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ORIGINAL ARTICLE

Total synthesis of *ent*-(+)-cinanthrenol A

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The first total synthesis of *ent*-(+)-cinanthrenol A of potent estrogenic activity was achieved with 10.9% overall yield in 13 steps from commercially available materials. Our synthesis features a photo-promoted oxidative 6π-electron electrocyclization/aromatization for construction of the cyclopenta[a]phenanthren-17-one and Furukawa hydroxyl-directed cyclopropanation for the rare spiro[2,4]heptane. The brevity of this synthetic strategy would allow an expedited access to cinanthrenol A and its analogs for further biological evaluation.
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INTRODUCTION

Cinanthrenol A[1] (Figure 1) was isolated in 2014 by Nakao and co-workers from the deep-water marine sponge *Cinachyrella* sp.[2–4] and has shown moderate cytotoxicity against two cancer cell lines P-388 and HeLa with IC_{50} 4.5 and 0.4 $\mu g\,ml^{-1}$, respectively. Remarkably, cinanthrenol A was found to show estrogenic activity: binding strongly to estrogen receptor (ER) with IC_{50} value of 10 nM and changing the gene expression level of ER responsive genes A-MYB and SMAD3 in MCF-7 cells in a way similar to estradiol (E2).[5] This estrogenic activity was believed to arise from its aromatic steroid structure that resembles estradiol and estrone (Figure 1). Structurally, cinanthrenol A contains a rare spiro[2,4]heptane and a cyclopenta[α]phenanthrene core, a common structural motif of widespread and carcinogenic steroid-related products (for example, 11-methyl-cyclco[α]phenanthren-17-one) found in petroleum, mineral oils, coal, lake sediments and cooking oils.[6,7] In addition, the presence of a hydroxyl group at C2, not C3, is very rare in the families of cyclopenta[α]phenanthrenes and steroids. The natural scarcity (3.5 mg obtained from 6.5 kg of the deep-water marine sponge, 5.4×10^{-5} wt% yield), potential biological activities, and the novel structure prompted us to undertake a synthetic study, culminating in the first total synthesis of cinanthrenol A.

While many triaromatic steroids serving as useful geochemical biomarkers in fossil fuels are usually synthesized by multiple aromatizations of the corresponding steroids with low overall yields,[8–13] the *de novo* synthesis of cyclopenta[α]phenanthrenes has been underdeveloped in the past decades. Only three different approaches have been reported (Scheme 1a): (i) Friedel–Crafts acylative cyclization of tricyclic dihydrophenanthrene derivatives followed by oxidative aromatization by Coombs *et al.*,[14,15] (ii) acid-mediated alkylative cyclization of cyclopentanone-tethered naphthalene derivatives and oxidative aromatization by Lee and Harvey,[16] and (iii) intermolecular Diels–Alder cycloaddition of Dane's diene and α-bromocyclopentenone followed by dehydrogenative aromatization by Woski and Koreeda.[17] Herein, we report a new strategy that revolves upon photo-promoted oxidative 6π-electron electrocyclization/aromatization to construct B-ring of the cyclopenta[α]phenanthren-17-one from readily available *cis*-stilbene-type compound **5**, leading to the first total synthesis of cinanthrenol A.

Retrosynthetically, as depicted in Scheme 1b, we proposed Furukawa hydroxyl-directed cyclopropanation[18] of **2** to install the unusual spiro[2,4]heptane. The allylic alcohol **2** could be prepared from ketone **3** through α-hydroxylation and Wittig olefination. Excellent *Z/E* selectivity was expected to avoid the potential steric interaction of methyl group and H_{12} of cyclopenta[α]phenanthrenone's *ortho*-hydrogen. The cyclopenta[α]phenanthren-17-one **3** could be constructed by photo-promoted oxidative 6π-electron electrocyclization[19] of *cis*-stilbene **5**, which would be readily available from the double Sonogashira coupling of aryl iodides **6** and **7** with alkyne **8**, followed by partial hydrogenation with Lindlar's catalyst.

RESULTS AND DISCUSSION

Our synthesis began with the preparation of alkyne **9** from the aryl iodide **6** (Scheme 2) through a high yielding three-step sequence: triisopropylsilyl (TIPS) protection, Sonogashira coupling, and chemoselective desilylation of trimethylsilyl (TMS) group. Alkyne **9** was subjected to another Sonogashira coupling with commercially available iodoindanone (**7**) under identical condition, providing alkyne **10** in a quantitative yield. After preliminary condition screenings of partial hydrogenation of the internal diarylalkyne, we quickly identified an optimized condition: 30 mol% Lindlar's catalyst, 3 equivalents of quinoline, hydrogen gas (1 atm, balloon), and MeOH (solvent) at room temperature (RT) for 6 days, producing the desired *cis*-alkene **5a** in excellent yield (85%). The oxidative 6π-electron electrocyclization proved to be challenging and extensive reaction conditions have been investigated for a better yield on a synthetically useful scale (Table 1). Initially, an oxidative thermal electrocyclization of **5a** was examined under classical conditions (entries 1-3). Apparent decomposition was observed under all attempted conditions ($FeCl_3$[20] at RT,

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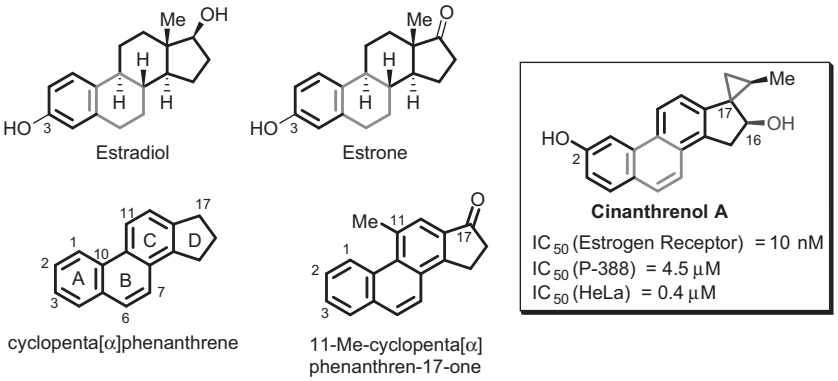
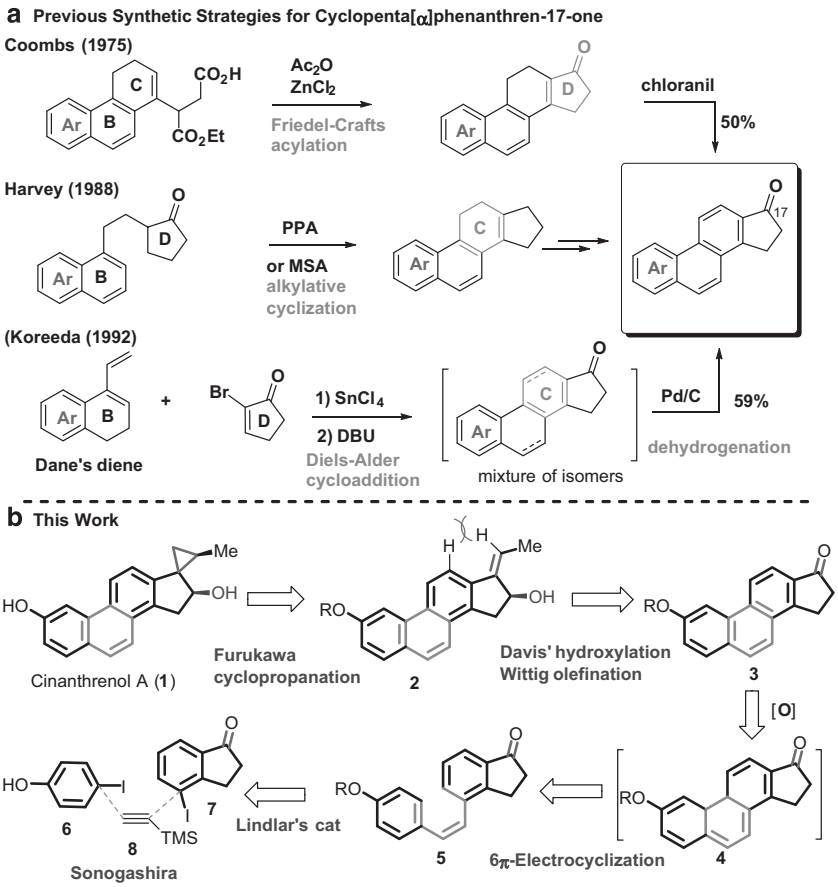
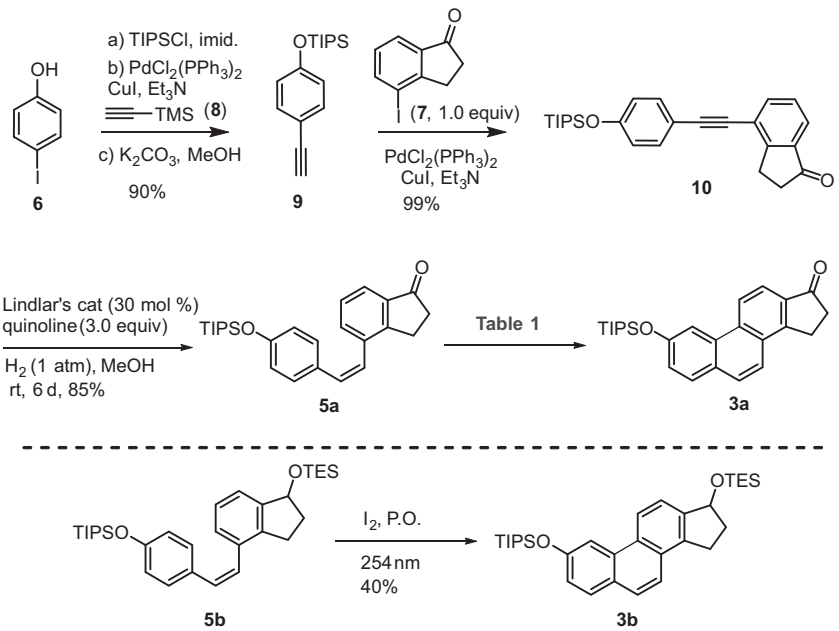


Figure 1 Estradiol, estrone, and cinanthrenol A. A full color version of this figure is available at *The Journal of Antibiotics* journal online.



Scheme 1 (**a**) Previous synthetic strategies for cyclopenta[α]phenanthren-17-one and (**b**) retrosynthetic analysis of cinanthrenol A. A full color version of this scheme is available at *The Journal of Antibiotics* journal online.

DMSO/DMF[21] at 140 °C, and *ortho*-dichlorobenenze at 200 °C) without any detectable cyclization product **3a**. As well-recognized, photoreactions were wavelength-dependent. Therefore, a suitable wavelength for UV irradiation should be identified for I_2-promoted oxidative photocyclization.[22] When 180 nm wavelength was used (entry 4), significant decomposition was observed. Although irradiation with 300 nm gave only trace amount of **3a** (mainly isomerization of *cis*-alkene to *trans*-alkene); 254 nm was found to be the optimal wavelength for the desired 6π electron electrocyclization, providing cyclopenta[α]phenanthren-17-one **3a** in synthetically meaningful yield (20%). Further optimization of the reaction conditions including reaction time (entry 8 and 9), solvent[23] (entry 10), oxidant (I_2 vs PIDA,[24] entry 13), and additive (propene oxide) (Katz's condition,[25–28] entry 11) allowed us to increase the overall yield to be synthetically useful (50%). In addition, cyclopenta[α]phenanthren-17-ol derivative **5b** was prepared from **5a** to examine the key oxidative electrocyclization because the unfavorable influence of ketone group (*c.f.*, **5a**) on the oxidative photocyclization were on record.[29,30] However, no better yield (40% of **3b**) was obtained from **5b** under various electrocyclization conditions attempted for **5a**. Finally, it should be noted that the concentration of the oxidative photocyclization must be within 0.001 M, because higher concentration resulted in



Scheme 2 Construction of cyclopenta[α]phenanthren-17-one **3a**. A full color version of this figure is available at *The Journal of Antibiotics* journal online.

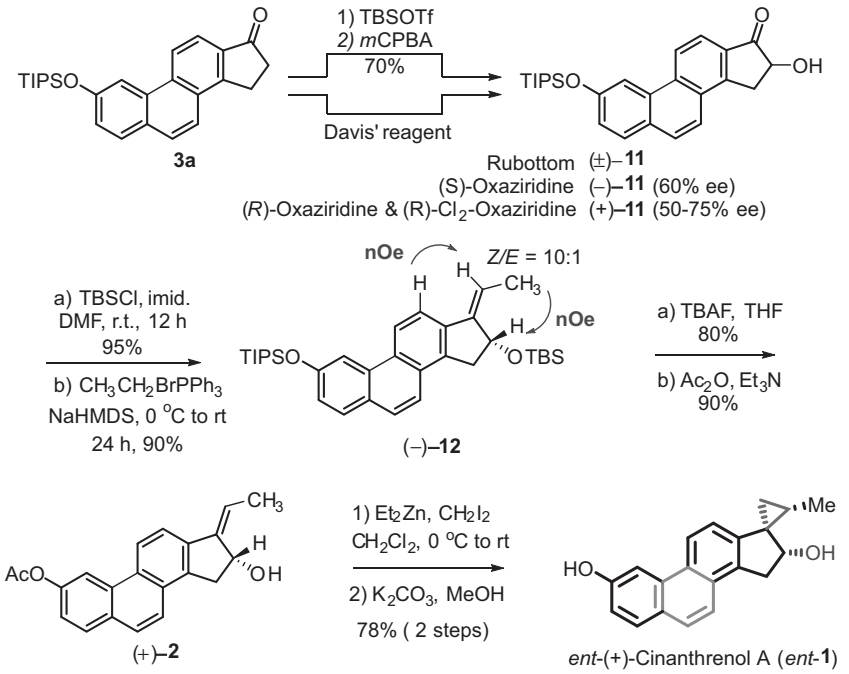
Table 1 Selected screening conditions for oxidative 6π-electron electrocyclization

Entry	*λ(hv) (nm)*	*Oxidant (equiv) solvent*	*Concentration (M)/time (h)*	*Conversion (%)*	*Yield (%)*[a]
1	—	$FeCl_3$, CH_2Cl_2	0.001/3	100	0
2	—	DMSO/DMF, 140 °C	0.001/3	60	0
3	—	200 °C, *o*-DCB	0.001/12	80	0
4	180	I_2 (1.0)/air, *c*hex	0.001/6	100	<5
5	254	I_2 (1.0)/air, *c*hex	0.001/6	60	20
6	300	I_2 (1.0)/air, *c*hex	0.001/6	100	<5
7	254	I_2 (1.0)/air, *c*hex	0.01/6	100	<10
8	254	I_2 (1.0)/air, *c*hex	0.001/12	90	40
9	254	I_2 (1.0)/air, *c*hex	0.001/24	100	35
10	254	I_2 (1.0)/air, *t*BuOH/benzene	0.001/12	100	20
11	254	I_2 (1.0)/PO, *c*hex	0.001/12	80	50
12	254	I_2 (1.0)/PO, *c*hex	0.001/24	100	30
13	254	PIDA, dioxane	0.001/12	30	10

Abbreviations: *c*hex, cyclohexane; equiv, equivalent; *o*-DCB, ortho-dichlorobenzene; PIDA, (diacetoxyiodo)benzene; PO, propene oxide.
[a]Isolated yield.

considerable intermolecular [2+2] cycloaddition and decomposition (entry 7 in Table 1).

After several repeated operations of oxidative photocyclization to provide sufficient amount of cyclopenta[α]phenanthren-17-one **3a**, we turned our attention to construct the unusual spiro[2,4]heptane through Furukawa modification of Simons–Smith cyclopropanation (Scheme 3). To this end, manipulations of ketone **3a** were needed to prepare enantiomerically pure allylic alcohol **2** for hydroxyl-directed cyclopropanation. Although the classical Rubottom hydroxylation[31] of the corresponding silyl enol ether proceeded smoothly to produce the desired α-hydroxyl ketone (±)-**11** in 70% yield, an enantioselective α-hydroxylation of ketone **3**a using Davis' (*S*)-oxaziridine,[32] surprisingly, gave (−)-**11** with only 60% ee in 50% yield. The use of Davis' (*R*)-oxaziridine led to the similar result: a 65% yield of with 50% ee. It was found that the dichloro derivative of Davis' (*R*)-oxaziridine could deliver (+)-**11** with a slight better ee value (75% ee) in 60% yield. In addition, we have made considerable attempts to increase the enantioenrichment of **11** including kinetic resolution via Sharpless asymmetric epoxidation protocol or lipase-mediated acetylation at a later stage without success.[33] Therefore, we chose to move forward with (+)-**11** (75% ee). It was noted that free alcohol of (+)-**11** did not undergo efficient Wittig olefination. Upon temporary protection as TBS ether, Wittig olefination with triphenyl phosphonium ylide generated *in situ* occurred efficiently to provide alkene (−)-**12** in 90% yield with excellent *Z*-selectivity (*Z*/*E* ⩾10:1), which was confirmed by nOe experiments. As chemoselective desilylation (TBS over TIPS) was problematic, desilylation of both TIPS and TBS groups with TBAF and regioselective acetylation of the aromatic alcohol were performed to provide the allylic alcohol (+)-**2**. It should be noted that the free phenol caused significant decomposition in the subsequent cyclopropanation. The Furukawa–Simons–Smith[18] cyclopropanation of (+)-**2** proceeded smoothly with Et_2Zn and diiodomethane to furnish *ent*-(+)-cinanthrenol A (*ent*-**1**) in 78% yield after deacetylation with K_2CO_3 in methanol. Remarkably, a single diastereomer was observed in cyclopropanation reaction, in supportive of the high hydroxyl-directed diastereoselectivity.[34] The opposite sign of optical



Scheme 3 Total Synthesis of *ent*-(+)-Cinanthrenol A. A full color version of this figure is available at *The Journal of Antibiotics* journal online.

rotation of synthetic *ent*-**1** (derived from (+)-**11** in 75% ee) and natural cinanthrenol A provided a confirmation of its absolute configuration ($[a]_D = +6.3$, c 0.3, MeOH; lit$[a]_D = -11.6$, c 0.16, MeOH). However, the ee% value of our synthetic cinanthrenol A (*ent*-**1**) was not clear.

In summary, we have accomplished the first total synthesis of *ent*-(+)-cinanthrenol A with 10.9% overall yield in 13 steps from commercially available starting materials. Our synthesis was enabled by some key reactions including Sonogashira coupling, oxidative 6π-electron electrocyclization, Davis' asymmetric hydroxylation, and Furukawa–Simons–Smith cyclopropanation. Our synthetic studies confirmed the absolute configuration of natural cinanthrenol A and provide an expedient access to the analogs for further biological evaluation.

MATERIALS AND METHODS

Reactions were carried out in oven or flame-dried glassware under a nitrogen atmosphere, unless otherwise noted. Tetrahydrofuran (THF) was freshly distilled before use from sodium using benzophenone as indicator. Dichloromethane was freshly distilled before use from calcium hydride (CaH2). All other solvents were dried over 3 or 4 Å molecular sieves. Solvents used in workup, extraction, and column chromatography were used as received from commercial suppliers without prior purification. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC, 0.25 mm) on Merck pre-coated silica gel plates (Sigma-Aldrich, St Louis, MO, USA). Flash chromatography was performed with silica gel 60 (particle size 0.040–0.062 mm) supplied by Grace. IR spectra were collected on a Bruker model TENSOR27 spectrophotometer (Bruker, Billerica, MA, USA). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C) (Bruker). Chemical shifts are reported in p.p.m. as values relative to the internal chloroform (7.26 p.p.m. for 1H and 77.0 p.p.m. for 13C) or pyridine (7.55 p.p.m. (tr) for 1H and 135.5 p.p.m. (tr) for 13C). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Optical rotations were measured on a JASCO Perkin–Elmer model P-2000 polarimeter (JASCO, Easton, MD, USA). High-resolution mass spectra were measured at the Hong Kong University of Science and Technology Mass Spectrometry Service Center on either an Agilent GC/MS 5975C system (Agilent, Santa Clara, CA, USA) or an API QSTAR XL System (Applied Biosystems, Waltham, MA, USA).

Preparation of alkyne 9

To a stirred solution of 4-iodophenol **6** (2.20 g, 10 mmol) in DMF (20 ml) at 0 °C were added imidazole (1.70 g, 25.0 mmol) and triisopropylsilyl chloride (2.67 mL, 12.5 mmol). The reaction mixture was allowed to warm to RT and stirred overnight. The reaction was quenched by addition of aq. satd. NH_4Cl (50 ml). The organic layer was collected and the aqueous layer was extracted with Et_2O (3 × 50 ml). The combined organic fractions were washed with H_2O (3 × 30 ml), brine, dried over $MgSO_4$, and concentrated under reduced pressure to give the crude TIPS ether **S-1**. A small amount of the residue was purified by flash column chromatography on silica gel using eluents (ethyl acetate/hexane = 1/10–1/5) to give the pure **S-1** as a colorless oil for data collection. IR (neat, cm^{-1}): 2945, 2892, 2867, 1581, 1485, 1388, 1273, 1168, 1003, 909, 883, 825, 726, 686. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.4 Hz, 2H), 6.65 (d, J = 8.4 Hz, 2H), 1.33–1.16 (m, 3H), 1.09 (d, J = 7.2 Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 138.2 (2C), 122.3 (2C), 83.2, 17.9 (6C), 12.6 (3C). HRMS (CI$^+$): m/z calculated for $C_{15}H_{25}IOSi$ $[M]^+$ 376.0719, found 376.0712.

To a stirred solution of crude **S-1** in dry THF (50 ml) at RT were added bis(triphenylphosphine)palladium(II) dichloride (351 mg, 0.5 mmol), CuI (195 mg, 1.0 mmol), triethylamine (4.18 ml, 30.0 mmol) and trimethylsilylacetylene **8** (7.0 ml, 50.0 mmol). The reaction mixture was refluxed overnight, cooled to RT, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using eluents (ethyl acetate/hexane = 1/10–1/5) to give the **S-2** as a colorless oil. IR (neat, cm^{-1}): 2947, 2895, 2869, 2158, 1602, 1505, 1278, 1250, 1096, 910, 865, 840, 686. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H), 1.30–1.16 (m, 3H), 1.08 (d, J = 7.2 Hz, 18H), 0.23 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 133.4 (2C), 119.9 (2C), 115.5, 105.3, 92.5, 17.8 (6C), 12.6 (3C), 0.0 (3C). HRMS (CI$^+$): *m/z* calculated for $C_{20}H_{34}OSi_2$ $[M]^+$ 246.2148, found 246.2155.

To a stirred solution of the alkyne **S-2** in MeOH (25 ml) and CH_2Cl_2 (25 ml) at RT was added potassium carbonate (138 mg, 1.0 mmol). The reaction mixture was stirred overnight at RT, filtered through a short pad of Celite. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using eluents (EtOAc/hexane = 1/20) to give the alkyne **9** (2.47 g, 90% over 3 steps) as a colorless oil. IR (neat,

cm^{-1}): 2946, 2893, 2868, 1603, 1505, 1464, 1278, 910, 882, 839, 686. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, $J=8.4$ Hz, 2H), 6.82 (d, $J=8.4$ Hz, 2H), 3.00 (s, 1H), 1.31–1.18 (m, 3H), 1.09 (d, $J=7.6$ Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 133.6 (2C), 119.9 (2C), 114.4, 83.8, 75.8, 17.8 (6C), 12.6 (3C). HRMS (CI^+): *m/z* calculated for $C_{17}H_{27}OSi$ $[M+H]^+$ 275.1831, found 275.1844.

Preparation of diarylalkyne 10

To a stirred solution of the alkyne **9** (2.47 g, 9.0 mmol) and 4-iodoindanone **7** (1.55 g, 6.0 mmol) in dry THF (50 ml) at RT were added bis(triphenylphosphine)palladium(II) dichloride (211 mg, 0.3 mmol), CuI (117 mg, 0.6 mmol) and triethylamine (2.53 ml, 18.0 mmol). The reaction mixture was refluxed overnight, cooled to RT, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using eluents (ethyl acetate/hexane = 1/10–1/5) to give the diarylalkyne **10** (2.41 g, >99% yield) as a brown oil. IR (neat, cm^{-1}): 3039, 2945, 2892, 2867, 1719, 1597, 1509, 1463, 1276, 908, 883, 839, 778, 687. ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, $J=7.6$ Hz, 2H), 7.42 (d, $J=8.4$ Hz, 2H), 7.33 (t, $J=7.6$ Hz, 1H), 6.87 (d, $J=8.4$ Hz, 2H), 3.30–3.13 (m, 2H), 2.78–2.65 (m, 2H), 1.36–1.19 (m, 3H), 1.10 (d, $J=7.6$ Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.6, 156.9, 156.7, 137.1, 136.5, 133.0 (2C), 127.4, 122.9, 122.5, 120.0 (2C), 115.0, 95.0, 84.3, 36.0, 25.5, 17.8 (6C), 12.6 (3C). HRMS (CI^+): *m/z* calculated for $C_{26}H_{33}O_2Si$ $[M+H]^+$ 405.2250, found 405.2263.

Preparation of *cis*-stilbene 5a

To a stirred solution of the diarylalkyne **10** (2.41 g, 6.0 mmol) in MeOH (30 ml) at RT were added Lindlar's catalyst (3.82 g, 1.8 mmol), quinoline (2.13 ml, 18.0 mmol). The reaction mixture was flushed with hydrogen gas three times. The reaction mixture under H_2 atmosphere (1.0 atm, balloon) was stirred at RT for 6 days. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using eluents (ethyl acetate /hexane = 1/10–1/5) to give the *cis*-stilbene **5a** (2.07 g, 85% yield) as a brown oil. IR (neat, cm^{-1}): 2944, 2867, 1716, 1601, 1509, 1464, 1270, 1169, 1090, 910, 883, 782, 686. ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, $J=7.6$ Hz, 1H), 7.49 (d, $J=7.6$ Hz, 1H), 7.25 (t, $J=7.6$ Hz, 1H), 7.00 (d, $J=8.4$ Hz, 2H), 6.69 (m, 3H), 6.51 (d, $J=12.0$ Hz, 1H), 2.93–2.83 (m, 2H), 2.63–2.60 (m, 2H), 1.27–1.16 (m, 3H), 1.07 (d, $J=7.2$ Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 155.6, 153.7, 137.3, 136.4, 134.4, 132.1, 129.8 (2C), 129.6, 127.3, 124.3, 122.3, 119.9 (2C), 36.1, 25.0, 17.8 (6C), 12.6 (3C). HRMS (CI^+): *m/z* calculated for $C_{26}H_{34}O_2Si$ $[M]^+$ 406.2328, found 406.2328.

Preparation of cis-Stilbene 5b

To a stirred solution of ketone **5a** (406 mg, 1.0 mmol) in MeOH (10 ml) was added sodium borohydride (56.7 mg, 1.5 mmol) at 0 °C. The reaction was stirred at 0 °C for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using eluents (EtOAc/hexane = 1/10–1/5) to give the secondary alcohol product. The alcohol product was dissolved in dry DMF (5 ml), and to the solution were added imidazole (170 mg, 2.5 mmol) and triethylsilyl chloride (0.20 ml, 1.2 mmol) at 0 °C. The reaction mixture was allowed to warm to RT and stirred overnight. The reaction was quenched by addition of aq. satd. NH_4Cl (10 ml). The organic layer was collected and the aqueous layer was extracted with Et_2O (3 × 20 ml). The combined organic fractions were washed with H_2O (3 × 10 ml), brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using eluents (ethyl acetate/hexane = 1/20–1/15) to give the *cis*-stilbene **5b** (571 mg, 90% over 2 steps) as a brown oil. IR (neat, cm^{-1}): 2948, 2869, 1603, 1508, 1462, 1267, 1106, 1013, 912, 883, 787, 744. ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, $J=6.4$ Hz, 1H), 7.11 (m, 2H), 7.04 (d, $J=8.4$ Hz, 2H), 6.70 (d, $J=8.4$ Hz, 2H), 6.51 (dd, $J=32.2$, 12.0 Hz, 2H), 5.22 (t, $J=7.2$ Hz, 1H), 2.82 (dd, $J=15.6$, 9.0 Hz, 1H), 2.51–2.40 (m, 1H), 2.40–2.30 (m, 1H), 1.84 (dq, $J=12.4$, 8.6 Hz, 1H), 1.28–1.17 (m, 3H), 1.08 (d, $J=7.2$ Hz, 17H), 1.03 (t, $J=8.0$ Hz, 10H), 0.71 (q, $J=8.0$ Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 145.9, 141.0, 134.3, 130.3, 130.3, 129.9 (2C), 127.7, 126.6, 126.5, 122.6, 119.7 (2C), 76.4, 36.3, 28.6, 17.9 (6C), 12.6 (3C), 6.9 (3C), 5.0 (3C). HRMS (CI^+): *m/z* calculated for $C_{30}H_{50}O_2Si_2$ $[M]^+$ 522.3349, found 522.3359.

Preparation of 3a/3b

To a round bottom quartz flask (150 ml) were added *cis*-stilbene **5a/5b** (0.1 mmol), cyclohexane (100 ml), I_2 (25 mg, 0.1 mmol), and propene oxide (1.16g, 1.4 ml, 20 mmol). The flask containing the reaction mixture was placed in a Rayonet chamber reactor (Rayonet-200 model, The Southern New England Ultraviolet Company, Branford, CT, USA) and irradiated with RPR-2537 lamps ($\lambda = 254$ nm) at RT for 3–24 h. The reaction was quenched by addition of aq. satd. $NaHCO_3$ (30 ml) and aq. satd. $Na_2S_2O_3$ (30 ml). The organic layer was collected and the aqueous layer was extracted with Et_2O (3 × 50 ml). The combined organic fractions were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give the crude mixture, which was purified by flash column chromatography on silica gel. **3a** was obtained in 50% yield (entry 11). IR (neat, cm^{-1}): 2926, 2866, 1711, 1614, 1509, 1457, 1264, 1232, 991, 924, 882, 864, 670. ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, $J=8.8$ Hz, 1H), 8.11 (s, 1H), 7.88 (d, $J=8.8$ Hz, 1H), 7.83–7.76 (m, 2H), 7.71 (d, $J=8.8$ Hz, 1H), 7.27 (d, $J=8.8$ Hz, 1H), 3.41 (br s, 2H), 2.82 (br s, 2H), 1.36 (m, 3H), 1.16 (d, $J=7.2$ Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9, 155.4, 155.37, 134.9, 133.4, 131.7, 130.2, 129.2, 128.1, 127.9, 122.8, 122.4, 119.9, 119.4, 112.3, 36.3, 24.6, 18.0 (6C), 12.7 (3C). HRMS (CI^+): *m/z* calculated for $C_{26}H_{32}O_2Si$ $[M]^+$ 404.2172, found 404.2176.

3b was obtained in 40% yield from **5b**. IR (neat, cm^{-1}): 2947, 2869, 1617, 1600, 1508, 1457, 1232, 1103, 879, 834, 753, 685. ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, $J=8.8$ Hz, 1H), 8.11 (s, 1H), 7.76 (d, $J=8.8$ Hz, 1H), 7.70 (d, $J=8.8$ Hz, 1H), 7.62 (d, $J=9.2$ Hz, 2H), 7.19 (d, $J=8.4$ Hz, 1H), 5.49 (t, $J=6.4$ Hz, 1H), 3.45 (m, 1H), 3.09 (dt, $J=16.0$, 8.0 Hz, 1H), 2.65 (m, $J=12.0$, 8.0 Hz, 1H), 2.12 (m, 1H), 1.36 (m, 3H), 1.17 (d, $J=7.6$ Hz, 18H), 1.07 (t, $J=8.0$ Hz, 9H), 0.75 (q, $J=8.0$ Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 143.2, 139.6, 132.2, 129.9, 129.4, 128.8, 126.7 (2C), 122.3, 121.9, 120.9, 120.7, 111.8, 77.0, 36.2, 28.4, 18.0 (6C), 12.8 (3C), 6.9 (3C), 5.1 (3C). HRMS (CI^+): *m/z* calculated for $C_{32}H_{48}O_2Si_2$ $[M]^+$ 520.3193, found 520.3198.

Preparation of α-Hydroxyl Ketone 11

α-Hydroxylation: To a stirred solution of ketone **3a** (202 mg, 0.5 mmol) in CH_2Cl_2 (5 ml) at 0 °C were added triethylamine (0.1 ml, 0.75 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 0.14 ml, 0.6 mmol). The reaction mixture was allowed to warm to RT and stirred for 2 h. The reaction was quenched by addition of aq. satd. $NaHCO_3$ (10 ml). The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 ml). The combined organic fractions were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (5 ml) at 0 °C, to the resulting solution were added $NaHCO_3$ (84 mg, 1.0 mmol) and 3-chloroperbenzoic acid (168 mg, 0.75 mmol). The reaction mixture was allowed to warm to RT and stirred for 4 h. The reaction was quenched by addition of aq. satd. $NaHCO_3$ (10 ml). The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 ml). The combined organic fractions were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using eluents (ethyl acetate/hexane = 1/6–1/3) to give the α-hydroxyl ketone **11** (147 mg, 70% yield) as a brown solid. **Asymmetric α-Hydroxylation**: to a stirred solution of sodium bis (trimethylsilyl)amide (1M in THF, 0.6 ml, 0.6 mmol) in THF (5 ml) at −78 °C was added the solution of ketone **3a** (202 mg, 0.5 mmol) in THF (2 ml), the reaction mixture was stirred at −78 °C for 30 min. Then a solution of Davis' (*S*)-oxaziridine (0.75 mmol) in THF (2 ml) was added via syringe, the reaction mixture was stirred at −78 °C for 30 min. The reaction was quenched by addition of aq. satd. NH_4I (10 ml). The organic layer was collected and the aqueous layer was extracted with Et_2O (3 × 10 ml). The combined organic fractions were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using eluents (ethyl acetate/hexane = 1/6–1/3) to give the α-hydroxyl ketone **11** as a brown solid. (+)-**11** was obtained following the same procedure using Davis' (*R*)-oxaziridine **or** dichloride derivative of Davis' (*R*)-oxaziridine.

(+)-**11** (75% *ee*): $[\alpha]_D^{20} = +7.5$(*c* 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3419, 2944, 2866, 1712, 1613, 1513, 1457, 1266, 1234, 983, 882, 841. ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 8.8 Hz, 1H), 8.13 (d, *J* = 2.0 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.85 (m, 2H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.31 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.72 (dd, *J* = 7.6, 4.0 Hz, 1H), 4.03 (dd, *J* = 16.8, 7.6 Hz, 1H), 3.27 (dd, *J* = 16.8, 4.0 Hz, 1H), 1.38 (m, 3H), 1.17 (d, *J* = 7.2 Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.2, 155.6, 151.6, 134.4, 131.8, 131.7, 130.3, 129.1, 128.3, 128.3, 123.5, 122.7, 120.2, 119.4, 112.3, 74.2, 33.7, 18.0 (6C), 12.8 (3C). HRMS (CI^+): *m/z* calculated for $C_{26}H_{32}O_3Si$ $[M]^+$ 420.2121, found 420.2122.

Preparation of Alkene (−)-12

To a stirred solution of α-hydroxyl ketone (+)-**11** (126 mg, 0.3 mmol, 75% ee) in DMF (5 ml) at 0 °C were added imidazole (51 mg, 0.75 mmol) and *tert*-butyldimethylsilyl chloride (54 mg, 0.36 mmol). The reaction mixture was allowed to warm to RT and stirred overnight. The reaction was quenched by addition of aq. satd. NH_4Cl (10 ml). The organic layer was collected and the aqueous layer was extracted with Et_2O (3 × 10 ml). The combined organic fractions were washed with H_2O (3 × 10 ml), brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using eluents (ethyl acetate/hexane = 1/20–1/15) to give the pure TBS ether **S-3** (152 mg, 95%) as a colorless oil. $[\alpha]_D^{20} = -5.0$ (*c* 0.5, $CHCl_3$). IR (neat, cm^{-1}): 2928, 2860, 1724, 1613, 1513, 1460, 1262, 1128, 868, 837, 672. ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.6 Hz, 1H), 8.13 (s, 1H), 7.90 (d, *J* = 8.6 Hz, 1H), 7.84 (d, *J* = 8.6 Hz, 2H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 4.77–4.64 (m, 1H), 3.95 (dd, *J* = 16.6, 7.4 Hz, 1H), 3.24 (dd, *J* = 16.6, 3.2 Hz, 1H), 1.43–1.33 (m, 3H), 1.17 (d, *J* = 7.2 Hz, 18H), 1.00 (s, 9H), 0.27 (d, *J* = 4.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 155.5, 150.7, 134.0, 132.4, 131.8, 130.2, 129.0, 128.2, 128.0, 123.2, 122.6, 120.3, 119.5, 112.3, 74.8, 35.2, 25.9 (3C), 18.5, 18.0 (6C), 12.8 (3C), −4.3, −5.0. HRMS (CI^+): *m/z* calculated for $C_{32}H_{47}O_3Si_2$ $[M]^+$ 535.3064, found 535.3047.

To a stirred suspension of $C_2H_5PPh_3Br$ (223 mg, 0.6 mmol) in THF (5 ml) at 0 °C was added sodium bis(trimethylsilyl)amide (1.0 M in THF, 0.5 ml, 0.5 mmol), the reaction mixture was stirred at 0 °C for 30 min. Then a solution of TBS ether **S-3** (134 mg, 0.25 mmol) in THF (3 ml) was added via syringe, the reaction mixture was allowed to warm to RT and stirred overnight. The reaction was quenched by addition of aq. satd. NH_4Cl (10 mL). The organic layer was collected and the aqueous layer was extracted with Et_2O (3 × 10 ml). The combined organic fractions were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using eluents (ethyl acetate/hexane = 1/20–1/15) to give the alkene (−)-**12** (123 mg, 90% yield) as a brown oil. $[\alpha]_D^{20} = -8.0$(*c* 0.1, $CHCl_3$). IR (neat, cm^{-1}): 2924, 2854, 1617, 1460, 1376, 1261, 1085, 1019, 800. ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.4 Hz, 1H), 8.07 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 6.30 (d, *J* = 6.8 Hz, 1H), 5.38 (d, *J* = 6.0 Hz, 1H), 3.62 (dd, *J* = 16.8, 7.0 Hz, 1H), 3.20 (d, *J* = 16.8 Hz, 1H), 2.02 (d, *J* = 6.8 Hz, 3H), 1.37 (m, 3H), 1.17 (d, *J* = 7.2 Hz, 18H), 0.93 (s, 9H), 0.18 (d, *J* = 9.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 145.2, 138.8, 138.1, 132.3, 129.9, 129.09, 129.06, 126.9, 126.7, 122.1, 120.72, 120.69, 119.2, 118.3, 111.6, 72.1, 40.5, 29.7, 25.9 (3C), 18.0 (6C), 14.7, 12.8 (3C), −3.7, −4.5. HRMS (CI^+): *m/z* calculated for $C_{34}H_{50}O_2Si_2$ $[M]^+$ 546.3349, found 546.3376.

Preparation of allylic alcohol (+)-2

To a solution of the allylic alcohol (−)-**12** (109 mg, 0.2 mmol) in THF (3 ml) at 0 °C was added tetrabutylammonium fluoride (TBAF, 1.0 M in THF, 0.6 ml, 0.6 mmol). The reaction mixture was allowed to warm to RT and stirred for 3 h. The reaction was quenched by addition of aq. satd. NH_4Cl (10 ml). The organic layer was collected and the aqueous layer was extracted with EtOAc (3 × 10 ml). The combined organic fractions were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give a crude product, which was washed through a short pad of silica gel using eluents (ethyl acetate) to remove TBAF to give the phenol intermediate (44 mg, 80%) as a yellow solid. To a stirred solution of the phenol intermediate (28 mg, 0.1 mmol) in CH_2Cl_2 (1 ml) at RT were added triethylamine (28 µl, 0.2 mmol) and acetic anhydride (14 µl, 0.15 mmol). The reaction mixture was stirred at RT for 2 h. The reaction was quenched by addition of aq. satd. $NaHCO_3$ (5 ml). The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 ml). The combined organic fractions were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using eluents (ethyl acetate/hexane = 1/3–1/1) to give acetate (+)-**2** (29 mg, 90%) as a colorless oil. $[\alpha]_D^{20} = +19.6$(*c* 0.5, $CHCl_3$). IR (neat, cm^{-1}): 3420, 2924, 1755, 1619, 1370, 1213, 1165, 840, 755. ^1H NMR (400 MHz, C_6D_6) δ 8.45 (d, *J* = 8.4 Hz, 1H), 8.33 (s, 1H), 7.90 (d, *J* = 8.8 Hz, 1H), 7.82–7.64 (m, 3H), 7.33 (d, *J* = 8.4 Hz, 1H), 6.36 (d, *J* = 7.2 Hz, 1H), 5.35–5.24 (m, 1H), 3.65 (dd, *J* = 17.6, 6.2 Hz, 1H), 3.32 (d, *J* = 17.6 Hz, 1H), 2.41 (s, 3H), 2.09 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 69.7, 149.4, 145.7, 139.2, 137.8, 131.7, 130.0, 129.8, 129.6, 129.3, 126.9, 123.0, 122.5, 120.8, 120.3, 118.8, 114.9, 71.1, 39.9, 21.3, 14.6. HRMS (CI^+): *m/z* calculated for $C_{21}H_{18}O_3$ $[M]^+$ 318.1256, found 318.1262.

Preparation of *ent*-cinanthrenol A

To a stirred solution of (+)-**2** (16 mg, 0.05 mmol) in CH_2Cl_2 (1 ml) at 0 °C was added diiodomethane (40 µl, 0.5 mmol) and diethylzinc solution (1M in hexanes, 0.5 ml, 0.5 mmol). The reaction mixture was stirred at 0 °C for 4 h. The reaction was quenched by addition of aq. satd. $NaHCO_3$ (5 ml). The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 ml). The combined organic fractions were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using eluents (ethyl acetate/hexane = 1/3–1/1) to give the cyclopropane intermediate as a yellow solid. To a stirred solution of the cyclopropane derivative in MeOH (1 ml) at RT was added potassium carbonate (1.4 mg, 0.01 mmol). The reaction mixture was stirred at RT for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using eluents (ethyl acetate/hexane = 1/3–1/1) to give the final product *ent*-**1** (11 mg, 78% over 2 steps) as a yellow solid. $[\alpha]_D^{20} = +6.3$(*c* 0.3, MeOH). IR (neat, cm^{-1}): 3422, 2921, 2864, 1742, 1513, 1460, 1385. ^1H NMR (400 MHz, Pyr) δ 12.00 (s, 1H), 8.64 (d, *J* = 8.0 Hz, 1H), 8.57 (s, 1H), 7.94 (d, *J* = 8.8 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.51 (d, *J* = 6.4 Hz, 1H), 4.86 (m, 1H), 3.87 (dd, *J* = 16.8, 7.4 Hz, 1H), 3.61 (d, *J* = 16.8 Hz, 1H), 1.46 (m, 1H), 1.36 (m, 1H), 1.30 (d, *J* = 4.8 Hz, 3H), 1.16 (m, 1H). ^{13}C NMR (100 MHz, C_5D_5N) δ158.2, 145.9, 137.1, 133.5, 130.8, 129.3, 128.5, 127.5, 125.8, 122.8, 120.4, 117.9, 117.7, 107.6, 71.8, 41.3, 38.5, 22.0, 19.6, 14.4. HRMS (LD^+): *m/z* calculated for $C_{20}H_{18}O_2$ $[M]^+$ 290.1307, found 290.1297.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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