# 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  $6\pi$ -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<sup>1</sup> (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<sub>50</sub> 4.5 and 0.4  $\mu$ g ml<sup>-1</sup>, respectively. Remarkably, cinanthrenol A was found to show estrogenic activity: binding strongly to estrogen receptor (ER) with IC<sub>50</sub> 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).<sup>5</sup> 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  $[\alpha]$ phenanthrene core, a common structural motif of widespread and carcinogenic steroid-related products (for example, 11-methyl-cyclco  $[\alpha]$  phenanthren-17-one) found in petroleum, mineral oils, coal, lake sediments and cooking oils.<sup>6,7</sup> In addition, the presence of a hydroxyl group at C2, not C3, is very rare in the families of cyclopenta[ $\alpha$ ] phenanthrenes and steroids. The natural scarcity (3.5 mg obtained from 6.5 kg of the deep-water marine sponge,  $5.4 \times 10^{-5}$  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,<sup>8–13</sup> the *de novo* synthesis of cyclopenta[ $\alpha$ ]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.*,<sup>14,15</sup> (ii) acid-mediated alkylative cyclization of cyclopentanone-tethered naphthalene derivatives and oxidative aromatization by Lee and Harvey,<sup>16</sup> and (iii) intermolecular Diels–Alder cycloaddition of Dane's diene and  $\alpha$ -bromocyclopentenone followed by dehydrogenative aromatization by Woski and Koreeda.<sup>17</sup> Herein, we report a new

strategy that revolves upon photo-promoted oxidative  $6\pi$ -electron electrocyclization/aromatization to construct B-ring of the cyclopenta [ $\alpha$ ]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<sup>18</sup> of **2** to install the unusual spiro[2,4]heptane. The allylic alcohol **2** could be prepared from ketone **3** through  $\alpha$ -hydroxylation and Wittig olefination. Excellent *Z/E* selectivity was expected to avoid the potential steric interaction of methyl group and H<sub>12</sub> of cyclopenta[ $\alpha$ ]phenanthrenone's *ortho*-hydrogen. The cyclopenta[ $\alpha$ ]phenanthren-17-one **3** could be constructed by photo-promoted oxidative  $6\pi$ -electron electrocyclization<sup>19</sup> 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  $6\pi$ -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<sub>3</sub><sup>20</sup> at RT,

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Synthesis of ent-(+)-cinanthrenol A L Zhu and R Tong



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[ $\alpha$ ]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<sup>21</sup> 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<sub>2</sub>-promoted oxidative photocyclization.<sup>22</sup> 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  $6\pi$  electron electrocyclization, providing cyclopenta[ $\alpha$ ]phenanthren-17-one **3a** in synthetically meaningful yield (20%). Further optimization of the reaction conditions including

reaction time (entry 8 and 9), solvent<sup>23</sup> (entry 10), oxidant (I<sub>2</sub> vs PIDA,<sup>24</sup> entry 13), and additive (propene oxide) (Katz's condition,<sup>25–28</sup> entry 11) allowed us to increase the overall yield to be synthetically useful (50%). In addition, cyclopenta[ $\alpha$ ]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.<sup>29,30</sup> 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 resulted in



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

Entry	λ(hv) (nm)	Oxidant (equiv) solvent	Concentration (M)/time (h)	Conversion (%)	Yield (%) <sup>a</sup>
1	_	FeCl <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub>	0.001/3	100	0
2	_	DMSO/DMF, 140 °C	0.001/3	60	0
3	_	200 °C, <i>o</i> -DCB	0.001/12	80	0
4	180	l <sub>2</sub> (1.0)/air, <i>c</i> hex	0.001/6	100	<5
5	254	l <sub>2</sub> (1.0)/air, <i>c</i> hex	0.001/6	60	20
6	300	l <sub>2</sub> (1.0)/air, <i>c</i> hex	0.001/6	100	<5
7	254	l <sub>2</sub> (1.0)/air, <i>c</i> hex	0.01/6	100	<10
8	254	l <sub>2</sub> (1.0)/air, <i>c</i> hex	0.001/12	90	40
9	254	I <sub>2</sub> (1.0)/air, <i>c</i> hex	0.001/24	100	35
10	254	I <sub>2</sub> (1.0)/air, <i>t</i> BuOH/benzene	0.001/12	100	20
11	254	I <sub>2</sub> (1.0)/PO, <i>c</i> hex	0.001/12	80	50
12	254	I <sub>2</sub> (1.0)/PO, <i>c</i> hex	0.001/24	100	30
13	254	PIDA, dioxane	0.001/12	30	10

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

Abbreviations: chex, cyclohexane; equiv, equivalent; o-DCB, ortho-dichlorobenzene; PIDA, (diacetoxyiodo)benzene; PO, propene oxide.

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[ $\alpha$ ]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<sup>31</sup> of the corresponding silvl enol ether proceeded smoothly to produce the desired  $\alpha$ -hydroxyl ketone (±)-11 in 70% yield, an enantioselective  $\alpha$ -hydroxylation of ketone 3a using Davis' (S)-oxaziridine,<sup>32</sup> 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.<sup>33</sup> 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  $\ge$ 10:1), which was confirmed by nOe experiments. As chemoselective desilylation (TBS over TIPS) was problematic, desilvlation 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<sup>18</sup> cyclopropanation of (+)-2 proceeded smoothly with Et<sub>2</sub>Zn and diiodomethane to furnish ent-(+)-cinanthrenol A (ent-1) in 78% yield after deacetylation with K<sub>2</sub>CO<sub>3</sub> 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  $6\pi$ -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). <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker AV-400 spectrometer (400 MHz for <sup>1</sup>H, 100 MHz for <sup>13</sup>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; g, quartet; m, multiplet. Optical rotations were measured on a JASCO Perkin-Elmer model P-2000 polarimeter (JASCO, Easton, MD, USA). Highresolution 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<sub>4</sub>Cl (50 ml). The organic layer was collected and the aqueous layer was extracted with Et<sub>2</sub>O (3 × 50 ml). The combined organic fractions were washed with H<sub>2</sub>O (3 × 30 ml), brine, dried over MgSO<sub>4</sub>, 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<sup>-1</sup>): 2945, 2892, 2867, 1581, 1485, 1388, 1273, 1168, 1003, 909, 883, 825, 726, 686. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  156.0, 138.2 (2C), 122.3 (2C), 83.2, 17.9 (6C), 12.6 (3C). HRMS (CI<sup>+</sup>): m/z calculated for C<sub>15</sub>H<sub>25</sub>IOSi [M]<sup>+</sup> 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 trimethylsilylace-tylene **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<sup>-1</sup>): 2947, 2895, 2869, 2158, 1602, 1505, 1278, 1250, 1096, 910, 865, 840, 686. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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<sup>+</sup>): *m/z* calculated for C<sub>20</sub>H<sub>34</sub>OSi<sub>2</sub> [M]<sup>+</sup> 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<sup>-1</sup>): 2946, 2893, 2868, 1603, 1505, 1464, 1278, 910, 882, 839, 686. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.37 (d,  $J\!=\!8.4\,\text{Hz}$ , 2H), 6.82 (d,  $J\!=\!8.4\,\text{Hz}$ , 2H), 3.00 (s, 1H), 1.31–1.18 (m, 3H), 1.09 (d,  $J\!=\!7.6\,\text{Hz}$ , 18H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  156.7, 133.6 (2C), 119.9 (2C), 114.4, 83.8, 75.8, 17.8 (6C), 12.6 (3C). HRMS (CI<sup>+</sup>): m/z calculated for  $C_{17}\text{H}_{27}\text{OSi}$  [M+H]<sup>+</sup> 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<sup>-1</sup>): 3039, 2945, 2892, 2867, 1719, 1597, 1509, 1463, 1276, 908, 883, 839, 778, 687. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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<sup>+</sup>): *m/z* calculated for C<sub>26</sub>H<sub>33</sub>O<sub>2</sub>Si [M+H]<sup>+</sup> 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<sub>2</sub> 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<sup>-1</sup>): 2944, 2867, 1716, 1601, 1509, 1464, 1270, 1169, 1090, 910, 883, 782, 686. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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<sup>+</sup>): m/z calculated for C<sub>26</sub>H<sub>34</sub>O<sub>2</sub>Si [M]<sup>+</sup> 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<sub>4</sub>Cl (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<sub>2</sub>O (3×10 ml), brine, dried over MgSO<sub>4</sub>, 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<sup>-1</sup>): 2948, 2869, 1603, 1508, 1462, 1267, 1106, 1013, 912, 883, 787, 744.  $^1\mathrm{H}$  NMR (400 MHz, CDCl<sub>3</sub>) 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). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta \ 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<sup>+</sup>): m/z calculated for  $C_{30}H_{50}O_2Si_2$  [M]<sup>+</sup> 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<sub>2</sub> (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  $(\lambda = 254 \text{ nm})$  at RT for 3–24 h. The reaction was guenched by addition of aq. satd. NaHCO3 (30 ml) and aq. satd. Na2S2O3 (30 ml). The organic layer was collected and the aqueous layer was extracted with Et<sub>2</sub>O (3×50 ml). The combined organic fractions were washed with brine, dried over MgSO4, 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% vield (entry 11). IR (neat, cm<sup>-1</sup>): 2926, 2866, 1711, 1614, 1509, 1457, 1264, 1232, 991, 924, 882, 864, 670. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) & 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<sup>+</sup>): m/z calculated for C<sub>26</sub>H<sub>32</sub>O<sub>2</sub>Si [M]<sup>+</sup> 404.2172, found 404.2176.

**3b** was obtained in 40% yield from **5b**. IR (neat, cm<sup>-1</sup>): 2947, 2869, 1617, 1600, 1508, 1457, 1232, 1103, 879, 834, 753, 685. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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<sup>+</sup>): *m/z* calculated for C<sub>32</sub>H<sub>48</sub>O<sub>2</sub>Si<sub>2</sub> [M]<sup>+</sup> 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<sub>2</sub>Cl<sub>2</sub> (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. NaHCO3 (10 ml). The organic layer was collected and the aqueous layer was extracted with CH2Cl2  $(3 \times 10 \text{ ml})$ . The combined organic fractions were washed with brine, dried over MgSO<sub>4</sub>, and concentrated under reduced pressure. The crude product was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) at 0 °C, to the resulting solution were added NaHCO3 (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 guenched by addition of aq. satd. NaHCO<sub>3</sub> (10 ml). The organic layer was collected and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>  $(3 \times 10 \text{ ml})$ . The combined organic fractions were washed with brine, dried over MgSO<sub>4</sub>, 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  $\alpha$ -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. NH4I (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 MgSO4 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  $\alpha$ -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*):  $[\alpha]_{D}^{D} = +7.5(c \ 1.0, \ CHCl_3)$ . IR (neat, cm<sup>-1</sup>): 3419, 2944, 2866, 1712, 1613, 1513, 1457, 1266, 1234, 983, 882, 841. <sup>1</sup>H NMR (400 MHz, CDCl\_3)  $\delta$  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). <sup>13</sup>C NMR (100 MHz, CDCl\_3)  $\delta$  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<sup>+</sup>): m/z calculated for C<sub>26</sub>H<sub>32</sub>O<sub>3</sub>Si [M]<sup>+</sup> 420.2121, found 420.2122.

#### Preparation of Alkene (-)-12

To a stirred solution of  $\alpha$ -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<sub>4</sub>Cl (10 ml). The organic layer was collected and the aqueous layer was extracted with Et2O (3×10 ml). The combined organic fractions were washed with H2O (3×10 ml), brine, dried over MgSO4, 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<sub>3</sub>). IR (neat, cm<sup>-1</sup>): 2928, 2860, 1724, 1613, 1513, 1460, 1262, 1128, 868, 837, 672. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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<sup>+</sup>): m/z calculated for C<sub>32</sub>H<sub>47</sub>O<sub>3</sub>Si<sub>2</sub> [M]<sup>+</sup> 535.3064, found 535.3047.

To a stirred suspension of C2H5PPh3Br (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<sub>4</sub>Cl (10 mL). The organic layer was collected and the aqueous layer was extracted with Et<sub>2</sub>O  $(3 \times 10 \text{ ml})$ . The combined organic fractions were washed with brine, dried over MgSO4 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.  $[\alpha]_{D}^{20} = -8.0(c \ 0.1, \text{CHCl}_3)$ . IR (neat, cm<sup>-1</sup>): 2924, 2854, 1617, 1460, 1376, 1261, 1085, 1019, 800. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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<sup>+</sup>): m/z calculated for C<sub>34</sub>H<sub>50</sub>O<sub>2</sub>Si<sub>2</sub> [M]<sup>+</sup> 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<sub>4</sub>Cl (10 ml). The organic layer was collected and the aqueous layer was extracted with EtOAc ( $3 \times 10$  ml). The combined organic fractions were washed with brine, dried over MgSO<sub>4</sub>, 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 µg, 0.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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. NaHCO3 (5 ml). The organic layer was collected and the aqueous layer was extracted with CH2Cl2  $(3 \times 5 \text{ ml})$ . The combined organic fractions were washed with brine, dried over MgSO<sub>4</sub>, 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<sup>-1</sup>): 3420, 2924, 1755, 1619, 1370, 1213, 1165, 840, 755. <sup>1</sup>H NMR (400 MHz,  $C_6D_6$ )  $\delta$  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). <sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>) 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<sup>+</sup>): m/z calculated for C<sub>21</sub>H<sub>18</sub>O<sub>3</sub> [M]<sup>+</sup> 318.1256, found 318.1262.

#### Preparation of ent-cinanthrenol A

To a stirred solution of (+)-2 (16 mg, 0.05 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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. NaHCO3 (5 ml). The organic layer was collected and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>  $(3 \times 5 \text{ ml})$ . The combined organic fractions were washed with brine, dried over MgSO<sub>4</sub>, 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.  $^1\mathrm{H}$  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). <sup>13</sup>C NMR (100 MHz, C<sub>5</sub>D<sub>5</sub>N) 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<sup>+</sup>): *m/z* calculated for C<sub>20</sub>H<sub>18</sub>O<sub>2</sub> [M]<sup>+</sup> 290.1307, found 290.1297.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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