Catalytic Asymmetric Synthesis of Halenaquinone and Halenaquinol

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Abstract: A catalytic asymmetric synthesis of halenaquinone (**1**) and halenaquinol (**2**) has been achieved using an asymmetric Heck reaction or a cascade Suzuki cross-coupling and an asymmetric Heck reaction as a key step. This synthesis also features the one-pot construction of a unique pentacyclic ring system from a tricyclic system using palladium chemistry. Moreover, the use of Ph_3As as an achiral ligand has been found to enhance both the cascade Suzuki cross-coupling and also the Heck reaction to a synthetically useful extent.

Key words: asymmetric Heck reaction, Suzuki cross-coupling, cascade reaction, triphenylarsine

Halenaquinone (**1**) and halenaquinol (**2**), which have a benzylic quaternary carbon center as well as a unique pentacyclic skeleton, have been isolated from a variety of sea sponges (Figure 1).[1] These marine natural products have been shown to possess antibiotic, cardiotonic and protein tyrosine kinase inhibitory activity.[2] To date, only Harada and co-workers have succeeded in the total synthesis of **1** and **2** starting from optically pure Wieland–Miescher ketone.[3] We report here a full account of a catalytic asymmetric synthesis of **1** and **2** starting from commercially available 6,7-dimethoxy-1-tetralone (**3**).[4,5,6] This synthesis features the use of an asymmetric Heck reaction or the first use of a cascade Suzuki cross-coupling and an asymmetric Heck reaction as well as the one-pot construction of a unique pentacyclic ring system from a tricyclic ring system using palladium chemistry. Moreover, a cascade Suzuki cross-coupling and a Heck reaction using Ph_3As as an achiral ligand, leading to an efficient synthesis of (±)-**1** and (±)-**2**, are also described.

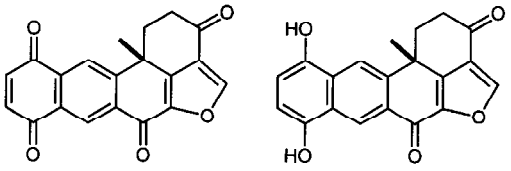
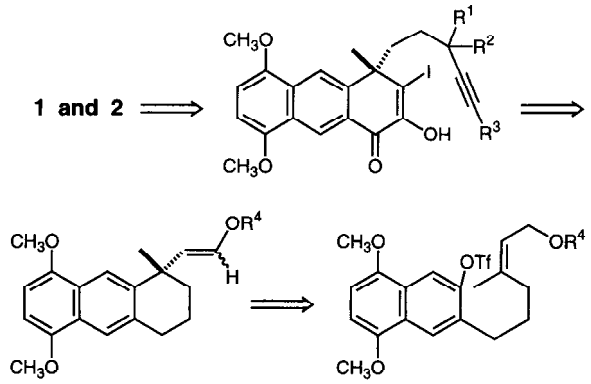


Figure 1

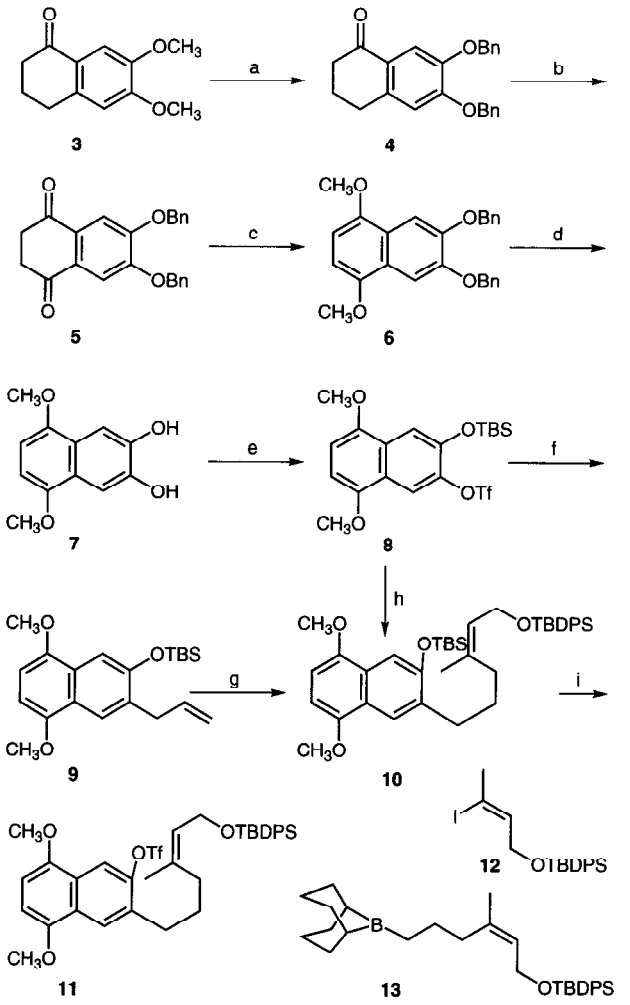
A retrosynthetic analysis for the catalytic asymmetric synthesis of **1** and **2** was made as shown in Scheme 1. The reason behind the adoption of the (*Z*)-configuration for the trisubstituted alkene substrate for the asymmetric Heck reaction stems from experience gained during a catalytic asymmetric synthesis of eptazocine, in which a benzylic quaternary carbon atom was introduced by similar means.[7] In that case we obtained a much higher enantiomeric excess when using the (*Z*)-trisubstituted alkene than when using the (*E*)-configuration.

In order to determine the feasibility of the above-described analysis, the substrate **11** was first of all prepared by two different routes (Scheme 2). Commercially available 6,7-dimethoxy-1-tetralone (**3**) was efficiently converted to the catechol derivative **7** in a five-step sequence of reactions in 58% overall yield. This synthetic route to **7** is applicable to a large scale synthesis because of the easy purification of **4** and **6** by recrystallization. The catechol derivative **7** was transformed into **8** by monosilylation followed by trifluoromethanesulfonylation in 85% yield. Then, cross-coupling using allylmagnesium bromide[8] gave **9** in quantitative yield. Treatment of **9** with 9-BBN followed by Suzuki cross-coupling[9] using the alkenyl iodide **12** afforded **10** in 90% yield. Alternatively, **10** was prepared in a single step (69%) using the alkylborane **13** with a trisubstituted alkenic double bond. The resulting silyl ether **10** was converted to the triflate **11** by conventional means.



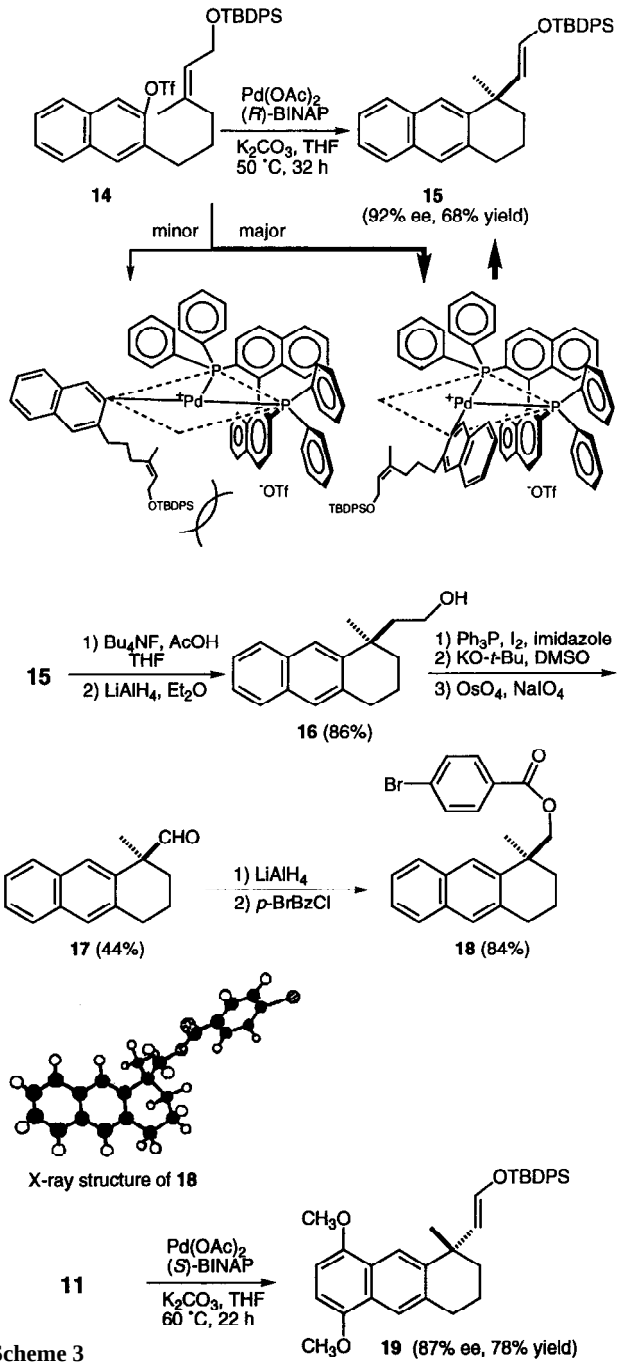
Scheme 1

With the substrate **11** for an asymmetric Heck reaction available in large quantities, we then focused our attention on the crucial catalytic asymmetric cyclization. First of all, using the model compound **14**, the feasibility of an intramolecular Heck reaction was examined, and it turned out that treatment of **14** with $Pd(OAc)_2$ (10 mol %), 1,3-bis(diphenylphosphino)propane (dppp) (20 mol %) and K_2CO_3 (3 equiv) in THF at 50 °C for 120 h gave (±)-**15** in 42% yield. Moreover, based on the previous information obtained in the catalytic asymmetric synthesis of eptazocine with a benzylic quaternary carbon center,[7] **14** was treated with $Pd(OAc)_2$ (10 mol %), (*R*)-BINAP[10] (20 mol %), and K_2CO_3 (3 equiv) in THF at 50 °C for 32 h, giving rise to **15** in 92% ee and in 68% yield. The enantiomeric excess of **15** was determined by HPLC analysis using DAICEL CHIRALCEL OD (hexane–propan-2-ol, 9:1) of the 4-nitrobenzoate of **16**, and the absolute configuration of **15** was unequivocally determined by X-ray analysis of **18** derived from **15**. Having developed an effective catalytic asymmetric synthesis of the model compound **15**, we next attempted a catalytic asymmetric synthesis of **19**, and we were pleased to find that treatment of **11** with $Pd(OAc)_2$ (10 mol %), (*S*)-BINAP (20 mol %),



Reaction conditions: (a) (1) BBr_3 (2.1 equiv), CH_2Cl_2, –78 °C to r.t., (2) BnBr (2.0 equiv), K_2CO_3, Bu_4NI, DMF, 60 °C (two steps, 92%); (b) CrO_3 (5 equiv), HOAc–H_2O, 0 °C to r.t.; (c) KHMDS (3 equiv), THF, –78 °C, then MeI (6 equiv), –78 °C to r.t. (63% from **4**); (d) H_2 (1 atm), Pd–C, EtOAc, r.t. (quant.); (e) (1) TBSCl (1.1 equiv), Et_3N, CH_2Cl_2, 0 °C, (2) Tf_2O (1.3 equiv), Et_3N, CH_2Cl_2, –78 °C to r.t. (two steps, 85%); (f) CH_2=$CHCH_2MgBr$ (5 equiv), $PdCl_2(dppf)$•CH_2Cl_2 (9 mol %), Et_2O, –78°C to r.t. (quant.); (g) (1) 9-BBN (2.1 equiv), THF, 0 °C to r.t., (2) **12** (1.5 equiv), $PdCl_2(dppf)$•CH_2Cl_2 (5 mol %), K_3PO_4•nH_2O, THF, 50 °C (90% from **9**); (h) **13** (1.3 equiv), $PdCl_2(dppf)$•CH_2Cl_2 (10 mol %), K_2CO_3, THF, 50 °C (69 %); (i) (1) Bu_4NF (1.0 equiv), THF, 0 °C, (2) Tf_2O (1.3 equiv), Et_3N, CH_2Cl_2, –78 °C to r.t. (two steps, 69 %).

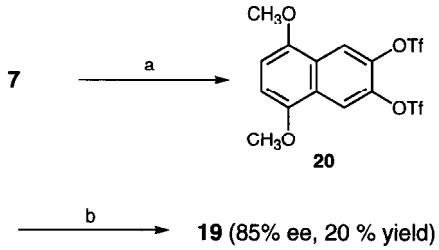
Scheme 2



Scheme 3

and K_2CO_3 (3 equiv) in THF at 60 °C for 22 h gave **19** with 87% ee in 78% yield. Expected *S* configuration of **19** was confirmed by the fact that **19** was successfully converted to natural **1** and **2**.

Is it possible to develop another shorter synthetic route to optically active **19**? We noticed that the catechol derivative **7** could be converted to the ditriflate **20**, which was expected to be transformable into **19** by way of a cascade Suzuki cross-coupling and an asymmetric Heck reaction in a single step. Since the reaction rate of an asymmetric Heck reaction is generally lower than that of a Suzuki cross-coupling, a similar substrate **11** for an asymmetric Heck reaction would be generated in the reaction medium, leading to **19** with high enantiomeric excess. In order to examine the feasibility of the above-mentioned cascade reaction, first of all **7** was converted to **20** in 99% yield. Then, the cascade reaction was investigated in detail under a variety of reaction conditions, and it turned out that, against our expectations, the cascade reaction didn't proceed effectively, instead giving rise to **21** and **22** as major products. The desired product **19**, however, was securely obtained in 20% yield under the conditions described in Scheme 4 and, as expected, the enantiomeric excess of resulting **19** was found to be 85%. Improvement of the cascade reaction to a synthetically useful extent is still under investigation.

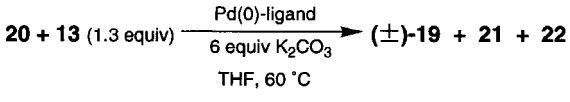


Reaction conditions: (a) Tf_2O (3 equiv), pyridine, CH_2Cl_2, –78 °C to r.t. (99%); (b) **13** (1.1 equiv), $Pd(OAc)_2$ (20 mol %), (*S*)-BINAP (40 mol %), K_2CO_3 (6 equiv), THF, 60 °C.

Scheme 4

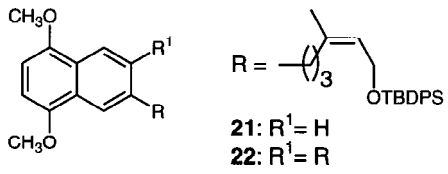
We felt that the cascade Suzuki cross-coupling and Heck reaction process had an intrinsic interest even if lacking the asymmetric aspect, and so we decided to experiment with a range of achiral ligands for the conversion of **20** to **19**. We were pleased to find that the use of Ph_3As as an achiral ligand gave racemic **19** in a much better yield (46%), and the results are summarized in Table 1.[11–13]

Table 1. Cascade Suzuki Cross-Coupling and Heck Reaction Using Achiral Ligands

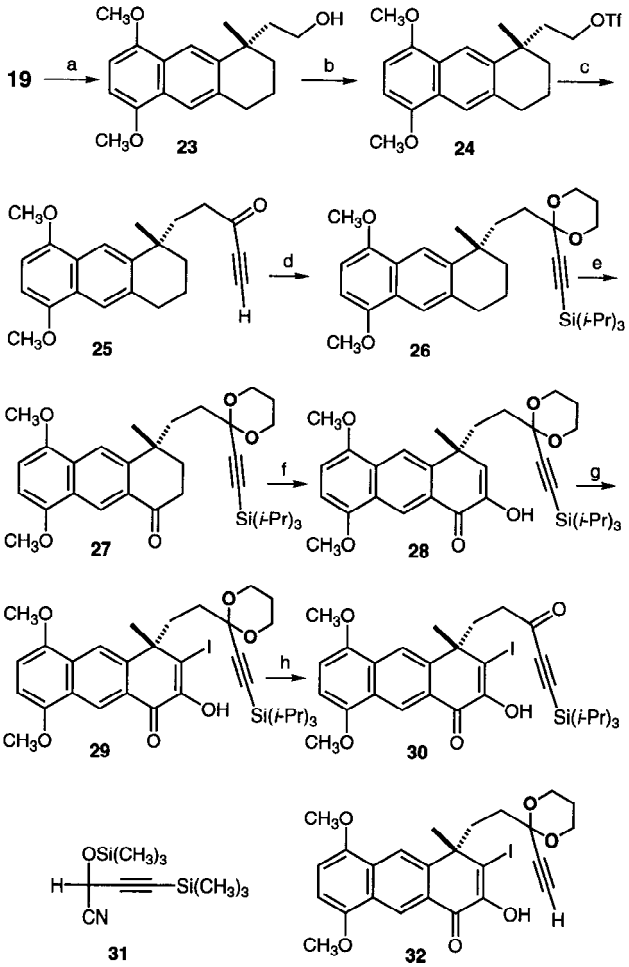


entry	ligand	yield **19** (%)	**21** (%)	**22** (%)
1[a]	Ph_3P	-	-	-
2[a]	$(o\text{-tol})_3P$	trace	22	31
3[a]	$(2\text{-furyl})_3P$	27	13	-
4[a]	Ph_3As	41	25	-
5[b]	DPPF	trace	30	20
6[b]	$(Ph_2AsCH_2)_2$	trace	28	17
7[c]	Ph_3As	46	16	-

a : 20 mol % $Pd(OAc)_2$, 80 mol % ligand were used
b : 20 mol % $Pd(OAc)_2$, 40 mol % ligand were used
c : 10 mol % $Pd_2(dba)_3$, 80 mol % ligand were used



With large quantities of optically active **19** in 87% ee and (±)-**19** in hand, we then pursued a catalytic asymmetric synthesis of **1** and **2**. In accordance with the retrosynthetic analysis shown in Scheme 1, optically active **19** was first converted to the aldehyde, followed by reduction with $NaBH_4$ to give the alcohol **23** (93%). The alcohol **23** underwent trifluoromethanesulfonylation to afford the triflate **24**, which was then treated with the acyl anion equivalent derived from **31**. The resulting product was further converted to the ketone **25** in 82 % overall yield from **23**. After protection of the carbonyl functionality as an acetal (98%), and of the ethynyl functionality with a triisopropylsilyl group (98%), **26** underwent benzylic oxidation to give **27** in 96% yield. Exposure of **27** to O_2 (1 atm) in the presence of KO-*t*-Bu in *tert*-butyl alcohol gave the enol **28** in 79% yield. Treatment of **28** with NaI and $CuSO_4 \cdot 5H_2O$ in aqueous methanol afforded the requisite alkenyl iodide **29** quite efficiently (97%),[14] and exposure of **29** to *p*-toluenesulfonic acid in aqueous acetone furnished **30** in 98% yield. Moreover, **32** was also synthesized from **24** in a five-step sequence of reactions (59% overall yield, i. LDA/**31**, –78 °C, then H^+, then ^-OH; ii. $HO(CH_2)_3OH$, $TsOH \cdot H_2O$; iii. DDQ; iv. O_2, KO-*t*-Bu; v. NaI, $CuSO_4 \cdot 5H_2O$).

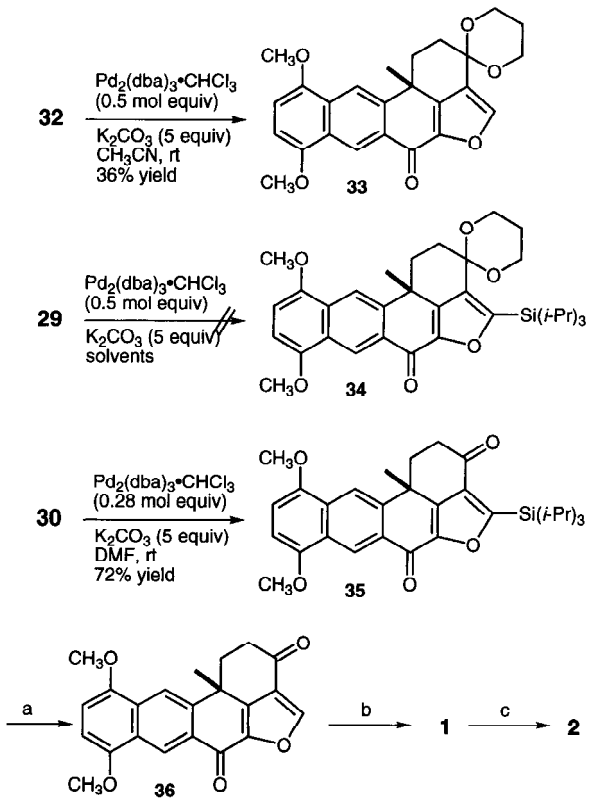


Reaction conditions: (a) (1) Bu_4NF (2 equiv), HOAc (3 equiv), THF, 0 °C to r.t., (2) $NaBH_4$ (5 equiv), MeOH, 0 °C to r.t. (two steps, 93%); (b) Tf_2O (1.2 equiv), pyridine, CH_2Cl_2, –78 °C to r.t.; (c) LDA/**31** (1.5 equiv), THF, –78 °C, then H^+, then –OH, then Bu_4NF, HOAc (82% from **23**); (d) (1) $HO(CH_2)_3OH$ (10 equiv), $TsOH \cdot H_2O$, benzene, reflux (98%), (2) BuLi (2 equiv), THF, –78 to –50 °C, then TIPSCl (2 equiv), –78 °C to r.t. (98%); (e) DDQ (3 equiv), CH_2Cl_2, H_2O, r.t. (96%); (f) O_2 (1 atm), KO-*t*-Bu (5 equiv), *t*-BuOH, 35 °C (79%); (g) NaI (10 equiv), $CuSO_4 \cdot 5H_2O$ (10 equiv), MeOH, H_2O, r.t. (97%); (h) $TsOH \cdot H_2O$, acetone, H_2O, 60 °C (98%).

Scheme 5

Having synthesized **29**, **30**, and **32** as substrates for the crucial construction of the unique pentacyclic skeleton, we examined the cascade reaction in detail. First of all, compound **32** was treated with $Pd_2(dba)_3 \cdot CHCl_3$ (0.5 molar equiv) and K_2CO_3 (5 equiv) in MeCN at room temperature for 24 h, and we were pleased to find that the expected product **33** was obtained albeit in a modest 36%

yield. In order to improve the yield, solvent and base effects as well as effects of additives such as Ag_2CO_3 and Bu_4NCl were investigated. Unfortunately, however, the chemical yield of **33** was not improved. Furthermore, in an attempt to improve the construction of the unique pentacyclic skeleton, the reaction of **29** was next examined under several reaction conditions, but no **34** was obtained, with **28** being obtained as the major product. Finally we were very pleased to find that treatment of **30** with $Pd_2(dba)_3$•$CHCl_3$ (0.28 molar equiv) and K_2CO_3 (5 equiv) in DMF at room temperature for 8 h gave the desired pentacycle **35** in a single step (72%). At the same time Larock and co-workers also reported a method for the synthesis of a variety of furan skeletons using a similar strategy.[15] The pentacyclic intermediate **35** was subjected to desilylation, which gave **36** in 83% yield: $[\alpha]_D^{23}$ +123.7 (c = 0.335, CH_2Cl_2, 87% ee). The compound **36** was then converted to halenaquinone (**1**) in 99% yield, and **1** was further converted to halenaquinol (**2**) using Harada's procedure (almost quantitative yield).[3]



Reaction conditions: (a) Bu_4NF (16 equiv), HOAc (24 equiv), CH_3CN, THF, 60 °C (83%); (b) CAN (6.7 equiv), CH_3CN, H_2O, r.t. (99%); (c) $Na_2S_2O_4$, acetone, H_2O, 0 °C (quant.).

Scheme 6

In conclusion, we have achieved an efficient catalytic asymmetric synthesis of halenaquinone (**1**) and halenaquinol (**2**), in which an asymmetric Heck reaction, and a cascade Suzuki cross-coupling and an asymmetric Heck reaction as well as a single step construction of a unique pentacyclic skeleton using palladium chemistry are involved. Moreover, a synthetically useful cascade Suzuki cross-coupling and a Heck reaction which use Ph_3As as an achiral ligand have been developed, demonstrating the versatility of modern palladium chemistry. The new chemistry described herein should be quite useful for the synthesis of a variety of biologically significant compounds. Further studies along these lines are currently under investigation.

Melting points were determined on a Yanagimoto Micro Melting Point Apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO A-300 diffraction grating infrared spectrometer. NMR spectra were measured on a JEOL JMN-EX 270 spectrometer, operating at 270 MHz for ^1H and 68 MHz for ^{13}C NMR. Chemical shifts are expressed in ppm (δ) with TMS as an internal standard. Mass spectra (MS) were measured on a JEOL JMS-DX303 or JEOL JMN-SX-102A instrument. Optical rotation was measured on a JASCO DIP-140 polarimeter. Column chromatography was carried out with silica gel, Merck Type 60 (230–400 mesh ASTM). In general, reactions were carried out in anhyd solvents, unless otherwise mentioned. THF and Et_2O were distilled from sodium benzophenone ketyl. CH_2Cl_2 was distilled from CaH_2.

6,7-Dibenzyloxy-3,4-dihydronaphthalen-1(2*H*)-one (4):
To a solution of 6,7-dimethoxy-3,4-dihydronaphthalen-1(2*H*)-one (25.0 g, 121 mmol) in CH_2Cl_2 (500 mL), was added a solution of BBr_3 (24.5 mL, 255 mmol) in CH_2Cl_2 (230 mL) at –78 °C. After stirring for 1 h at r.t., the mixture was poured into an ice-water mixture, extracted with EtOAc (3000 mL) and the extract was washed with brine (1000 mL), dried (Na_2SO_4), and concentrated. To a solution of the deep red colored residue (21.5 g) in DMF (368 mL) was added K_2CO_3 (66.9 g, 484 mmol), BnBr (28.8 mL, 24.2 mmol), and Bu_4NI (8.94 g, 24.2 mmol). After stirring for 9 h at 60 °C, the mixture was poured into H_2O, extracted with EtOAc (2000 mL) and the extract was washed with brine (1000 mL), dried (Na_2SO_4), and concentrated. The residue was purified by recrystallization from MeOH, and the residue from the mother liquor was purified by silica gel column chromatography (hexane–EtOAc, 4:1) to give 33.6 g and 6.30 g of **4** respectively (2 steps, 92%) as a white powder; mp 96 °C.

IR (Nujol): ν =1652, 1594, 1152, 1022 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 2.01–2.12 (m, 2H), 2.55 (t, J = 6.8 Hz, 2H), 2.82 (t, J = 6.2 Hz, 2H), 5.16 (s, 2H), 5.20 (s, 2H), 6.72 (s, 1H), 7.24–7.49 (m, 10H), 7.62 (s, 1H).
MS m/z = 358 (M^+).
Anal. Calcd for $C_{24}H_{22}O_3$: C, 80.42; H, 6.19; Found: C, 80.28; H, 6.25.

6,7-Dibenzyloxy-1,4-dimethoxynaphthalene (6):
To a mixture of **4** (1.05 g, 2.93 mmol), HOAc (8.0 mL), and H_2O (2.0 mL) was added CrO_3 (1.46 g, 14.6 mmol) under ice bath cooling. After stirring for 36 h at r.t., the mixture was poured into an ice-water mixture, extracted with CH_2Cl_2 (100 mL) and the extract was washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL) successively, dried (Na_2SO_4), and concentrated to give 1.08 g of crude **5**. A solution of crude **5** (1.08 g) in anhyd THF (42 mL) was added to potassium bis(trimethylsilyl)amide (0.5 M in toluene, 17.6 mL, 8.79 mmol) at –78 °C. After stirring for 30 min, MeI (1.1 mL, 17.7 mmol) was added to the mixture. After stirring for an additional 1.5 h at r.t., the mixture was poured into sat. NH_4Cl, extracted with EtOAc (100 mL) and the extract was washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2–EtOAc, 1:1) to give **6** (0.75 g, 2 steps, 63%) as a white powder; mp 124 °C. In larger scale experiments, the residue was also purified by recrystallization from cyclohexane.

IR (Nujol): ν = 1598, 1377, 1269 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 3.93 (s, 6H), 5.27 (s, 4H), 6.60 (s, 2H), 7.26–7.57 (m, 10H), 7.63 (s, 2H).
^{13}C NMR ($CDCl_3$): δ = 55.7, 70.6, 102.1, 103.8, 121.9, 127.3, 127.7, 128.4, 137.2, 148.7, 149.1.
MS m/z = 400 (M^+).

Anal. Calcd for $C_{26}H_{24}O_4$: C, 77.98; H, 6.04; Found: C, 77.79: H, 5.97.

6-*tert*-Butyldimethylsilyloxy-1,4-dimethoxy-7-trifluoromethanesulfonyloxynaphthalene (8):
A mixture of **6** (1.63 g, 4.07 mmol), EtOAc (70 mL), and 10% Pd–C (0.71 g) was stirred under H_2 atmosphere (1 atm) at r.t. for 5 h. The insoluble material was filtered off, and the filtrate was concentrated in vacuo, and the residue was triturated with hexane to give 6,7-dihydroxy-1,4-dimethoxynaphthalene (**7**) (0.95 g, 100%). To a mixture of **7** (896 mg, 4.07 mmol), Et_3N (1.13 mL, 8.14 mmol), and CH_2Cl_2 (20 mL) was added a solution of TBSCl (673 mg, 8.95 mmol) in CH_2Cl_2 (8.1 mL) under ice bath cooling. After stirring for 3 h, the mixture was poured into sat. NH_4Cl, extracted with CH_2Cl_2 (50 mL) and the extract was washed with brine (50 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane–CH_2Cl_2, 1:1) to give 6-*tert*-butyldimethylsilyloxy-7-hydroxy-1,4-dimethoxynaphthalene (1.26 g, 93%). To a mixture of 6-*tert*-butyldimethylsilyloxy-7-hydroxy-1,4-dimethoxynaphthalene (11.7 g, 35.0 mmol), Et_3N (12.7 mL, 90.9 mmol), and CH_2Cl_2 (100 mL) was added Tf_2O (7.65 mL, 45.5 mmol) at –78 °C. After stirring for 30 min at r.t., the mixture was poured into sat. $NaHCO_3$, extracted with CH_2Cl_2 (500 mL) and the extract was washed with 1*M* HCl (200 mL) and brine (300 mL) successively, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane–CH_2Cl_2, 7:3) to give **8** (14.9 g, 91%) as a white solid; mp 79–80 °C.
IR (neat): ν = 2933, 1605 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 0.34 (s, 6H), 1.05 (s, 9H), 3.93 (s, 6H), 6.61 (d, *J* = 8.3 Hz, 1H), 6.71 (d, *J* = 8.3 Hz, 1H), 7.68 (s, 1H), 8.03 (s, 1H).
MS *m/z* = 466 (M^+).

6-Allyl-7-*tert*-butyldimethylsilyloxy-1,4-dimethoxynaphthalene (9):
To a solution of **8** (10.55 g, 22.6 mmol) in anhyd Et_2O (200 mL) were added $PdCl_2$(dppf)•CH_2Cl_2 (1.65 g, 2.02 mmol), and allylmagnesium bromide (1.27 *M* in Et_2O, 89 mL, 113 mmol) under Ar at –78 °C. After stirring for 42 h at r.t., the mixture was poured into sat. NH_4Cl, extracted with EtOAc (500 mL) and the extract was washed with brine (200 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane–CH_2Cl_2, 4:1) to give **9** (8.10 g, 100%) as a colorless syrup.

IR (neat): ν = 1601, 1406, 1332, 1260 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 0.31 (s, 6H), 1.04 (s, 9H), 3.53 (d, *J* = 6.2 Hz, 2H), 3.93 (s, 6H), 5.02–5.13 (m, 2H), 6.00–6.16 (m, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 7.49 (s, 1H), 7.98 (s, 1H).
MS *m/z* = 358 (M^+, 100), 301 (M^+-*t*-Bu, 86), 286 (M^+-*t*-BuMe, 23).
Anal. Calcd for $C_{21}H_{30}O_3Si$: C, 70.35; H, 8.43; Found: C, 70.44; H, 8.60.

6-*tert*-Butyldimethylsilyloxy-7-[(*Z*)-6-*tert*-butyldiphenylsilyloxy-4-methylhex-4-enyl]-1,4-dimethoxynaphthalene (10):
To a solution of **9** (4.30 g, 12.0 mmol) in anhyd THF (28 mL), was added 9-BBN (0.5 *M* in THF, 50.4 mL, 25.2 mmol) under Ar at 0 °C. After stirring for 6 h at r.t., to the mixture were added $K_3PO_4 \cdot nH_2O$ (13.8 g), a solution of **12** (7.85 g, 18.0 mmol) in THF (5 mL), and $PdCl_2$(dppf)•CH_2Cl_2 (490 mg, 0.60 mmol). After stirring for 4 h at 50 °C, the mixture was poured into sat. NaCl, extracted with EtOAc (200 mL) and the extract was washed with brine (300 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane–CH_2Cl_2, 4:1, then hexane–EtOAc, 19:1) to give **10** (7.22 g, 90%).

To a solution of **8** (50.0 mg, 0.107 mmol) in THF (0.1 mL) were added K_2CO_3 (73.9 mg, 0.535 mmol), a THF solution of **13** (0.139 mmol), and $PdCl_2$(dppf)•CH_2Cl_2 (16.8 mg, 0.0205 mmol). After stirring for 13 h at 50 °C, the mixture was poured into brine (20 mL), extracted with EtOAc (50 mL) and the exract was washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane–CH_2Cl_2, 4:1) to give **10** (49.5 mg, 69%) as a colorless syrup.

IR (neat): ν = 1602, 1460, 1332, 1259 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 0.25 (s, 6H), 0.98 (s, 9H), 1.03 (s, 9H), 1.57–1.68 (m, 2H), 1.69 (s, 3H), 1.95 (t, *J* = 7.1 Hz, 2H), 2.60 (t, *J* = 7.8 Hz, 2H), 3.92 (s, 6H), 4.21 (d, *J* = 6.3 Hz, 2H), 5.39 (t, *J* = 6.3 Hz, 1H), 6.52 (d, *J* = 7.7 Hz, 1H), 6.60 (d, *J* = 7.7 Hz, 1H), 7.30–7.44 (m, 6H), 7.45 (s, 1H), 7.62–7.74 (m, 4H), 7.87 (s, 1H).
MS *m/z* = 668 (M^+, 16), 611 (M^+-*t*-Bu, 5), 596 (M^+-*t*-BuMe, 30), 199 (100).
Anal. Calcd for $C_{41}H_{56}O_4Si$: C, 73.60; H, 8.44; Found: C, 73.44; H, 8.59.

(*Z*)-6-(9-Borabicyclo[3.3.1]nonan-9-yl)-1-*tert*-butyldiphenylsilyloxy-3-methylhex-2-ene (13):
To a solution of **12**[16] (2.00 g, 4.58 mmol) in anhyd Et_2O (40 mL) were added $PdCl_2$(dppf•CH_2Cl_2 (374 mg, 0.458 mmol), and allylmagnesium bromide (1.27 *M* in Et_2O, 18 mL, 22.9 mmol) under Ar at –78 °C. After stirring for 10 h at r.t., the mixture was poured into sat. NH_4Cl (100 mL), extracted with CH_2Cl_2 (300 mL) and the extract was washed with brine (100 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane–CH_2Cl_2, 5:1) to give (*Z*)-6-*tert*-butyldiphenylsilyloxy-4-methylhexa-1,4-diene (1.22 g, 76%).

(Z)-6-tert-Butyldiphenylsilyloxy-4-methylhexa-1,4-diene: colorless syrup; bp 180 °C (bath temp)/0.005 mmHg.
IR (neat): ν = 1598, 1377, 1269 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 1.13 (s, 9H), 1.75 (t, *J* = 1.0 Hz, 3H), 2.68 (d, *J* = 6.6 Hz, 2H), 4.29 (d, *J* = 6.3 Hz, 2H), 4.94–5.06 (m, 2H), 5.55 (t, *J* = 6.3 Hz, 1H), 5.58–5.79 (m, 1H), 7.38–7.53 (m, 6H), 7.73–7.81 (m, 1H).
^{13}C NMR ($CDCl_3$): δ = 19.2, 23.3, 26.9, 36.6, 60.7, 115.4, 125.6, 127.6, 129.5, 134.0, 135.3, 135.6.
MS *m/z* = 350 (M^+).
Anal. Calcd for $C_{23}H_{30}OSi$: C, 78.80; H, 8.63; Found: C, 78.52; H, 8.39.

To a solution of freshly distilled (*Z*)-6-*tert*-butyldiphenylsilyloxy-4-methylhexa-1,4-diene (1.0 mmol) in anhyd THF (2.0 mL) was added a freshly prepared 9-BBN solution in THF (from 9-BBN dimer and anhyd THF, then titrated) (ca. 0.5 *M*, 1.0 mmol) under Ar at 0 °C. After stirring for 6 h at r.t., the mixture was used for the next reaction.

6-[(*Z*)-6-*tert*-Butyldiphenylsilyloxy-4-methylhex-4-enyl]-1,4-dimethoxy-7-trifluoromethanesulfonyloxynaphthalene (11):
To a solution of **10** (6.53 g, 9.76 mmol) in THF (60 mL) was added Bu_4NF (1.0 *M* in THF, 9.76 mL, 9.76 mmol) under ice bath cooling. After stirring for 10 min, the mixture was poured into sat. NH_4Cl (100 mL), extracted with Et_2O (300 mL) and the extract was washed with brine (100 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2) to give the 7-naphthol derivative (4.48 g) as a pale-yellow syrup. To a mixture of the naphthol (4.48 g, 8.07 mmol), Et_3N (3.54 mL, 25.4 mmol), and CH_2Cl_2 (65 mL) was added Tf_2O (2.13 mL, 12.7 mmol) at –78 °C. After stirring for 30 min at r.t., the mixture was poured into sat. $NaHCO_3$ (100 mL), extracted with CH_2Cl_2 (300 mL) and the extract was washed with brine (100 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane–CH_2Cl_2, 3:1) to give **11** (4.70 g, 2 steps, 69%) as a white solid; mp 57–59 °C.
IR (neat): ν = 2934, 1419 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 1.04 (s, 9H), 1.64–1.73 (m, 2H), 1.72 (s, 3H), 1.96 (t, *J* = 8.4 Hz, 2H), 2.70 (t, *J* = 8.1 Hz, 2H), 3.93 (s, 3H), 3.94 (s, 3H), 4.19 (d, *J* = 6.6 Hz, 2H), 5.43 (t, *J* = 6.6 Hz, 1H), 6.71 (s, 2H), 7.31–7.43 (m, 6H), 7.63–7.71 (m, 4H), 8.035 (s, 1H), 8.041 (s, 1H).
MS *m/z* = 686 (M^+).
Anal. Calcd for $C_{36}H_{41}F_3O_6SSi$: C, 62.95; H, 6.07; Found: C, 62.65; H, 6.20.

(1*S*)-1-[(*E*)-2-*tert*-Butyldiphenylsilyloxyethenyl]-5,8-dimethoxy-1-methyl-1,2,3,4-tetrahydroanthracene (19):
After degassing (freeze-pump-thaw cycle (F.P.T. method)) a mixture of **11** (68.7 mg, 0.10 mmol), K_2CO_3 (41.5 mg, 0.30 mmol), (*S*)-

BINAP (12.5 mg, 0.020 mmol), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol), and anhyd THF (2.0 mL) was stirred for 22 h at 60 °C, diluted with EtOAc (30 mL), washed with water (10 mL) and brine (10 mL), and the organic layer was dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane–EtOAc, 9:1) to give **19** (41.8 mg, 78%) as a colorless syrup.
IR (neat): ν = 2929, 1653 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 1.05 (s, 9H), 1.37 (s, 3H), 1.59–1.83 (m, 4H), 2.85–2.96 (m, 2H), 3.91 (s, 3H), 3.93 (s, 3H), 5.31 (d, *J* = 13.1 Hz, 1H), 6.01 (d, *J* = 13.1 Hz, 1H), 6.54 (d, *J* = 9.2 Hz, 1H), 6.59 (d, *J* = 9.2 Hz, 1H), 7.26–7.43 (m, 6H), 7.57–7.72 (m, 4H), 7.81 (s, 1H), 8.07 (s, 1H).
MS *m/z* = 536 (M^+).
$[\alpha]_D^{24}$ –31.5 (*c* = 0.60, $CHCl_3$) (87% ee).

Enantiomeric Excess Determination of Compound 19:
To a solution of **19** (1.00 g, 1.86 mmol) in THF (18.6 mL) were added HOAc (0.32 mL, 5.59 mmol), and Bu_4NF (1.0 *M* in THF, 3.73 mL, 3.73 mmol) under ice bath cooling. After stirring for 3 h at r.t., the mixture was poured into sat. NH_4Cl (20 mL), extracted with EtOAc (50 mL) and the extract was washed with brine (20 mL), dried (Na_2SO_4), and concentrated. To a solution of the residue in MeOH (8.4 mL) was added $NaBH_4$ (352 mg, 9.31 mmol) under ice bath cooling. After stirring for 1 h at r.t., the solvent was removed in vacuo. To the residue was carefully added 1*M* HCl (10 mL), the resulting mixture was extracted with CH_2Cl_2 (20 mL) and the extract was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2–EtOAc, 9:1) to give **23** (523 mg, 2 steps, 93%).

(1S)-1-(2-Hydroxyethyl)-5,8-dimethoxy-1-methyl-1,2,3,4-tetrahydroanthracene (**23**)*:*
White solid; mp 74–75 °C.
IR (neat): ν = 3380, 2930, 1597 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 1.42 (s, 3H), 1.62–2.03 (m, 5H), 2.14–2.30 (m, 1H), 2.92–3.03 (m, 2H), 3.54–3.76 (m, 2H), 3.93 (s, 3H), 3.94 (s, 3H), 6.56 (d, *J* = 7.8 Hz, 1H), 6.60 (d, *J* = 7.8 Hz, 1H), 7.88 (s, 1H), 8.13 (s, 1H).
^{13}C NMR ($CDCl_3$): δ = 19.9, 31.1, 31.5, 36.2, 36.4, 46.2, 55.4, 55.6, 59.9, 101.7, 102.2, 119.2, 121.0, 124.6, 125.1, 135.5, 143.1, 148.9, 149.1.
MS *m/z* = 300 (M^+).
HRMS Calcd for $C_{19}H_{24}O_3$: 300.1725, Found: 300.1737.
$[\alpha]_D^{24}$ –31.3 (*c* = 0.70, $CHCl_3$) (87% ee).

To a mixture of **23** (11.1 mg, 0.037 mmol), Et_3N (0.013 mL, 0.0813 mmol), DMAP (1.3 mg, 0.0111 mmol), and CH_2Cl_2 (0.8 mL) was added 4-nitrobenzoyl chloride (7.5 mg, 0.0406 mmol) under ice bath cooling. After stirring for 30 min, the mixture was poured into sat. NH_4Cl (5 mL), extracted with CH_2Cl_2 (10 mL) and the extract was washed with brine (5 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane–CH_2Cl_2, 1:2) to give (*1S*)-5,8-dimethoxy-1-methyl-1-[2-(4-nitrobenzoyloxy)ethyl]-1,2,3,4-tetrahydroanthracene (16.0 mg, 96%).

(1S)-5,8-Dimethoxy-1-methyl-1-[2-(4-nitrobenzoyloxy)ethyl]-1,2,3,4-tetrahydroanthracene: yellow syrup.
IR (neat): ν = 1724, 1600, 1528, 1274 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 1.46 (s, 3H), 1.66–2.16 (m, 5H), 2.49–2.63 (m, 1H), 2.97 (t, *J* = 5.9 Hz, 2H), 3.91 (s, 6H), 4.44 (t, *J* = 5.9 Hz, 2H), 6.50 (d, *J* = 7.4 Hz, 1H), 6.54 (d, *J* = 7.4 Hz, 1H), 7.78 (d, *J* = 8.9 Hz, 2H), 7.80 (s, 1H), 8.02 (d, *J* = 8.9 Hz, 2H), 8.10 (s, 1H).
MS *m/z* = 449 (M^+, 90), 255 (100).
HRMS Calcd for $C_{26}H_{27}NO_6$: 449.1832, Found: 449.1831.
$[\alpha]_D^{24}$ –48.4 (*c* = 0.52, $CHCl_3$) (87% ee).
HPLC conditions for ee determination of (1*S*)-5,8-dimethoxy-1-methyl-1-[2-(4-nitrobenzoyloxy)ethyl]-1,2,3,4-tetrahyroanthracene: column: DAICEL CHIRALCEL OD; solvent : hexane – propan-2-ol, 9 : 1; flow rate: 0.5 mL/min; detector: UV detector (254 nm); retention time: 23.1 min (for (*S*)), 31.7 min (for (*R*)); retention volume: V_0 = 5.0 mL, 23 °C.

1,4-Dimethoxy-6,7-bis(trifluoromethanesulfonyloxy)naphthalene (20):
To a mixture of **7** (300 mg, 1.36 mmol), pyridine (0.661 mL, 8.17 mmol), and CH_2Cl_2 (4 mL) was added Tf_2O (0.688 mL, 4.09 mmol) at –78 °C. After stirring for 3 h at r.t., the mixture was poured into sat. $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (30 mL) and the extract was washed with 1*M* HCl (10 mL) and brine (10 mL) successively, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (hexane–CH_2Cl_2, 4:1) to give **20** (655 mg, 99%) as a white solid; mp 83–85 °C.
IR (KBr): ν = 2951, 2847, 2361, 1603 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 3.97 (s, 6H), 6.84 (s, 2H), 8.27 (s, 2H).
MS *m/z* = 484 (M^+), 351 (M^+-SO_2CF_3), 190 (bp).
Anal. Calcd for $C_{14}H_{10}O_8F_6S_2$: C, 34.72; H, 2.08; Found: C, 34.84; H, 1.95.

Cascade Suzuki Cross-Coupling–Asymmetric Heck Reaction:
To a mixture of **20** (24.2 mg, 0.050 mmol), K_2CO_3 (41.5 mg, 0.30 mmol), (*S*)-BINAP (12.5 mg, 0.020 mmol), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol), and anhyd THF (0.50 mL) was added a solution of **13** (0.054 mmol) in THF. After degassing (F.P.T. method), the mixture was stirred for 42 h at 60 °C, diluted with EtOAc (10 mL), and the organic extract was washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane–EtOAc, 9:1, then hexane–CH_2Cl_2, 3:1) to give **19** (5.30 mg, 20%, 85% ee). (Ee of **19** was determined by HPLC analysis as described above.)

Cascade Suzuki Cross-Coupling–Heck Reaction; General Procedure:
To a mixture of **20** (41.4 mg, 0.10 mmol), K_2CO_3 (83.0 mg, 0.60 mmol), ligand (see Table 1), Pd-source (see Table 1), and anhyd THF (1.0 mL), was added a solution of **13** (0.13 mmol) in THF. After degassing (F.P.T. method), the mixture was stirred for 24 h at 60 °C, diluted with EtOAc (20 mL), and the organic extract was washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2 and then hexane–EtOAc, 9:1 to 4:1) to give (±)-**19**, **21**, and **22**.

4-Trimethylsilyl-2-trimethylsilyloxybut-3-ynenitrile (31):
To a mixture of 3-trimethylsilylpropynal[17] (1.00 g, 7.92 mmol), and trimethylsilyl cyanide (1.16 mL, 8.71 mmol) was added ZnI_2 (25.3 mg, 0.079 mmol) under Ar at r.t. After stirring for 30 min at r.t., the mixture was purified by distillation to give **31** (1.68 g, 91%) as a light-yellow oil; bp 90 °C (bath temp)/1 mmHg.
IR (neat): ν = 3422, 2963, 1688, 1414, 1254 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 0.20 (s, 9H), 0.26 (m, 9H), 5.23 (s, 1H).
^{13}C NMR ($CDCl_3$): δ = -0.72, 0.11, 51.8, 95.9, 96.7, 116.2.
MS *m/z* = 225 (M^+).
HRMS Calcd for $C_{10}H_{19}NOSi$: 225.1005, Found: 225.1001.

(1*S*)-5,8-Dimethoxy-1-methyl-1-(3-oxopent-4-ynyl)-1,2,3,4-tetrahydroanthracene (25):
To a solution of **23** (825.0 mg, 2.75 mmol) in CH_2Cl_2 (9.0 mL) were added pyridine (0.289 mL, 3.57 mmol) and then Tf_2O (0.554 mL, 3.30 mmol) at –78 °C. After stirring for 20 min at r.t., the mixture was washed with H_2O (10 mL), and the organic layer was dried ($MgSO_4$), and concentrated in vacuo (below at 25 °C) to give crude triflate **24**.
To a solution of LDA (8.24 mmol) in anhyd THF (8.0 mL) was added a solution of **31** (930 mg, 4.12 mmol) in anhyd THF (8.0 mL) at –78 °C. After stirring for 30 min at –78 °C, a solution of crude **24** in anhyd THF (8.0 mL) was added to the mixture at –78 °C. After stirring for 30 min at –50 °C, the mixture was quenched with sat. NH_4Cl (50 mL), extracted with EtOAc (50 mL) and the extract was washed with brine, dried (Na_2SO_4), and concentrated. To the residue was added THF (10 mL), and 1*M* HCl (2 mL), and the mixture was stirred for 30 min at r.t., diluted with EtOAc (50 mL). The organic layer was separated, shaken with 2% aq. NaOH for 10 min, and washed with 2% NaOH (20 mL), and brine (30 mL) successively, dried ($MgSO_4$), and concentrated. To a solution of the residue in THF (20 mL) were added HOAc (1.5 mL, 5.59 mmol), and Bu_4NCl (1.0 *M* in THF, 3.5 mL,

3.5 mmol) under ice bath cooling. After stirring for 10 min at r.t., the mixture was poured into sat. NH_4Cl (20 mL), extracted with EtOAc (70 mL) and the extract was washed with aq sat. $NaHCO_3$ (30 mL) and brine (30 mL) successively, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (hexane–EtOAc, 9:1) to give **25** (750 mg, 82%) as a colorless syrup.
IR (neat): ν = 3264, 2936, 2093, 1683, 1593 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 1.40 (s, 3H), 1.60–1.73 (m, 1H), 1.74–1.94 (m, 3H), 1.95–2.08 (m, 1H), 2.24–2.42 (m, 1H), 2.42–2.64 (m, 2H), 2.87–3.05 (m, 2H), 3.15 (s, 1H), 3.94 (s, 6H), 6.57 (d, *J* = 8.3 Hz, 1H), 6.61 (d, *J* = 8.3 Hz, 1H), 7.89 (s, 1H), 8.07 (s, 1H).
^{13}C NMR ($CDCl_3$): δ = 19.7, 31.1, 31.4, 35.7, 36.7, 37.1, 41.6, 55.5, 55.7, 78.3, 81.5, 101.9, 102.4, 119.3, 121.2, 124.7, 125.2, 135.7, 142.3, 148.9, 149.2, 187.5.
MS *m/z* = 336 (M^+), 255 (M^+-CH_2CH_2COCCH, 100).
HRMS Calcd for $C_{22}H_{24}O_3$: 336.1725, Found: 336.1747.
$[\alpha]_D^{27}$ –68.8 (*c* = 0.20, $CHCl_3$) (87% ee).

(1*S*)-1-[3-(1,3-Dioxan-2-yl)pent-4-ynyl]-5,8-dimethoxy-1-methyl-1,2,3,4-tetrahydroanthracene:
A mixture of **25** (18.0 mg, 0.0535 mmol), propane-1,3-diol (0.039 mL, 0.535 mmol), $TsOH•H_2O$ (1.0 mg, 0.0054 mmol), and benzene (10 mL) was refluxed for 6 h with azeotropic removal of water using a Dean–Stark trap. The mixture was poured into sat. $NaHCO_3$ (10 mL), extracted with EtOAc (20 mL) and the extract was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane–EtOAc, 9:1) to give the title compound (20.6 mg, 98%) as a white powder; mp 132–134 °C.
IR (neat): ν = 3245, 2961, 2870, 2099, 1597 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 1.25–1.38 (m, 1H), 1.40 (s, 3H), 1.57–2.22 (m, 9H), 2.63 (s, 1H), 2.97 (t, *J* = 6.6 Hz, 2H), 3.80–4.00 (m, 2H), 3.93 (s, 6H), 4.22 (ddd, *J* = 2.6, 12.5, 12.5 Hz, 2H), 6.55 (d, *J* = 8.3 Hz, 1H), 6.59 (d, *J* = 8.3 Hz, 1H), 7.86 (s, 1H), 8.14 (s, 1H).
^{13}C NMR ($CDCl_3$): δ = 19.6, 25.2, 30.8, 31.2, 35.5, 36.4, 36.9, 37.1, 55.6, 55.7, 62.26, 62.30, 75.2, 79.5, 96.5, 101.7, 102.1, 119.5, 120.8, 124.6, 125.3, 135.8, 143.7, 148.9, 149.3.
MS *m/z* = 394 (M^+), 255 (M^+-$CH_2CH_2C(OCH_2CH_2CH_2O)CCH$, 100).
Anal. Calcd for $C_{25}H_{30}O_4$: C, 76.11; H, 7.67; Found: C, 76.10; H, 7.61.
$[\alpha]_D^{24}$ –52.1 (*c* = 1.04, $CHCl_3$) (87% ee).

(1*S*)-1-[3-(1,3-Dioxan-2-yl)-5-triisopropylsilylpent-4-ynyl]-5,8-dimethoxy-1-methyl-1,2,3,4-tetrahydroanthracene (26):
To a solution of (1*S*)-1-[3-(1,3-dioxan-2-yl)pent-4-ynyl]-5,8-dimethoxy-1-methyl-1,2,3,4-tetrahydroanthracene (95 mg, 0.241 mmol) in anhyd THF (1 mL) was added BuLi (1.5 *M* in hexane, 0.321 mL, 0.482 mmol) at –78 °C. After stirring for 30 min at –50 °C, TIPSCl (0.103 mL, 0.482 mmol) was added to the mixture at –78 °C. After stirring for 30 min at r.t., the mixture was quenched with sat. NH_4Cl (10 mL), extracted with EtOAc (100 mL) and the extract was washed with brine (30 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane–Et_2O, 9:1) to give **26** (130 mg, 98%) as a colorless syrup.
IR (neat): ν = 2940, 2865, 2833, 1598, 1433 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 1.10 (m, 21H), 1.15–1.39 (m, 1H), 1.39 (s, 3H), 1.61–1.75 (m, 1H), 1.75–2.08 (m, 8H), 2.96 (t, *J* = 6.3 Hz, 2H), 3.86 (dd, *J* = 4.0, 11.6 Hz, 2H), 3.92 (s, 3H), 3.93 (s, 3H), 4.21–4.34 (m, 2H), 6.53 (d, *J* = 8.3 Hz, 1H), 6.58 (d, *J* = 8.3 Hz, 1H), 7.84 (s, 1H), 8.11 (s, 1H).
^{13}C NMR ($CDCl_3$): δ = 11.1, 18.6, 19.6, 25.3, 30.0, 31.1, 35.6, 36.6, 37.0, 55.4, 55.6, 62.3, 88.5, 96.9, 101.4, 102.1, 102.6, 119.4, 120.7, 124.6, 125.2, 135.5, 144.2, 148.9, 149.4.
MS *m/z* = 550 (M^+).
Anal. Calcd for $C_{34}H_{50}O_4Si$: C, 74.13; H, 9.15; Found: C, 74.20; H, 9.36.
$[\alpha]_D^{28}$ –32.8 (*c* = 0.825, $CHCl_3$) (87% ee).

(1*S*)-1-[3-(1,3-Dioxan-2-yl)-5-triisopropylsilylpent-4-ynyl]-5,8-dimethoxy-1-methyl-4-oxo-1,2,3,4-tetrahydroanthracene (27):
To a solution of **26** (31.0 mg, 0.0563 mmol) in CH_2Cl_2 (3.6 mL) were added H_2O (0.3 mL), and DDQ (38.3 mg, 0.169 mmol). After stirring for 10 h at r.t., the mixture was diluted with CH_2Cl_2 (30 mL), and the organic layer was washed with sat. $NaHCO_3$ (10 mL) and brine (10 mL) successively, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane–EtOAc, 4:1) to give **27** (30.5 mg, 96%) as a greenish yellow syrup.
IR (neat): ν = 2941, 2360, 1685 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 1.00–1.14 (m, 1H), 1.05 (s, 21H), 1.23–1.38 (m, 1H), 1.50 (s, 3H), 1.66–2.18 (m, 6H), 2.71 (ddd, *J* = 5.3, 5.3, 18.1 Hz, 1H), 2.87 (ddd, *J* = 6.3, 10.9, 18.1 Hz, 1H), 3.78–3.92 (m, 2H), 3.94 (s, 6H), 4.25 (ddd, *J* = 2.3, 10.9, 10.9 Hz, 2H), 6.63 (d, *J* = 8.3 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 8.13 (s, 1H), 8.96 (s, 1H).
^{13}C NMR ($CDCl_3$): δ = 11.1, 18.6, 25.3, 26.9, 34.2, 34.9, 36.3, 37.1, 55.6, 62.3, 88.8, 96.6, 102.4, 102.9, 105.8, 118.9, 123.6, 124.5, 128.7, 129.3, 132.7, 146.8, 148.9, 150.9, 198.5.
MS *m/z* = 564 (M^+).
HRMS Calcd for $C_{34}H_{48}O_5Si$: 564.3271, Found: 564.3239.
$[\alpha]_D^{28}$ –11.0 (*c* = 0.74, $CHCl_3$) (87% ee).

(4*R*)-4-[3-(1,3-Dioxan-2-yl)-5-triisopropylsilylpent-4-ynyl]-2-hydroxy-5,8-dimethoxy-4-methyl-1-oxo-1,4-dihydroanthracene (28):
A mixture of **27** (58.0 mg, 0.103 mmol), *t*-BuOK (58.0 mg, 0.517 mg), and *t*-BuOH (5.8 mL) was stirred under an O_2 atmosphere (1 atm) for 7 h at 35 °C. The mixture was poured into sat. NH_4Cl (10 mL), extracted with CH_2Cl_2 (50 mL), and the extract was washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (hexane–EtOAc, 4:1) to give **28** (47.0 mg, 79%) as a yellow amorphous solid.
IR (neat): ν = 3395, 2941, 2360, 1652, 1626 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 1.05 (s, 21H), 1.15–1.40 (m, 1H), 1.50–1.59 (m, 1H), 1.62 (s, 3H), 1.82–2.07 (m, 1H), 2.14 (ddd, *J* = 2.3, 13.2, 13.2 Hz, 1H), 2.41 (ddd, *J* = 5.3, 13.2, 13.2 Hz, 1H), 3.70–3.88 (m, 2H), 3.95 (s, 3H), 3.98 (s, 3H), 4.12–4.33 (m, 2H), 6.14 (s, 1H), 6.51 (s, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 8.33 (s, 1H), 9.13 (s, 1H).
^{13}C NMR ($CDCl_3$): δ = 11.1, 18.6, 25.2, 30.9, 37.1, 38.3, 40.2, 55.6, 55.7, 62.2, 88.8, 96.2, 102.3, 103.1, 105.8, 119.6, 123.2, 124.9, 125.2, 127.4, 128.5, 144.2, 146.5, 148.8, 150.7, 181.7.
MS *m/z* = 578 (M^+).
HRMS Calcd for $C_{34}H_{46}O_6Si$: 578.3064, Found: 578.3085.
$[\alpha]_D^{28}$ –58.5 (*c* = 1.03, $CHCl_3$) (87% ee).

(1*S*)-1-[3-(1,3-Dioxan-2-yl)-5-triisopropylsilylpent-4-ynyl]-3-hydroxy-2-iodo-5,8-dimethoxy-1-methyl-4-oxo-1,4-dihydroanthracene (29):
To a solution of **28** (47.5 mg, 0.0821 mmol) in MeOH (6 mL) were added a solution of $CuSO_4•5H_2O$ (205 mg, 0.821 mmol) in H_2O (2 mL), and then NaI (12 mg, 0.821 mmol). After stirring for 21 h at r.t., the mixture was quenched with 5% $Na_2S_2O_3$(20 mL), extracted with CH_2Cl_2 (50 mL) and the extract was washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane–EtOAc, 4:1) to give **29** (56.1 mg, 97%) as a yellow amorphous solid.
IR (neat): ν = 3853, 2940, 2360, 1653, 1623 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 1.10 (s, 21H), 1.18–1.32 (m, 1H), 1.42 (ddd, *J* = 4.3, 12.9, 12.9 Hz, 1H), 1.75 (s, 3H), 1.80–2.02 (m, 1H), 2.30–2.60 (m, 2H), 3.65–3.87 (m, 2H), 3.96 (s, 3H), 3.98 (s, 3H), 4.10–4.30 (m, 2H), 6.69 (d, *J* = 8.2 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 7.36 (s, 1H), 8.47 (s, 1H), 9.16 (s, 1H).
^{13}C NMR ($CDCl_3$): δ = 11.1, 18.7, 25.1, 33.8, 36.4, 39.4, 46.0, 55.66, 55.69, 62.0, 88.9, 95.6, 101.9, 103.3, 106.2, 111.3, 121.5, 123.8, 125.0, 126.2, 128.5, 142.5, 148.7, 150.2, 150.5, 176.6.
MS *m/z* = 704 (M^+).
HRMS Calcd for $C_{34}H_{45}IO_6Si$: 704.2030, Found: 704.2058.
$[\alpha]_D^{24}$ –44.6 (*c* = 1.00, $CHCl_3$) (87% ee).

(1*S*)-3-Hydroxy-2-iodo-5,8-dimethoxy-1-methyl-4-oxo-1-(3-oxo-5-triisopropylsilylpent-4-ynyl)-1,4-dihydroanthracene (30):
A mixture of **29** (7.10 mg, 0.010 mmol), $TsOH•H_2O$ (0.5 mg, 0.0026 mmol), and acetone (1.0 mL) was stirred for 12 h at 60 °C. The mixture was poured into sat. $NaHCO_3$ (5 mL), extracted with EtOAc (20 mL) and the extract was washed with brine (10 mL), dried

($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane–EtOAc, 4:1) to give **30** (6.37 mg, 98%) as a yellow amorphous solid.
IR (neat): ν = 3356, 2943, 2866, 1655, 1624 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 1.03 (s, 21H), 1.57–1.72 (m, 1H), 1.75 (s, 3H), 2.12–2.38 (m, 1H), 2.48–2.69 (m, 2H), 3.98 (s, 3H), 4.00 (s, 3H), 6.73 (d, *J* = 8.3 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 7.43 (s, 1H), 8.46 (s, 1H), 9.21 (s, 1H).
^{13}C NMR ($CDCl_3$): δ = 10.9, 18.5, 33.9, 39.2, 40.6, 45.7, 55.68, 55.73, 96.0, 103.7, 103.8, 106.6, 109.9, 121.5, 124.2, 125.1, 126.0, 128.5, 141.5, 148.6, 150.4, 150.5, 176.4, 186.1.
MS *m/z* = 646 (M^+).
HRMS Calcd for $C_{31}H_{39}IO_5Si$: 646.1612, Found: 646.1602.
$[\alpha]_D^{24}$ –128.4 (*c* = 1.03, $CHCl_3$) (87% ee).

(12b*S*)-8,11-Dimethoxy-12b-methyl-3,3-trimethylenedioxy-2,3-dihydro-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-6(12b*H*)-one (33):
To a mixture of **32** (3.00 mg, 0.00547 mmol), K_2CO_3 (0.0274 mmol), and MeCN (0.5 mL) was added $Pd_2(dba)_3$•$CHCl_3$ (0.00274 mmol). After stirring for 24 h at r.t., the mixture was quenched with sat. NH_4Cl (5 mL), extracted with EtOAc (10 mL) and the extract was washed with brine (5 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane–EtOAc, 5:1) to give **33** (0.83 mg, 36%) as a yellow amorphous solid.
^1H NMR ($CDCl_3$): δ = 1.57 (s, 3H), 1.70–1.83 (m, 1H), 1.95–2.09 (m, 1H), 2.12–2.26 (m, 1H), 2.37–2.52 (m, 1H), 2.57–2.68 (m, 2H), 3.91–4.02 (m, 2H), 3.98 (s, 6H), 4.07–4.15 (m, 2H), 6.71 (d, *J* = 8.3 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 8.03 (s, 1H), 8.25 (s, 1H), 9.26 (s, 1H).
MS *m/z* = 420 (M^+).

(12b*S*)-8,11-Dimethoxy-12b-methyl-4-triisopropylsilyl-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-3,6(2*H*,12b*H*)-dione (35):
To a mixture of **30** (4.00 mg, 0.00619 mmol), K_2CO_3 (4.30 mg, 0.0309 mmol), and DMF (2.0 mL) was added $Pd_2(dba)_3$•$CHCl_3$ (1.80 mg, 0.00174 mmol). After stirring for 8 h at r.t., the mixture was quenched with sat. NH_4Cl (10 mL), extracted with EtOAc (20 mL) and the extract was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane–EtOAc, 5:1) to give **35** (2.30 mg, 72%) as a yellow amorphous solid.
IR (neat): ν = 2943, 2359, 1672, 1629, 1614 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 1.11 (d, J = 7.6 Hz, 9H), 1.14 (d, *J* = 7.6 Hz, 9H), 1.66 (s, 3H), 1.70–1.81 (m, 3H), 2.32 (ddd, *J* = 5.0, 13.2, 13.2 Hz, 1H), 2.72–3.10 (m, 3H), 3.99 (s, 3H), 4.00 (s, 3H), 6.73 (d, *J* = 8.3 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 8.32 (s, 1H), 9.30 (s, 1H).
^{13}C NMR ($CDCl_3$): δ = 11.3, 18.6, 18.7, 32.1, 34.0, 36.0, 37.1, 55.7, 103.6, 106.2, 118.3, 124.5, 124.8, 127.6, 130.9, 131.5, 144.8, 147.5, 148.7, 150.8, 172.2, 172.5, 192.8.
MS *m/z* = 518 (M^+), 475 (M^+-$CH(CH_3)_2$, 100).
HRMS Calcd for $C_{31}H_{38}O_5Si$: 518.2489, Found: 518.2501.
$[\alpha]_D^{25}$ +38.3 (*c* = 0.68, $CHCl_3$) (87% ee).

(12b*S*)-8,11-Dimethoxy-12b-methyl-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-3,6(2*H*,12b*H*)-dione (Halenaquinol Dimethyl Ether) (36):
To a solution of **35** (8.13 mg, 0.0157 mmol) in MeCN (3.0 mL) were added HOAc (0.0215 mL, 0.376 mmol), and Bu_4NCl (1.0 *M* in THF, 0.250 mL, 0.250 mmol) under ice bath cooling. After stirring for 2.5 h at 60 °C, the mixture was poured into sat. NH_4Cl (10 mL), extracted with EtOAc (20 mL) and the extract was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane–EtOAc, 1:1, and then $CHCl_3$) to give **36** (4.71 mg, 83%) as a yellow solid; mp 220–225 °C.
IR (neat): ν = 1697, 1673, 1628, 1464, 1339 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 1.677 (s, 3H), 2.334 (ddd, *J* = 4.6, 12.9, 12.9 Hz, 2H), 2.75–3.12 (m, 3H), 3.989 (s, 3H), 3.992 (s, 3H), 6.734 (d, *J* = 8.6 Hz, 1H), 6.848 (d, *J* = 8.6 Hz, 1H), 8.220 (s, 1H), 8.310 (s, 1H), 9.301 (s, 1H).
^{13}C NMR ($CDCl_3$): δ = 31.74, 34.20, 35.76, 36.80, 55.73, 103.76, 106.52, 118.47, 122.53, 124.73, 124.80, 127.58, 130.44, 144.42, 145.71, 146.99, 148.25, 148.66, 150.80, 172.72, 192.16.
MS *m/z* = 362 (M^+,100), 347 (M^+-CH_3, 98).
HRMS Calcd for $C_{22}H_{18}O_5$: 362.1154, Found: 362.1154.
$[\alpha]_D^{23}$ +123.7 (*c* = 0.335, CH_2Cl_2) (87% ee).

(12b*S*)-12b-Methyl-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-3,6,8,11(2*H*,12b*H*)-tetrone (Halenaquinone) (1):
To a solution of **36** (56.0 mg, 0.115 mmol) in MeCN (15 mL) was added a solution of cerium(IV) ammonium nitrate (CAN, 424 mg, 0.773 mmol) in H_2O (1.5 mL) at r.t. After stirring for 10 min, the mixture was poured into brine (15 mL), extracted with EtOAc (50 mL), and the extract was washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane–EtOAc, 2:1) to give **1** (51.0 mg, 99%) as a yellow solid.
^1H NMR (DMSO-d_6): δ = 1.66 (s, 3H), 2.21 (ddd, *J* = 4.4, 13.2, 13.2 Hz, 1H), 2.68 (ddd, *J* = 3.9, 4.4, 18.6 Hz, 1H), 2.94 (ddd, *J* = 4.4, 5.4, 13.2 Hz, 1H), 3.11 (ddd, *J* = 5.4, 13.2, 18.6 Hz, 1H), 7.19 (s, 2H), 8.32 (s, 1H), 8.69 (s, 1H), 8.89 (s, 1H).
^{13}C NMR (DMSO-d_6): δ = 29.9, 32.3, 36.4, 36.8, 122.5, 123.9, 125.1, 130.4, 133.7, 136.5, 139.2, 139.3, 144.1, 148.7, 151.1, 154.7, 170.1, 184.0, 184.4, 191.7.
MS *m/z* = 332 (M^+,48), 317 (M^+-CH_3, 100), 304 (14), 248 (22).
HRMS Calcd for $C_{20}H_{12}O_5$: 332.0685, Found: 332.0659.

(12b*S*)-8,11-Dihydroxy-12b-methyl-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-3,6(2*H*,12b*H*)-dione (Halenaquinol) (2):
To a solution of **1** (1.02 mg, 0.0031 mmol) in acetone (1 mL) was added aqueous $Na_2S_2O_4$ (0.57 *M*, 0.11 mL, 0.063 mmol) at 0 °C in the absence of light. After stirring for 30 min, the mixture was diluted with CH_2Cl_2, and the organic layer was separated, dried (Na_2SO_4), and carefully evaporated in vacuo giving **2** in an almost quantitative yield as a yellow solid.
^1H NMR (DMSO-d_6): δ = 1.63 (s, 3H), 2.0–2.4 (m, 1H), 2.6–3.3 (m, 3H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.87 (d, *J* = 7.9 Hz, 1H), 8.26 (s, 1H), 8.82 (s, 1H), 9.00 (s, 1H), 9.63 (s, 1H), 9.82 (s, 1H).
Other spectral data have not been measured, because this compound is very sensitive to light, heat, and air as previously reported.[3]

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