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Two approaches to 14,15-secoergostane intermediates for the synthesis of strophasterols

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ABSTRACT

Two protected 14,15-secoergostane derivatives suitable as pivotal intermediates for the synthesis of strophasterols A and B, anti-MRSA and neuronal cell-protecting natural products bearing a recently discovered strophastane skeleton, have been synthesized by two different routes. The first approach employed an oxidative cleavage of an α-hydroxy ketone intermediate with the Jones reagent as the key step to reach the targeted secoergostane from ergosterol in ten steps. In the second approach, an unprecedented reaction cascade composed of four reactions enabled us to obtain the secoergostane more efficiently in six steps.

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Secosteroid; strophasterol; oxidative cleavage; cascade reaction

Strophasterol A (**1**) discovered by Kawagishi and co-workers from the edible mushroom *Stropharia rugosoannulata* is a rearranged ergostane with an unprecedented carbon skeleton that exhibits anti-MRSA and neuronal cell-protecting activities (Scheme 1) [1]. Recently, the new skeletal name "strophastane" was proposed for the secosteroidal carbon framework [2], and five strophastane-type natural products including **1** and 22-*epi*-**1** (strophasterol B) have been isolated from two species of mushrooms so far [1–3]. The totally unique carbon skeleton as well as the interesting biological profiles prompted synthetic studies on this small family of natural products, which recently culminated in the first synthesis of strophasterol A (**1**) from ergosterol (**4**) by the Heretsch group as well as our stereodivergent synthesis of strophasterols A and B from the same starting material [4,5]. In our synthesis, ergosterol (**4**) was converted into **3** by a three-step sequence involving an acid-promoted double bond migration, and the Δ^{14} double bond of **3** was oxidatively cleaved in two steps to afford 14,15-secoergostane derivative **2** (R = Ac), which was elaborated in a stereodivergent manner to strophasterols A (**1**) and B *via* D'-ring formation (see structure **1** in Scheme 1) followed by B-ring functionalization [5]. Before establishing the synthetic pathway from **4** to **2** depicted in Scheme 1, we developed two alternative approaches to the pivotal intermediate **2**, which contained some notable chemical transformations of steroidal compounds. We describe herein our first successful synthetic route from **4** to **2** [R = *tert*-butyldiphenylsilyl (TBDPS)] as well as a more efficient second approach to **2** (R = Ac) which involves an unusual cascade reaction of a γ-hydroxy-α,β-unsaturated ketone with zinc under acidic conditions.

Results and discussion

Scheme 2 delineates our first approach to **2**. To obtain the 14,15-secosteroid **2**, we initially aimed to prepare intermediate **10** bearing a keto functionality at the C15 position on the D-ring, which would probably be convertible into **2** via thermodynamically controlled formation of a tetrasubstituted silyl enol ether derivative and subsequent oxidative cleavage of its double bond. Toward this relay compound **10**, our synthetic efforts commenced with double bond migration of ergosterol (**4**) by its treatment with methanolic hydrogen chloride in chloroform at 60 °C to give **5**, which was, without purification, acetylated to afford **6** in a satisfactory yield of 90% for the two steps. This two-step conversion from **4** to **6** had previously been conducted by treating **4** with hydrogen chloride in a mixture of acetic acid and chloroform at reflux and subsequently acetylating the resulting product, providing **6** in a lower yield of 60% [6]. The installation of a keto functionality at the C15 position of **6** was effected by the Jones oxidation of **6** according to the literature procedure [7], giving **7** in 44% yield in a small-scale experiment (50 mg of **6**); unfortunately, this oxidation reaction, when conducted on gram scales, resulted in lower yields of **7** (25–30%). Reduction of the resulting γ-hydroxy-α,β-unsaturated ketone **7** with zinc dust (12 equiv.) and sulfuric acid (5 equiv.) in MeOH/

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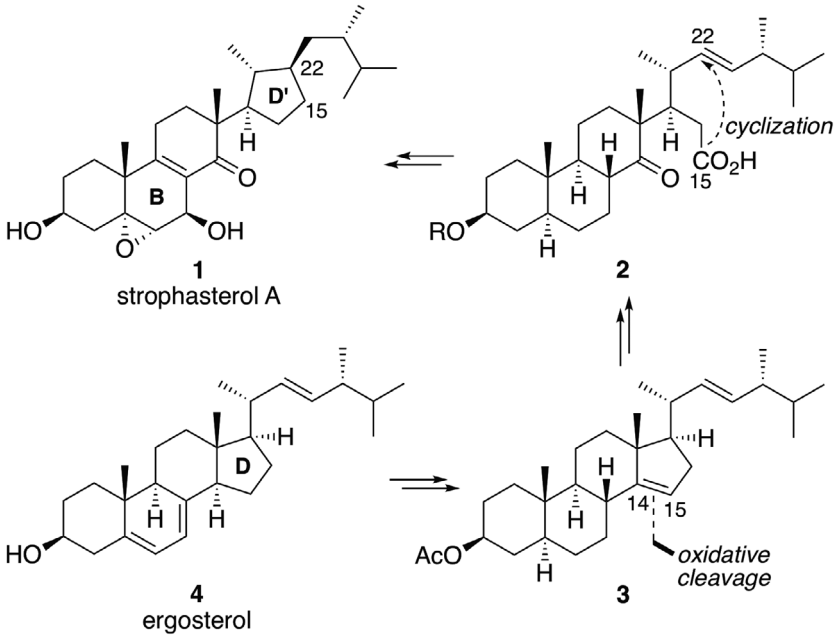
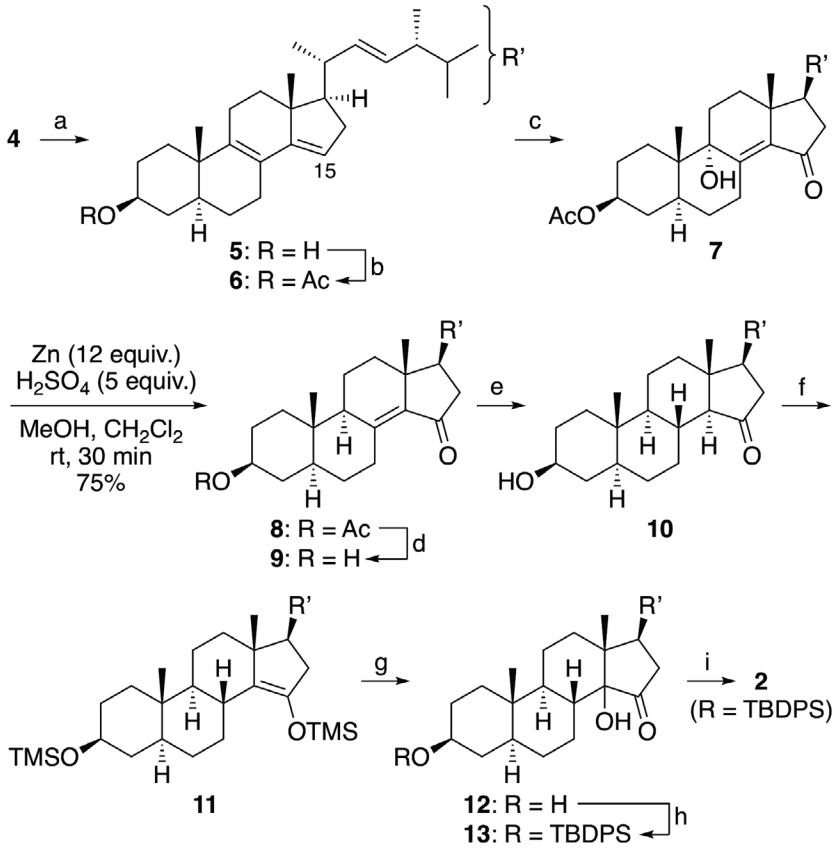


Scheme 1. Outline of our previous synthesis of strophasterol A (**1**) from ergosterol (**4**) *via* 14,15-secoergostane intermediate **2**.

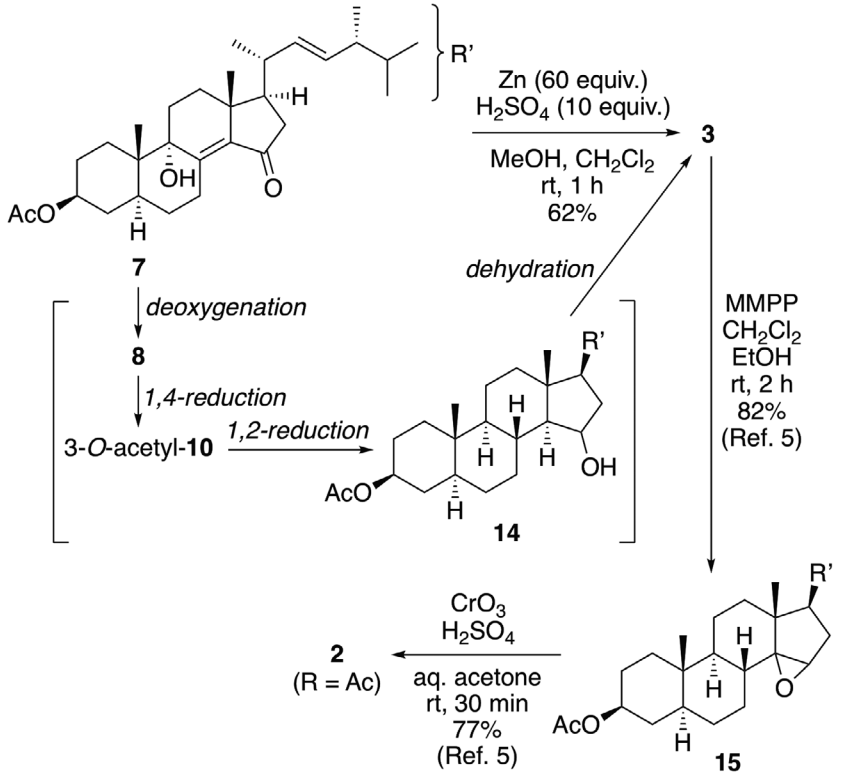


Scheme 2. First approach to 14,15-secoergostane intermediate **2**. Reagents and conditions: (a) HCl/MeOH, $CHCl_3$, 60 °C, 3 h; (b) AcCl, Py, rt, 1 h, 90% from **4**; (c) CrO_3, H_2SO_4, aq. acetone, rt, 10 min, 44%; (d) KOH, CH_2Cl_2, MeOH, rt, 30 min, 85%; (e) Li, liq. NH_3, THF, –78 °C, 3 h, 80%; (f) TMSCl, LiI, $(TMS)_2NH$, CH_2Cl_2, rt, 12 h; (g) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 2 h, then 2 M HCl, rt, 3 h, 75% from **10**; (h) TBDPSCl, imidazole, THF, DMF, rt, 3 h; (i) CrO_3, H_2SO_4, aq. acetone, rt, 30 min, 79% from **12**.

CH_2Cl_2 gave the corresponding deoxygenated enone **8** [8], which was then subjected to methanolysis under basic conditions to afford enone **9** [9,10]. The Birch reduction of **9** furnished **10** bearing a keto group on the D-ring, the ^1H and ^{13}C NMR spectral data of which showed good agreement with those of an authentic compound prepared *via* a different route by Litvinovskaya and co-workers [11]. Treatment of **10** with trimethylsilyl

(TMS) chloride, LiI, and $(TMS)_2NH$ in CH_2Cl_2 at room temperature brought about silyl enol etherification of the C15 carbonyl and protection of the C3 hydroxyl to afford **11** [12], which was immediately exposed to the Rubottom oxidation conditions, giving α-hydroxy ketone **12**; the TMS protecting group of the C3 hydroxy function was removed by aqueous HCl treatment during the workup of the oxidation reaction. It is noteworthy that compound **12** was obtained as a single stereoisomer, although its stereochemistry was not determined. To obtain the target molecule **2** (R = TBDPS), the α-hydroxy ketone **12** was protected as its TBDPS ether **13** and subjected to various conditions including $NaIO_4$ in acetone at 60 °C, $Pb(OAc)_4$ in benzene at room temperature, and $Pb(OAc)_4$ in aq. AcOH at 50 °C. All the conditions using $NaIO_4$ or $Pb(OAc)_4$ as the oxidizing agent, however, resulted in the recovery of the starting material **13**. The only successful outcome was obtained by treating **13** with the Jones reagent in acetone at room temperature, furnishing **2** (R = TBDPS) in 79% yield from **12** [13]; it is worth mentioning that the use of the Jones reagent for this type of cleavage was rare in the total synthesis of natural products [14,15]. Although the transformation of ergosterol **4** into the D-ring cleaved intermediate **2** suitable for the synthesis of strophasterols was thus achieved, it required a considerably lengthy 10-step sequence (12% overall yield), which prompted us to seek a more efficient synthetic route.

During the efforts to convert **7** into **8** in our first approach, we noticed that a trace amount of the dienic product **3** (see Scheme 1) existed in the crude product mixture by carefully inspecting minor products in the deoxygenation step. We envisaged that if regioselective epoxidation of the Δ^{14} double bond in the 14,22-diene **3** could be realized, the epoxide ring installed might be oxidatively cleaved to give **2** . According to these considerations, we scrutinized reaction conditions capable of producing more amounts of **3** directly from **7**, and found that the use of a large excess of zinc as the reducing agent was effective to give **3** as the major product (Scheme 3). The best result was obtained by treating **7** with 60 equiv. of zinc dust and sulfuric acid (10 equiv.) in $MeOH/CH_2Cl_2$, providing **3** in a much improved yield of 62%. The direct formation of **3** from **7** might mean that the following four-reaction cascade took place under the reductive conditions: (1) γ-deoxygenation of the γ-hydroxy-α,β-unsaturated ketone **7** to enone **8**; (2) 1,4-reduction of **8** to form saturated ketone 3-*O*-acetyl-**10**; (3) 1,2-reduction of 3-*O*-acetyl-**10** to alcohol **14**; and (4) dehydration of **14** in the presence of an excess amount of sulfuric acid to deliver trisubstituted olefin **3**. During this cascade reaction, the formation of **8** was clearly observed by TLC monitoring and it gradually changed into **3**, although we could not confirm the formation of 3-*O*-acetyl-**10** and **14**. To the best of our knowledge, this type consecutive transformations in one pot have never been reported in the literature. The regioselective epoxidation of **3** and the oxidative cleavage of the resulting epoxide **15** were conducted, as reported previously [5], with magnesium bis(monoperoxyphthalate) (MMPP) and chromic acid, respectively, furnishing **2** (R = Ac) in 63% yield for the two steps;



Scheme 3. Second approach to 14,15-secoergostane intermediate **2**.

the conversion of **15** into **2** would probably involve the epoxide ring opening of **15** to the corresponding vicinal diol intermediate (14,15-diol) under the acidic conditions and subsequent oxidation of its secondary hydroxy group with chromic acid to afford **13** (R = Ac) (see Scheme 1). By this second approach, we were able to obtain **2** in a more efficient manner from ergosterol **4** (6 steps, 16% overall yield).

In summary, the 14,15-secoergostane **2**, a key intermediate in our synthesis of strophasterols, was synthesized by two different approaches. In the first approach, we could reach the target molecule **2** (R = TBDPS) from ergosterol **4** *via* 15-keto steroidal intermediate **10** by a ten-step sequence that involved oxidative cleavage of the α-hydroxy ketone intermediate **13** with the Jones reagent. In the second approach, we found an unusual four-reaction cascade to convert the γ-hydroxy-α,β-unsaturated ketone intermediate **7** into the olefinic intermediate **3** with a large excess of zinc, which enabled us to obtain **2** (R = Ac) more efficiently in a smaller number of steps (6 steps).

Experimental

General procedure

IR spectra were recorded by a Jasco FT/IR-4100 spectrometer using an ATR (ZnSe) attachment. NMR spectra were recorded with TMS as an internal standard in $CDCl_3$ by a Varian 400-MRTT spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C). Optical rotation values were measured with a Jasco P-2200 polarimeter. Mass spectra were obtained with JEOL JMS-700 spectrometer operated in the EI mode. Melting points were determined with a Yanaco MP-J3 apparatus and are uncorrected. Kanto Kagaku silica gel 60 N (100–210 μm) was used for column chromatography. Solvents for reactions were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2 and DMF from CaH_2; MeOH from $Mg(OMe)_2$. All air- or moisture-sensitive reactions were conducted under a nitrogen atmosphere.

*(3S,5S,10S,13R,17R)-17-((2R,5R,E)-5,6-dimethylhept-3-en-2-yl)-10,13-dimethyl-2,3,4,5,6,7,10,11,12,13,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate (**6**)*

To a stirred solution of **4** (10.0 g, 25.2 mmol) in $CHCl_3$ (133 mL) was added 1.25 M HCl in MeOH (26.2 mL, 27.2 mmol) at room temperature and the mixture was stirred at 60 °C for 3 h. The mixture was quenched with satd aq $NaHCO_3$ and extracted with $CHCl_3$. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo* to give crude **5** (10.2 g) as a yellow solid which was used in the next step without further purification. To a stirred solution of crude **5** (10.2 g) in pyridine (64 mL) was added AcCl (3.0 mL, 42.8 mmol) at room temperature. After 1 h of stirring, the mixture was diluted with water and extracted with $CHCl_3$. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20:1) to give **6** (9.95 g, 90% from **4**) as a white solid. Mp 145–146 °C; $[\alpha]_D^{20}$ −54.6 (*c* 1.57, $CHCl_3$); IR: ν_{max} 3053 (w), 1730 (s), 1371 (m), 1265 (s); ^1H NMR: δ 0.81–0.86 (9H, m), 0.93 (3H, d, *J* = 6.8 Hz), 1.00 (3H, s), 1.04 (3H, d, *J* = 6.6 Hz), 1.30 (1H, dt, *J* = 4.2, 13.6 Hz), 1.37–1.62 (8H, m), 1.69–1.75 (1H, m), 1.83–1.93 (3H, m), 1.96–2.41 (11H, m), 4.71 (1H, tt, *J* = 5.4, 11.0 Hz), 5.20 (1H, dd, *J* = 7.6, 15.2 Hz), 5.26 (1H, dd, *J* = 7.0, 15.2 Hz), 5.34 (1H, br s); ^{13}C NMR: δ 15.8, 17.6, 18.2, 19.6, 19.9, 20.9, 21.4, 21.7, 25.1, 26.5, 27.6, 33.0, 34.1, 35.0, 36.5, 36.6, 36.8, 38.9, 40.7, 42.8, 44.7, 57.0, 73.3, 117.9, 123.2, 132.0, 135.5, 140.3, 150.7, 170.6; HRMS (EI): *m*/*z* calcd. for $C_{30}H_{46}O_2$, 438.3498; found, 438.3501 (M^+).

*(3S,5S,9S,10S,13R,17R)-17-((2R,5R,E)-5,6-dimethylhept-3-en-2-yl)-9-hydroxy-10,13-dimethyl-15-oxo-2,3,4,5,6,7,9,10,11,12,13,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate (**7**)*

To a stirred solution of **6** (50 mg, 0.114 mmol) in acetone (4 mL) was added dropwise the Jones reagent (2.65 M, 84 μL, 0.228 mmol) at room temperature. After 10 min of stirring at the same temperature, the mixture was quenched with 2-propanol, diluted with water, and concentrated *in vacuo* to some extent. The residue was extracted with ether and the extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to give **7** (23.7 mg, 50.3 μmol, 44%) as a white solid. Mp 197–198 °C; $[\alpha]_D^{20}$ + 110.1 (*c* 1.38, $CHCl_3$); IR: ν_{max} 3471 (m), 1722 (s), 1687 (s), 1620 (m), 1252 (s); ^1H NMR: δ 0.80–0.85 (9H, m), 0.91 (3H, d, *J* = 6.8 Hz), 0.98 (3H, s), 1.10 (3H, d, *J* = 6.7 Hz), 1.22–1.37 (2H, m), 1.39–1.66 (8H, m), 1.72–2.08 (11H, m), 2.13–2.24 (2H, m), 2.29 (1H, dd, *J* = 8.0, 19.2 Hz), 3.92 (1H, ddd, *J* = 2.0, 4.5, 14.6 Hz), 4.72 (1H, tt, *J* = 5.4, 11.0 Hz), 5.16 (1H, dd, *J* = 8.5, 15.3 Hz), 5.27 (1H, dd, *J* = 7.9, 15.3 Hz); ^{13}C NMR: δ 15.5, 17.5, 17.7, 19.7, 20.0, 21.4 (2C), 22.6, 26.9, 27.8, 28.3, 29.4, 33.0, 33.5, 33.7, 35.1, 39.2, 41.3, 42.91, 42.93, 43.0, 50.5, 72.9, 74.3, 133.6, 134.0, 141.6, 148.0, 170.6, 208.4; HRMS (EI): *m*/*z* calcd. for $C_{30}H_{46}O_4$, 470.3396; found, 470.3399 (M^+).

*(3S,5S,9R,10S,13R,17R)-17-((2R,5R,E)-5,6-dimethylhept-3-en-2-yl)-10,13-dimethyl-15-oxo-2,3,4,5,6,7,9,10,11,12,13,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate (**8**)*

To a stirred solution of **7** (1.63 g, 3.47 mmol) in a mixed solvent of MeOH (181 mL) and CH_2Cl_2 (44 mL) was added at room temperature a solution of concentrated H_2SO_4 (0.92 mL, 17 mmol) in MeOH (17.1 mL) by using a syringe pump over a period of 1 h, during which activated zinc powder (1.36 g, 20.8 mmol) was also added portionwise. After 15 min, additional activated

zinc powder (1.36 g, 20.8 mmol) was added, and the stirring was continued for another 15 min. The mixture was quenched with solid $NaHCO_3$ and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to remove MeOH and extracted with CH_2Cl_2. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 15:1) to give **8** (1.19 g 75%) as a white solid. Mp 160 °C; $[\alpha]_D^{20}$ + 65.7 (*c* 1.08, $CHCl_3$); IR: ν_{max} 1739 (s), 1698 (s), 1623 (m), 1264 (s); ^{1}H NMR: δ 0.73 (3H, s), 0.82 (3H, d, *J* = 6.9 Hz), 0.84 (3H, d, *J* = 7.0 Hz), 0.91 (3H, d, *J* = 6.8 Hz), 0.99 (3H, s), 1.09 (3H, d, *J* = 6.6 Hz), 1.20–1.78 (14H, m), 1.80–1.91 (3H, m), 1.98–2.28 (7H, m), 4.12 (1H, ddd, *J* = 1.9, 4.1, 14.2 Hz), 4.73 (1H, tt, *J* = 5.4, 11.0 Hz), 5.16 (1H, dd, *J* = 8.5, 15.3 Hz), 5.26 (1H, dd, *J* = 7.8, 15.3 Hz); ^{13}C NMR: δ 12.7, 17.6, 18.8, 19.4, 19.5, 19.9, 21.26, 21.34, 27.1, 27.3, 28.9, 32.9, 33.5, 36.1, 36.7, 38.5, 39.2, 42.2, 42.77, 42.79, 43.8, 50.6, 50.7, 73.0, 133.1, 134.2, 140.2, 149.9, 170.4, 207.7; HRMS (EI): *m*/*z* calcd. for $C_{30}H_{46}O_3$, 454.3447; found, 454.3444 (M^+).

*(3S,5S,9R,10S,13R,17R)-17-((2R,5R,E)-5,6-dimethylhept-3-en-2-yl)-3-hydroxy-10,13-dimethyl-1,2,3,4,5,6,7,9,10,11,12,13,16,17-tetradecahydro-15H-cyclopenta[a]phenanthren-15-one (**9**)*

To a stirred solution of **8** (1.04 g, 2.29 mmol) in CH_2Cl_2 (20 mL) was added a solution of KOH (5% in MeOH, 70 mL, 62 mol) at room temperature. After stirring for 30 min, the reaction mixture was quenched with satd aq NH_4Cl and extracted with CH_2Cl_2. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3:1) to give **9** (0.810 g, 85%) as a white solid. Mp 157–158 °C; $[\alpha]_D^{20}$ + 81.7 (*c* 0.50, $CHCl_3$); IR: ν_{max} 3417 (br), 1704 (s), 1623 (s), 1455 (m); ^{1}H NMR: δ 0.72 (3H, s), 0.82 (3H, d, *J* = 7.0 Hz), 0.83 (3H, d, *J* = 7.0 Hz), 0.91 (3H, d, *J* = 6.9 Hz), 0.99 (3H, s), 1.09 (3H, d, *J* = 6.6 Hz), 1.15–1.76 (15H, m), 1.80–1.90 (3H, m), 1.99–2.28 (4H, m), 3.65 (1H, tt, *J* = 5.2, 10.7 Hz), 4.09–4.16 (1H, m), 5.16 (1H, dd, *J* = 8.5, 15.4 Hz), 5.26 (1H, dd, *J* = 7.8, 15.4 Hz); ^{13}C NMR: δ 12.8, 17.6, 18.9, 19.5, 19.6, 19.9, 21.4, 27.5, 29.1, 31.0, 32.9, 36.5, 36.8, 37.7, 38.7, 39.1, 42.3, 42.84, 42.85, 44.1, 50.8, 50.9, 70.7, 133.2, 134.2, 140.2, 150.5, 207.9; HRMS (EI): *m*/*z* calcd. for $C_{28}H_{44}O_2$, 412.3341; found, 412.3340 (M^+).

*(3S,5S,8R,9S,10S,13R,14S,17R)-17-((2R,5R,E)-5,6-dimethylhept-3-en-2-yl)-3-hydroxy-10,13-dimethylhexadecahydro-15H-cyclopenta[a]phenanthren-15-one (**10**)*

To a stirred solution of Li (1.11 g, 160 mmol) in liq. NH_3 (300 mL) was added a solution of **9** (3.00 g, 7.27 mmol) in THF (80 mL) at –78 °C. After 3 h of stirring at the same temperature, the mixture was quenched with solid NH_4Cl and stirred at ambient temperature to remove NH_3. The mixture was diluted with water and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to give **10** (2.42 g, 80%) as a white solid. Mp 183–184 °C; $[\alpha]_D^{20}$ + 11.1 (*c* 0.13, $CHCl_3$); IR: ν_{max} 3419 (br), 1733 (s), 1457 (w); ^{1}H NMR: δ 0.60–0.68 (1H, m), 0.76 (3H, s), 0.79–0.85 (9H, m), 0.90 (3H, d, *J* = 6.8 Hz), 0.98 (1H, dt, *J* = 3.8, 13.4 Hz), 1.04–1.89 (22H, m), 2.06–2.17 (2H, m), 2.29 (1H, dd, *J* = 8.7, 18.8 Hz), 2.65 (1H, dq, *J* = 13.1, 3.3 Hz), 3.59 (1H, tt, *J* = 5.3, 10.8 Hz), 5.13 (1H, dd, *J* = 8.4, 15.4 Hz), 5.24 (1H, dd, *J* = 7.8, 15.3 Hz); ^{13}C NMR: δ 12.2, 13.2, 17.7, 19.6, 20.0, 20.8, 21.3, 28.2, 29.7, 30.6, 31.4, 31.9, 33.0, 35.6, 36.9, 38.1, 39.8, 42.2, 42.3, 42.9, 44.8, 51.2, 54.0, 66.0, 71.2, 133.3, 134.3, 216.2; HRMS (EI): *m*/*z* calcd. for $C_{28}H_{46}O_2$, 414.3498; found, 414.3498 (M^+).

*(3R,4R,7R,E)-3-((2R,4aS,4bS,7S,8aS,10aR)-7-acetoxy-2,4b-dimethyl-1-oxotetradecahydrophenanthren-2-yl)-4,7,8-trimethylnon-5-enoic acid (**12**)*

To a stirred solution of **10** (1.89 g, 4.56 mmol) and $(TMS)_2NH$ (14.9 mL, 71.4 mmol) in CH_2Cl_2 (63 mL) were successively added LiI (2.24 g, 16.7 mmol) and TMSCl (6.08 mL, 47.6 mmol) at room temperature. After 12 h of stirring at same temperature, the mixture was quenched with satd aq $NaHCO_3$ and Et_3N, and extracted with ether. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo* to give crude **11** as a white solid. To a stirred mixture of crude **11** (2.56 g, 4.58 mmol) and $NaHCO_3$ (0.60 g, 7.1 mmol) in CH_2Cl_2 (35 mL) was added *m*-CPBA (1.17 g, 4.76 mmol) at 0 °C. After 2 h of stirring at room temperature, the mixture was quenched with satd aq $Na_2S_2O_3$ and extracted with CH_2Cl_2. The CH_2Cl_2 solution was mixed with 2 M HCl and stirred for 3 h at room temperature. The resulting mixture was extracted with CH_2Cl_2 and the extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to give **12** (1.47 g, 75%) as a white solid. Mp 241–242 °C; $[\alpha]_D^{20}$ + 7.7 (*c* 0.65, $CHCl_3$); IR: ν_{max} 3750 (br), 1733 (s), 1457 (w); ^{1}H NMR: δ 0.78–0.85 (12H, m), 0.90 (3H, d, *J* = 6.9 Hz), 0.94–2.21 (26H, m), 2.45 (1H, dq *J* = 12.5, 3.4 Hz), 2.53 (1H, dd, *J* = 9.0, 19.3 Hz), 3.59 (1H, tt, *J* = 5.3, 10.7 Hz), 5.14 (1H, dd, *J* = 8.4, 15.3 Hz), 5.24 (1H, dd, *J* = 7.7 15.3 Hz); ^{13}C NMR: δ 12.1, 14.2, 17.6, 19.6, 19.9, 20.0, 21.3, 25.8, 28.2, 30.3, 31.4, 33.0, 34.6, 35.8, 37.0, 38.0, 39.8, 40.7, 42.8, 44.3, 44.6, 45.8, 46.8, 71.1, 82.6, 133.1, 134.7, 214.6; HRMS (EI): *m*/*z* calcd. for $C_{28}H_{46}O_3$, 430.3447; found, 430.3446 (M^+).

*(3R,4R,7R,E)-3-((2R,4aS,4bS,7S,8aS,10aR)-7-((tert-butyldiphenylsilyl)oxy)-2,4b-dimethyl-1-oxotetradecahydrophenanthren-2-yl)-4,7,8-trimethylnon-5-enoic acid (**2**: R = TBDPS)*

To a stirred solution of **12** (1.52 g, 3.65 mmol) in a mixed solvent of DMF (10 mL) and THF (4 mL) were

successively added imidazole (0.745 g, 11.0 mmol) and TBDPSCl (1.42 mL, 5.48 mmol) at room temperature. After 3 h of stirring at the same temperature, the mixture was quenched with satd aq NH_4Cl and extracted with ether. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo* to give crude **13** (2.35 g) as a white solid, which was taken up in acetone (100 mL). To the solution was added dropwise the Jones reagent (2.65 M, 7.97 mL, 21.1 mmol) while stirring at room temperature. After 30 min, the mixture was quenched with 2-propanol, diluted with water, and concentrated *in vacuo* to some extent. The residue was extracted with ether and the extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to give **2** (R = TBDPS) (1.98 g, 79% from **12**) as an amorphous solid. $[\alpha]_D^{20}$ + 6.6 (*c* 1.00, $CHCl_3$); IR: ν_{max} 3070 (br), 1737 (m), 1704 (s), 1427 (m), 1251 (m); ^{1}H NMR: δ 0.72–1.69 (43H, m), 1.78–1.91 (3H, m), 2.19 (1H, dd, *J* = 4,3, 16.3 Hz), 2.25–2.37 (2H, m), 2.41–2.52 (2H, m), 3.57 (1H, tt, *J* = 5.1, 10.4 Hz), 5.21 (1H, dd, *J* = 7.6, 15.3 Hz), 5.29 (1H, dd, *J* = 8.2, 15.3 Hz), 7.33–7.44 (6H, m), 7.65–7.69 (4H, m); ^{13}C NMR: δ 11.8, 14.1, 17.4, 19.1, 19.7, 20.0, 20.3, 20.6, 22.0, 22.6, 26.2, 26.9 (3C), 27.5, 31.5, 31.6, 33.0, 34.5, 36.2, 36.7, 37.8, 37.9, 43.1, 43.5, 44.2, 45.1, 51.6, 54.3, 72.4, 127.41, 127.43, 129.41, 129.44, 132.0, 134.6 (2C), 134.7 (2C), 135.0, 135.71, 135.72, 179.3, 218.0; HRMS (EI): *m*/*z* calcd. for $C_{44}H_{64}O_4Si$, 685.4574; found, 685.4576 (M^+).

*(3S,5S,8R,9S,10S,13R,17R)-17-((2R,5R,E)-5,6-dimethylhept-3-en-2-yl)-10,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate (**3**)*

To a stirred solution of **7** (1.63 g, 3.47 mmol) in a mixed solvent of MeOH (180 mL) and CH_2Cl_2 (44 mL) were added dropwise a solution of concentrated H_2SO_4 (1.84 mL, 35 mmol) in MeOH (36.5 mL) over a period of 1 h, during which activated zinc powder (13.6 g, 208 mmol) was also added portionwise. The mixture was quenched with solid $NaHCO_3$ and filtered through a pad of Celite. The filtrate was extracted with CH_2Cl_2 and the extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20:1) to give **3** (0.948 g, 62%) as a white solid. The physical and spectroscopic properties of **3** were identical with those of an authentic sample [5].

Author contribution

S.K. and S.S. designed the synthetic route. S.K., Y.O., and S.S. wrote the manuscript. Y.F. conducted the synthetic experiments with the aid of Y.O. and S.S.

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Disclosure statement

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