 0.50 mmol, 85%) as a white solid. R_f = 0.25 (silica gel, $CHCl_3$/MeOH) = 50:1); mp 197−199 °C; $[\alpha]^{25}_D$ −54.3 (*c* 0.05, CH_2Cl_2); IR (KBr) 3469, 2940, 2928, 2854, 2700, 1757, 1625, 1499, 1309, 1240, 1017, 899 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.93 (s, 1H), 9.75 (t, *J* = 1.5 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 4.87−4.69 (m, 2H), 3.72 (d, *J* = 1.4 Hz, 1H), 3.70 (d, *J* = 1.4 Hz, 1H), 3.27−3.16 (m, 1H), 2.83−2.78 (m, 2H), 2.58−2.48 (m, 2H), 2.46−2.36 (m, 1H), 1.85−1.75 (m, 1H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 198.9, 173.2, 161.9, 159.5, 151.4, 138.5, 126.0, 120.5, 115.1, 114.0, 69.9, 60.3, 44.1, 40.2, 36.6, 36.2, 31.5, 21.6, 17.7; ESIMS *m*/*z* 327.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{19}H_{19}O_5$ $[M + H]^+$ 327.1232, found 327.1235.

Preparation of Compound **37**. To a stirred solution of compound **36** (49 mg, 0.15 mmol) in methanol (5 mL) at 0 °C was added sodium borohydride (23 mg, 0.60 mmol). After stirring at 0 °C for 30 min, the mixture was quenched with aqueous saturated NH_4Cl, extracted with *n*-BuOH−EtOAc (1:2), washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give a crude product, which was dissolved in MeOH (5 mL). Then a solution of $NaIO_4$ (39 mg, 0.18 mmol) in water (2.5 mL) was added at 0 °C. After stirring at 0 °C for 50 min, the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give a crude product, which was purified by flash chromatography on silica gel (50:1, $CHCl_3$/MeOH) to provide **37** (36.1 mg, 0.11 mmol, 73%) as a white solid; R_f = 0.25 (silica gel, $CHCl_3$/MeOH = 25:1), mp 226−228 °C; $[\alpha]^{25}_D$ −157.4 (*c* 0.08, CH_2Cl_2); IR (KBr) 3567, 2945, 2909, 2884, 1756, 1645, 1573, 1522, 1279, 1102, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, *J* = 6.7 Hz, 1H), 6.44 (d, *J* = 6.8 Hz, 1H), 4.70 (s, 2H), 4.10 (d, *J* = 5.4 Hz, 1H), 3.72−3.53 (m, 2H), 3.21−2.97 (m, 1H), 2.65−2.36 (m, 2H), 2.35−2.07 (m, 4H), 2.02−1.95 (m, 1H), 1.69−1.55 (m, 1H), 1.16 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.1, 173.0, 159.2, 151.6, 139.6, 133.5, 125.2, 120.3, 69.3, 67.1, 61.1, 56.9, 43.4, 38.2, 32.5, 23.9, 17.1, 16.4; ESIMS *m*/*z* 329.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{19}H_{21}O_5$ $[M + H]^+$ 329.1389, found 329.1385.

13-Hydroxyethyltriptonide (**38**). To a stirred solution of compound **37** (75.5 mg, 0.23 mmol) in acetonitrile (5 mL) was added an aqueous $Na_2(EDTA)$ solution (4×10^{-4} M, 5 mL). The resulting homogeneous solution was cooled to 0 °C followed by addition of 1,1,1-trifluoroacetone (0.5 mL). To this homogeneous solution was added in portions a mixture of sodium bicarbonate (59 mg, 0.69 mmol) and Oxone (300 mg, 0.46 mmol). After stirring at 0 °C for 5 h, the mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give a crude product. To a solution of the resulting crude product and K_2CO_3 (65 mg, 0.46 mmol) in MeOH (10 mL) was added H_2O_2 (1 mL, 30% aq solution) at 0 °C. After stirring for 2 h, the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give a crude product which was purified by flash chromatograph on silica gel (30:1, $CHCl_3$/MeOH) to give **38** (62 mg, 0.172 mmol, 75%) as a white solid. R_f = 0.35 (silica gel, $CHCl_3$/MeOH) = 25:1); mp 243−245 °C; $[\alpha]^{25}_D$ −177.4 (*c* 0.04, CH_2Cl_2); IR (KBr) 3677, 3594, 2951, 1753, 1607, 1434, 1305, 1072, 998 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.81−4.59 (m, 2H), 4.07 (s, 2H), 3.74 (t, *J* = 5.8 Hz, 2H), 3.44 (d, *J* = 5.3 Hz, 1H), 2.82 (br d, *J* = 12.7 Hz, 1H), 2.40−2.19 (m, 1H), 2.27- 2.12 (m, 3H), 2.18−1.92 (m, 2H), 1.80−1.70 (m, 1H), 1.70−1.64 (m, 1H), 1.37−1.28 (m, 1H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 173.3, 159.6, 125.6, 70.0, 65.2, 62.1, 61.3, 60.74, 60.71, 58.0, 56.1, 40.5, 35.3, 31.2, 30.4, 23.1, 17.0, 13.8; ESIMS *m*/*z* 361.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{19}H_{21}O_7$ $[M + H]^+$ 361.1287, found 361.1288.

General Procedure for the Synthesis of Compounds **39**−**43**. To a stirred solution of **38** (0.1 mmol) in dichloromethane (3.0 mL) at 0 °C were added TEA (0.2 mmol), DMAP (0.02 mmol), and acyl chloride (0.2 mmol). When TLC showed no traces of the starting material **38**, the mixture was extracted with dichloromethane, washed with brine, dried over Na_2SO_4, and concentrated to give a crude product which was purified by flash chromatograph on silica gel to give a target analogue.

13-Acetoxyethyltriptonide (**39**). White solid (31 mg, 0.085 mmol, 85%), mp 199−201 °C; $[\alpha]^{25}_D$ −109.4 (*c* 0.07, CH_2Cl_2); IR (KBr) 2966, 2935, 1679, 1635, 1504, 1345, 1092, 1010; ^1H NMR (300 MHz, $CDCl_3$) δ 4.70 (s, 2H), 4.18 (t, *J* = 6.3 Hz, 2H), 4.06 (d, *J* = 2.7 Hz, 1H), 3.92 (d, *J* = 2.7 Hz, 1H), 3.45 (d, *J* = 5.4 Hz, 1H), 2.83 (br d, *J* = 15.3 Hz, 1H), 2.37−2.17 (m, 5 H), 2.09−1.94 (m, 4 H), 1.65−1.57 (m, 1H), 1.33−1.27 (m, 1H), 1.08 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.8, 173.0, 170.7, 159.2, 125.8, 69.9, 65.2, 61.6, 61.1, 60.6, 59.5, 55.9, 40.5, 35.4, 30.5, 28.0, 23.2, 20.9, 17.1, 13.8; ESIMS *m*/*z* 403.4 $[M + H]^+$; HRMS (ESI) calcd for $C_{21}H_{23}O_8$ $[M + H]^+$ 403.1393, found 403.1390.

13-Pivaloyloxyethyltriptonide (**40**). White solid (35.6 mg, 0.080 mmol, 80%), mp 187−189 °C; $[\alpha]^{25}_D$ −132.9 (*c* 0.06, CH_2Cl_2); IR (KBr) 2987, 2930, 1680, 1645, 1584, 1533, 1426, 1309, 1011, 776; ^1H NMR (300 MHz, $CDCl_3$) δ 4.70 (br s, 2H), 4.20−4.13 (m, 2H), 4.06 (d, *J* = 2.1 Hz, 1H), 3.92 (d, *J* = 2.2 Hz, 1H), 3.45 (d, *J* = 5.4 Hz, 1H), 2.83 (br d, *J* = 14.0 Hz, 1H), 2.43−2.26 (m, 3H), 2.26−2.14 (m, 2H), 2.00 (t, *J* = 14.4 Hz, 1H), 1.67−1.54 (m, 1H), 1.39−1.28 (m, 1H), 1.20 (s, 9H), 1.08 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 196.8, 175.4, 173.0, 159.3, 125.8, 70.0, 65.2, 61.5, 61.1, 60.64, 60.61, 59.7, 55.9, 40.6, 35.4, 30.6, 28.2, 27.2, 23.3, 17.1, 13.8; ESIMS *m*/*z* 445.5 $[M + H]^+$; HRMS (ESI) calcd for $C_{24}H_{29}O_8$ $[M + H]^+$ 445.1862, found 445.1861.

13-Benzoyloxyethyltriptonide (**41**). White solid (39 mg, 0.084 mmol, 84%), mp 164−166 °C; $[\alpha]^{25}_D$ −155.0 (*c* 0.10, CH_2Cl_2); IR

(KBr) 2979, 2941, 1684, 1639, 1577, 1545, 1397, 1325, 1117, 778; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (dd, J = 7.8, 2.0 Hz, 2H), 7.65−7.54 (m, 3H), 4.70 (br s, 2 H), 4.50−4.36 (m, 2H), 4.05 (d, J = 2.7 Hz, 1H), 3.96 (d, J = 2.6 Hz, 1H), 3.45 (d, J = 5.4 Hz, 1H), 2.82 (d, J = 14.6 Hz, 1H), 2.47−2.15 (m, 5 H), 2.01 (t, J = 13.9 Hz, 1H), 1.61 (dd, J = 16.6, 5.8 Hz, 1H), 1.33−1.27 (m, 1H), 1.08 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.9, 173.0, 166.2, 159.3, 133.2, 129.6, 128.4, 125.8, 69.9, 65.2, 61.6, 61.2, 60.7, 60.6, 60.1, 55.9, 40.5, 35.4, 30.5, 28.1, 23.2, 17.1, 13.8; ESIMS m/z 465.5 $[M + H]^+$; HRMS (ESI) calcd for $C_{26}H_{25}O_8$ $[M + H]^+$ 465.1549, found 465.1544.

*13-Isonicotinoyloxyethyltriptonide (**42**).* White solid (35 mg, 0.075 mmol, 75%), mp 197−199 °C; $[\alpha]^{25}_D$ −167.7 (c 0.09, CH_2Cl_2); IR (KBr) 2955, 2924, 2897, 1685, 1623, 1588, 1539, 1456, 1344, 1320, 998; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (s, 2H), 7.81 (d, J = 10.0 Hz, 2 H), 4.70 (br s, 2H), 4.48 (4.53−4.44, m, 2H), 4.06 (d, J = 2.4 Hz, 1H), 3.93 (d, J = 2.4 Hz, 1H), 3.45 (d, J = 5.3 Hz, 1H), 2.82 (d, J = 13.7 Hz, 1H), 2.38 (br d, J = 8.9 Hz, 1H), 2.34−2.14 (m, 4H), 1.99 (t, J = 14.0 Hz, 1H), 1.65−1.53 (m, 1H), 1.33−1.29 (m, 1H), 1.07 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.9, 172.9, 164.8, 159.1, 150.8, 137.0, 129.7, 125.8, 69.9, 65.3, 61.4, 61.3, 61.0, 60.7, 60.6, 55.8, 40.5, 35.4, 30.5, 28.2, 23.2, 17.1, 13.8; ESIMS m/z 466.5 $[M + H]^+$; HRMS (ESI) calcd for $C_{25}H_{24}NO_8$ $[M + H]^+$ 466.1502, found 466.1505.

*13-(1,3-Dimethyl-1H-pyrazole-5-carbonyloxy)ethyltriptonide (**43**).* White solid (34 mg, 0.070 mmol, 70%), mp 211−223 °C; $[\alpha]^{25}_D$ −144.4 (c 0.07, CH_2Cl_2); IR (KBr) 2975, 2933, 2890, 1677, 1619, 1562, 1533, 1497, 1382, 1309, 1212, 1009, 769; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (s, 1H), 4.70 (br s, 2H), 4.46−4.35 (m, 2H), 4.03 (d, J = 2.8 Hz, 1H), 3.99 (d, J = 2.7 Hz, 1H), 3.85 (s, 3H), 3.46 (d, J = 5.4 Hz, 1H), 2.81 (br d, J = 13.2 Hz, 1H), 2.36−2.15 (m, 8H), 2.00 (dd, J = 9.6, 3.7 Hz, 1H), 1.66−1.55 (m, 1H), 1.33−1.28 (m, 1H), 1.06 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.9, 173.0, 162.1, 159.3, 141.5, 140.0, 125.7, 108.3, 69.9, 65.2, 61.7, 61.1, 60.7, 60.5, 59.7, 56.0, 40.5, 36.9, 35.3, 30.5, 28.0, 23.2, 17.1, 13.8, 11.2; ESIMS m/z 483.5 $[M + H]^+$; HRMS (ESI) calcd for $C_{25}H_{27}N_2O_8$ $[M + H]^+$ 483.1767, found 483.1766.

*13-(2-(Thiophene-2-carbonyloxy)ethyltriptonide (**44**).* White solid (36 mg, 0.077 mmol, 77%), mp 175−177 °C; $[\alpha]^{25}_D$ −98.7 (c 0.03, CH_2Cl_2); IR (KBr) 2970, 2936, 1755, 1667, 1623, 1568, 1544, 1539, 1400, 1351, 1292, 1050, 739; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 3.0 Hz, 1H), 7.86 (d, J = 3.8 Hz, 1H), 7.12 (dd, J = 8.5, 3.7 Hz, 1H), 4.70 (br s, 2H), 4.48−4.33 (m, 2H), 4.07 (d, J = 2.6 Hz, 1H), 3.98 (d, J = 2.3 Hz, 1H), 3.46 (d, J = 5.2 Hz, 1H), 2.83 (br d, J = 12.1 Hz, 1H), 2.47- 2.14 (m, 5H), 1.99 (t, J = 14.1 Hz, 1H), 1.61 (dd, J = 11.6, 4.8 Hz, 1H), 1.33−1.28 (m, 1H), 1.07 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.9, 173.0, 161.7, 159.3, 133.5, 133.2, 132.7, 126.7, 125.8, 69.9, 65.2, 61.5, 61.2, 60.7, 60.6, 60.2, 55.9, 40.5, 35.4, 30.5, 28.2, 23.2, 17.1, 13.8; ESIMS m/z 471.5 $[M + H]^+$; HRMS (ESI) calcd for $C_{24}H_{23}O_8S$ $[M + H]^+$ 471.1114, found 471.1111.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H, ^{13}C NMR spectra and HPLC chromatograms of new compounds and crystal structure reports. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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