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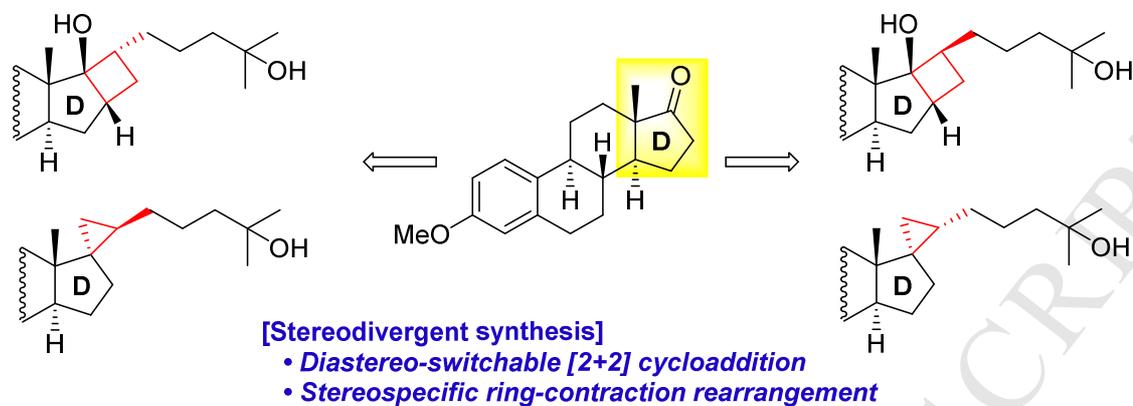
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## Graphical Abstract



### Synthesis of Steroidal Derivatives Bearing a Small Ring Using a Catalytic [2+2] Cycloaddition and a Ring-Contraction Rearrangement

Norihito Arichi, Kenji Hata, Yoshiji Takemoto, Ken-ichi Yamada, Yousuke Yamaoka, and Kiyosei Takasu\*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

E-mail: kay-t@pharm.kyoto-u.ac.jp

Fax: +81 75 753 4604; Tel: +81 75 753 4553

**Abstract**

Fixing conformation by introducing a ring structure is a common strategy in drug development. We demonstrate a synthesis that installs a small carbocyclic ring as a structurally-rigid unit in drug lead compounds. Both *trans*- and *cis*-cyclobutane rings were constructed in excellent selectivities by controlling the reaction temperature of an EtAlCl<sub>2</sub>-catalyzed [2+2] cycloaddition between a silyl enol ether and an  $\alpha,\beta$ -unsaturated ester. Spirocyclopropane rings were stereospecifically formed by our previously reported ring-contraction rearrangement of fused cyclobutanols. This strategy allowed stereodivergent access to a new class of steroidal derivatives bearing a small ring.

**Keywords:**

steroids; cyclopropanes; cyclobutanes; [2+2] cycloaddition; ring contraction.

## 1. Introduction

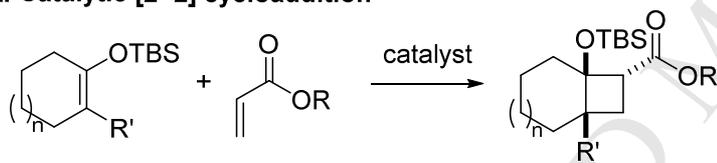
Rational drug design using protein crystal structures is a rapidly growing area in which several drug discovery success stories have emerged in recent decades. Once the structure of the binding site of the receptor or enzyme is identified, discovery of new small molecule drug leads can be accelerated by using computer simulations such as docking studies. The X-ray crystallographic structure also provides a great opportunity for the optimization of the structure of late-stage leads. For example, the spatial arrangement of the functional groups can be finely tuned at sub-angstrom ( $\text{\AA}$ ) resolution in accordance with the crystallographic structure of the binding site. Conformational fixation of flexible drug leads is a popular tactic used to increase activity and/or reduce side effects. A rotatable side chain on the drug scaffold can be restricted by incorporating a structurally rigid moiety such as a double bond, alkyne, amide or aromatic ring. Small-membered carbocycles such as cyclopropane and cyclobutane rings are also used to restrict rotatable side chains in drug development, owing to their structural rigidity.<sup>1</sup> However, limited numbers of these exist, probably because of the lack of practical and stereoselective synthetic methods.<sup>2</sup>

We have reported several unique synthetic methods to construct a cyclobutane ring or a spirocyclopropane ring bearing several functional groups with high stereoselectivity. Catalytic [2+2] cycloaddition of readily available silyl enol ethers and  $\alpha,\beta$ -unsaturated esters in the presence of an acid

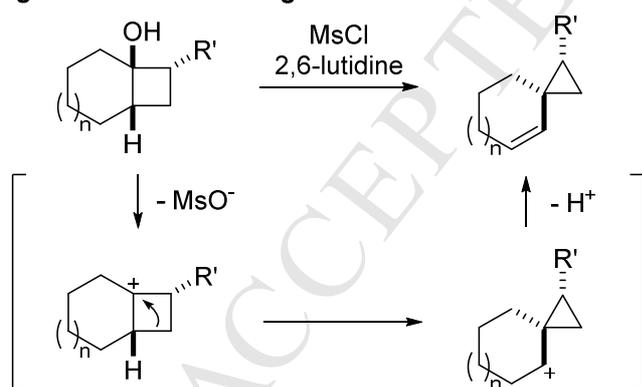
catalyst, such as  $\text{EtAlCl}_2$  and triflic imide ( $\text{Tf}_2\text{NH}$ ), affords functionalized cyclobutanes (Scheme 1A).<sup>3</sup> The cycloaddition occurs through a stepwise Michael–aldol addition pathway in a diastereoselective manner. A stereospecific ring-contraction rearrangement of fused cyclobutanols to give spirocyclopropanes was also reported (Scheme 1B).<sup>4</sup> This rearrangement proceeds through a tertiary carbocationic intermediate, which then undergoes rearrangement of the adjacent carbon–carbon bond with release of strain energy.

### Scheme 1. Our Methods for Constructing Small Rings

#### A. Catalytic [2+2] cycloaddition



#### B. Ring-contraction rearrangement



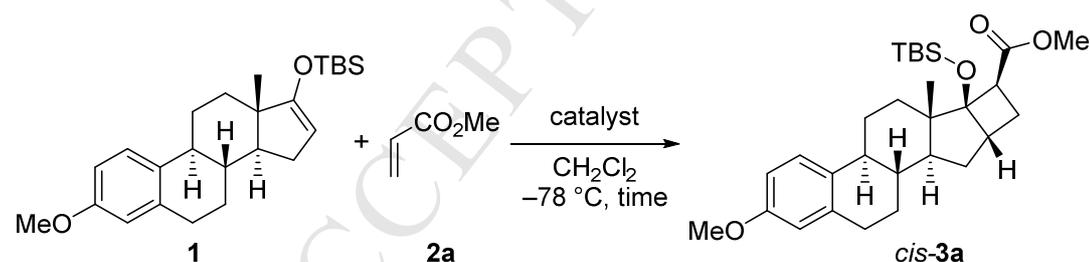
We envisaged application of this methodology to the stereoselective synthesis of drug derivatives, incorporating a cyclobutane ring or a spirocyclopropane moiety to restrict the conformation. A steroidal

scaffold was chosen as a model drug lead. Steroids are a family of bioactive compounds composed of a unique fused ring system and are widely used as drugs. However, the side effects sometimes become a limiting problem because they have diverse biological activities. For example, calcitriol, which has a steroidal backbone with an opened B-ring, modulates a broad range of biological functions such as bone homeostasis, immunity, cellular growth and differentiation through binding to the vitamin D receptor.<sup>5</sup> Although synthetic analogues of calcitriol are effective in the treatment of osteoporosis and psoriasis,<sup>6</sup> their therapeutic use is limited by severe side effects such as hypercalcemia and hypercalciuria.<sup>5c</sup> Thus, a number of calcitriol analogues have been synthesized to discover which ones display biological activities and reduced side effects better than natural steroid hormones.<sup>5c,7</sup> Mouriño reported calcitriol analogues with a locked side chain by introducing an unsaturated bond or an additional ring.<sup>8</sup> Some of the analogues exhibited significant biological activities, such as the induction of the transcriptional activity of vitamin D receptors in human colon cancer cells.<sup>8c</sup> Herein, we report a stereodivergent synthesis of steroidal derivatives bearing a small ring using a [2+2] cycloaddition and stereospecific ring-contraction rearrangement. During the course of our synthetic study, switching the diastereoselectivity of the [2+2] cycloaddition depending on the reaction temperature was observed. The mechanistic insight of this is also discussed.<sup>9</sup>

## 2. Results and discussion

At the outset of the study, the [2+2] cycloaddition of silyl enol ether **1**, prepared from estrone 3-methyl ether, with methyl acrylate (**2a**) was investigated (Table 1). When silyl enol ether **1** was treated with 1.3 equivalents of **2a** at  $-78\text{ }^{\circ}\text{C}$  in the presence of 1.0 mol% of  $\text{Tf}_2\text{NH}$ , cyclobutane *cis*-**3a** was afforded in only 5% yield (entry 1). There was a decrease or slight increase in yield when using more equivalents of  $\text{Tf}_2\text{NH}$  and methyl acrylate (entries 2–4). Reaction with 1,1,3,3-tetrakis(triflyl)propane ( $\text{Tf}_2\text{CHCH}_2\text{CHTf}_2$ )<sup>10</sup> resulted in no significant improvement in yield (entry 5), whereas  $\text{EtAlCl}_2$  was an effective catalyst and afforded *cis*-**3a** in 77% yield (entry 6).

**Table 1.** Catalyst Screening for the [2+2] Cycloaddition of **1** with **2a**

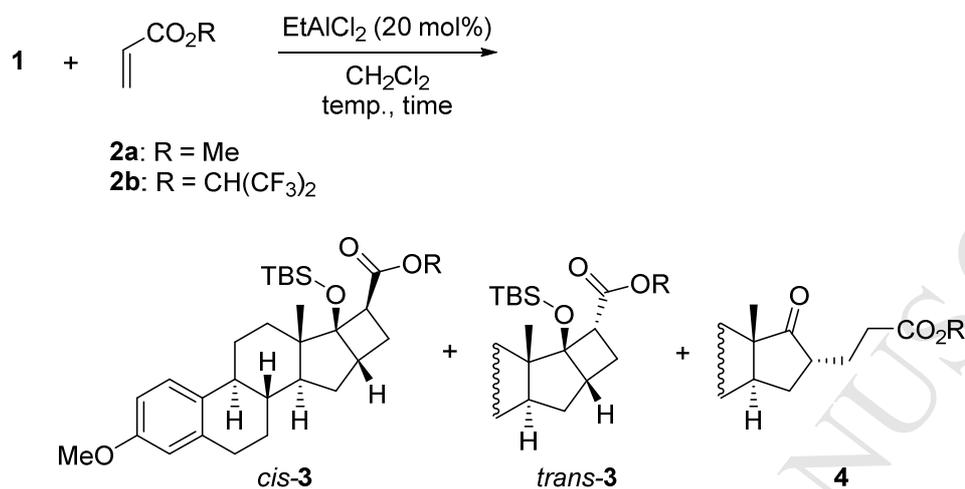


entry	catalyst (mol%)	<b>2a</b> (equiv)	time (h)	yield of <i>cis</i> - <b>3a</b> (%) <sup>a</sup>
1	$\text{Tf}_2\text{NH}$ (1.0)	1.3	2.5	5
2	$\text{Tf}_2\text{NH}$ (5.0)	1.3	2.5	4
3	$\text{Tf}_2\text{NH}$ (5.0)	2.5	1.0	33
4	$\text{Tf}_2\text{NH}$ (20)	2.5	2.0	10

5	Tf <sub>2</sub> CHCH <sub>2</sub> CHTf <sub>2</sub> (20)	2.5	2.0	17
6	EtAlCl <sub>2</sub> (20)	2.0	2.0	77

<sup>a</sup> Isolated yields.

Interestingly, when using hexafluoroisopropyl (HFIP) acrylate (**2b**) instead of **2a**, we observed that the diastereoselectivity in the [2+2] cycloaddition switched depending on the reaction conditions (Table 2). Treatment of silyl enol ether **1** with **2b** in the presence of EtAlCl<sub>2</sub> at -78 °C produced *trans*-**3b** in 85% yield with high diastereoselectivity (entry 1). The *trans*-selectivity remained approximately constant regardless of the reaction time (entries 1 and 2). In contrast, the *trans*-selectivity of **3b** decreased with an increase in reaction temperature (entries 1, 3–5). When the reaction was carried out at room temperature, *cis*-**3b** was obtained exclusively in 74% yield along with 12% yield of the Michael adduct **4** (entry 5). The reaction conducted at -78 °C for 10 min, followed by stirring at room temperature for an additional 10 min, afforded only the *cis*-adduct (entry 6). The results clearly indicate that *trans*-**3b** is the kinetically favored product whereas *cis*-**3b** is the thermodynamically more stable one. Reactions with methyl acrylate (**2a**) at both room temperature (rt) and -78 °C afforded *cis*-**3a** exclusively (entry 8 and Table 1 entry 6). Even when the reaction temperature was lowered to -90 °C, *trans*-**3a** was obtained only as a minor diastereomer (entry 7). It appears that the activation energy required for isomerization of *trans*-**3** to *cis*-**3** is dependent on the ester substituent.

**Table 2.** Effect of Acrylate and Reaction Temperature in the [2+2] Cycloaddition

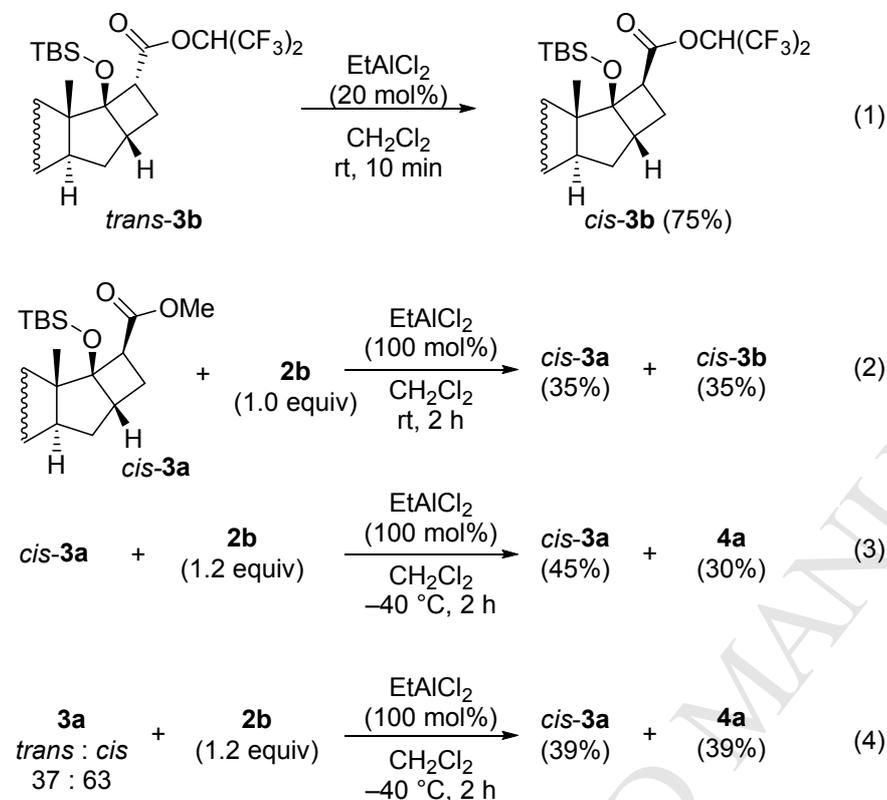
entry	acrylate <b>2</b>	temp. (°C)	time (min)	yield of <b>3</b> (%) <sup>a</sup>	<i>trans</i> : <i>cis</i>
1	<b>2b</b>	-78	10	85	95:5
2	<b>2b</b>	-78	120	89	94:6
3	<b>2b</b>	-60	10	86	64:36
4	<b>2b</b>	-40	10	89	5:95
5	<b>2b</b>	rt	120	74 <sup>b</sup>	0:100
6	<b>2b</b>	-78 then rt	10 then 10	70 <sup>b</sup>	0:100
7	<b>2a</b>	-90	10	77	35:65
8	<b>2a</b>	rt	120	72	0:100

<sup>a</sup> Isolated yields. <sup>b</sup> Michael adduct **4** was obtained in 5–12 % yield.

Crossover experiments were performed to investigate the diastereoselectivity switch further.

Treatment of *trans-3b* with EtAlCl<sub>2</sub> at ambient temperature resulted in complete conversion into *cis-3b*

(Scheme 2, eq 1), whereas no reaction occurred in the absence of EtAlCl<sub>2</sub>. Using the same catalyst at the same temperature, *cis*-**3b** did not isomerize to *trans*-**3b**. When a mixture of the methyl ester *cis*-**3a** and an equimolar of HFIP acrylate (**2b**) was treated with EtAlCl<sub>2</sub> at ambient temperature, the crossover adduct *cis*-**3b** was afforded in 35% yield as a single diastereomer, along with 35% yield of recovered *cis*-**3a** (eq 2). These results indicate that EtAlCl<sub>2</sub> promotes the retro [2+2] process to reproduce silyl enol ether **1** and acrylate **2**. HFIP acrylate (**2b**) competes with *in situ* generated methyl acrylate (**2a**) in the [2+2] cycloaddition of the regenerated silyl enol ether **1**, which results in the isolation of a mixture of *cis*-**3a** and *cis*-**3b**. In contrast, the reaction of methyl ester *cis*-**3a** at -40 °C did not provide the crossover adduct, but rather the ring-opened product **4a** in 30% yield (eq 3). In the reaction of a mixture of *trans*- and *cis*-**3a** at -40 °C, epimerization of *trans*-**3a** into *cis*-**3a** occurred along with the formation of **4a**, but no crossover product was observed (eq 4).

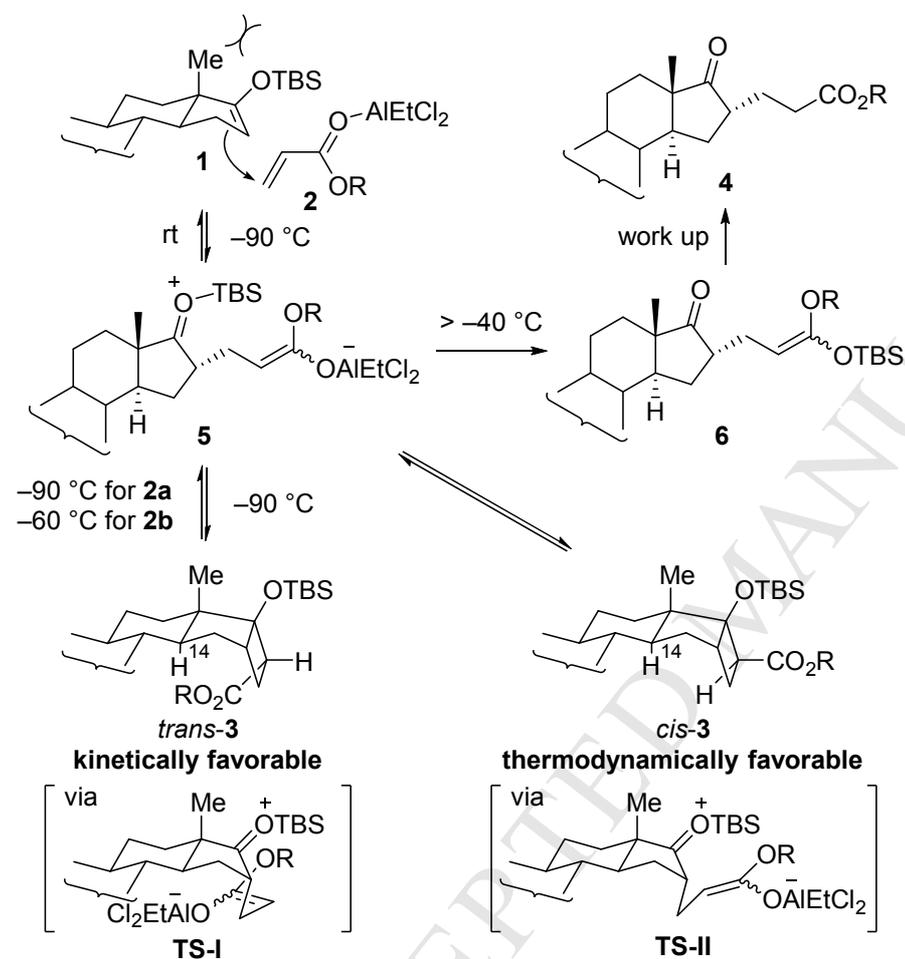
**Scheme 2.** Mechanistic Insights into the EtAlCl<sub>2</sub>-Catalyzed [2+2] Cycloaddition

Based on the above results, a possible mechanism for the EtAlCl<sub>2</sub>-catalyzed [2+2] cycloaddition of **1** is shown in Figure 1. Michael addition of silyl enol ether **1** to acrylate **2** proceeds predominantly at the less hindered  $\alpha$ -face to give zwitterionic intermediate **5**. At lower temperatures, intramolecular aldol-type addition of **5** takes place via the preferred transition state **TS-I** to give *trans*-**3**, whereas less favored **TS-II** affords *cis*-**3** because of steric effects. The product *trans*-**3** would be less stable than *cis*-**3** because of steric repulsion between the axial hydrogen atom at the C14 position and the ester moiety, which is supported by

DFT calculations of *cis*- and *trans*-**3b** ( $\Delta G^{\circ}_{cis-trans} = -12.6$  kJ/mol).<sup>11</sup> The epimerization process is rather complicated. At ambient temperature, *trans*- and *cis*-**3** equilibrate through a retro [2+2] cycloaddition via silyl enol ether **1** to provide the thermodynamically more stable *cis*-**3**. In contrast, the retro [2+2] cycloaddition does not proceed at  $-40$  °C, which indicates that the epimerization to *cis*-**3** at this temperature occurs via siloxonium ion **5** through a retro aldol reaction. In addition, ketone **4** was presumably formed by desilylation of ketene silyl acetal **6** during work-up.

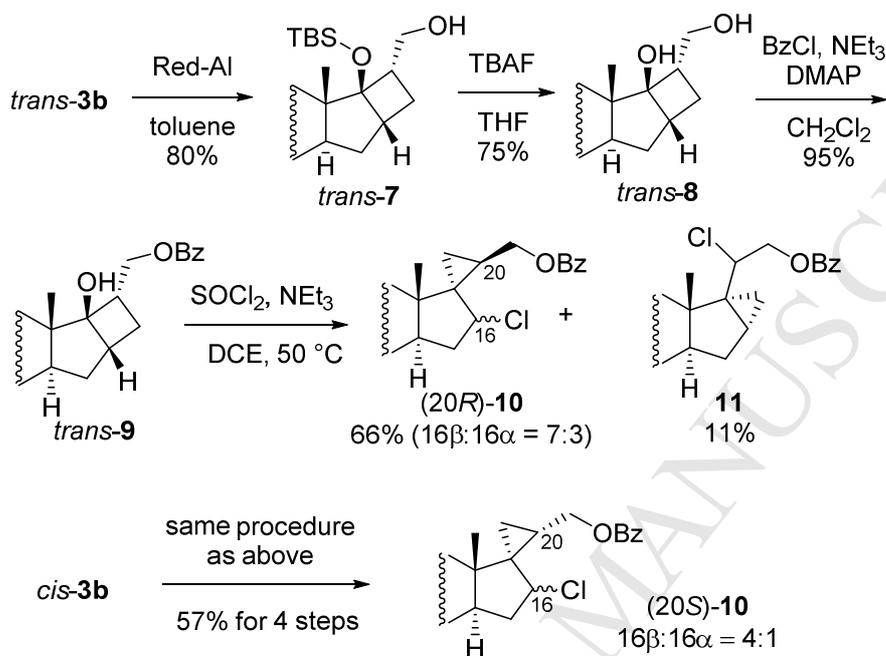
**Figure 1.** Possible Mechanism for the EtAlCl<sub>2</sub>-Catalyzed [2+2] Cycloaddition under Kinetic and

Thermodynamic Conditions



With the cyclobutane scaffolds constructed, we next investigated the ring-contraction rearrangement of cyclobutanols to give spirocyclopropanes (Scheme 3). To prepare the substrate for the ring-contraction rearrangement, *trans*-3b was treated with Red-Al to afford cyclobutanol *trans*-7 in 89% yield. Removal of the *tert*-butyldimethylsilyl (TBS) group on the tertiary hydroxyl function followed by

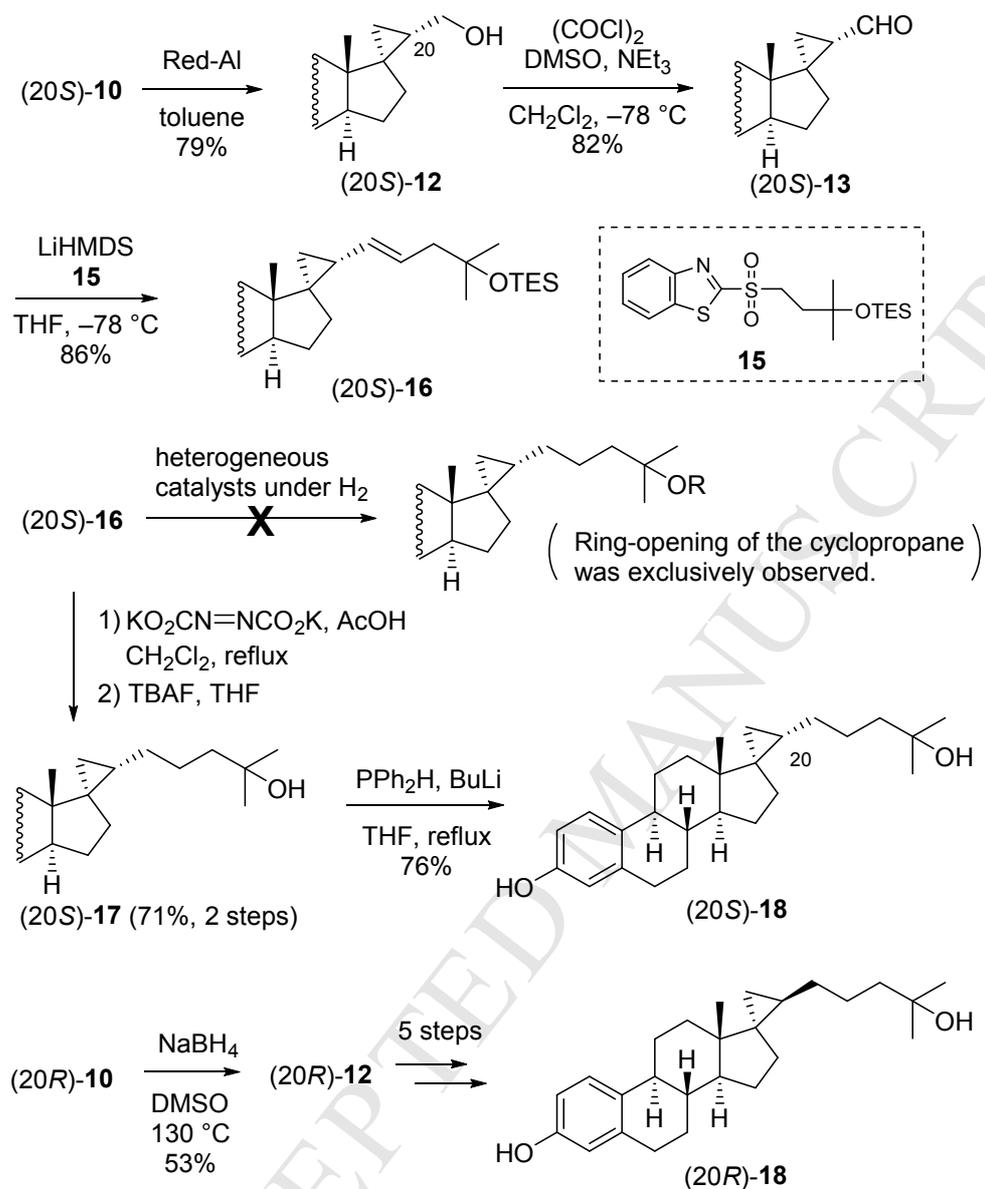
benzoyl protection of the primary hydroxyl group furnished *trans*-**9**. *Cis*-**9** was also prepared through the same procedure from *cis*-**3b**. With the substrates **9** for the ring contraction reaction in hands, the reaction conditions was firstly screened by using *cis*-**9**. According as our previous conditions,<sup>4</sup> *cis*-**9** was treated with methanesulfonyl chloride (MsCl) in 2,6-lutidine, which resulted in the formation of the mesylated product (*ca.* 30%), along with recovered starting material (*ca.* 40%). We tried other conditions such as oxalyl chloride/triethylamine and triflic anhydride/triethylamine to convert the tertiary hydroxyl group to a good leaving group; however, these attempts proved unsuccessful, and no spirocyclopropane product was observed. The ring contraction rearrangement of *cis*-**9** was finally achieved by using thionyl chloride/triethylamine to afford (2*S*)-**10** in 87% yield (16 $\beta$ :16 $\alpha$  = 4:1), the relative configuration was determined by the NOE Spectroscopy. The same conditions were successfully applied to the rearrangement of *trans*-**9** to afford (2*R*)-**10** in a stereospecific manner, albeit in lower yield (66%, 16 $\beta$ :16 $\alpha$  = 7:3). In these reactions, the carbocationic intermediates predominantly undergo nucleophilic attack by the chloride ion to afford (2*S*)- or (2*R*)-**10**, and no elimination products are observed. The difference in yield between (2*S*)- and (2*R*)-**10** was due to the formation of byproduct **11**. We do not fully understand why the ring-contraction rearrangement of *trans*-**9** yielded this unusual product, but it may be influenced by the dihedral angle between the migrating carbon–carbon bond and the empty p-orbital of the carbocationic intermediate.

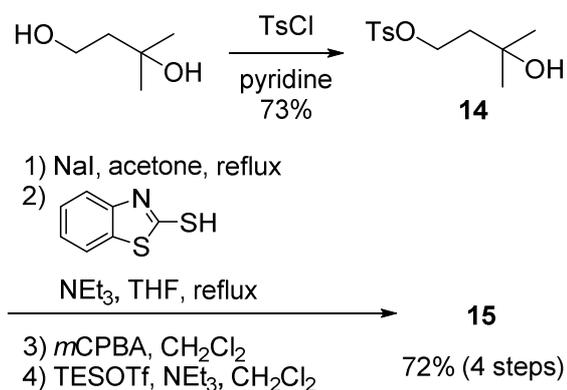
**Scheme 3.** Construction of a Spirocyclopropane Ring by Ring-Contraction Rearrangement

With the estrone derivatives bearing a small ring in hand, our attention turned toward the installation of a cholestane side chain (Scheme 4). Initially, removal of the benzoyl group and dechlorination of (20*S*)-**10** were performed in one-pot using Red-Al to give cyclopropanol (20*S*)-**12**, which was then subjected to Swern oxidation to afford aldehyde (20*S*)-**13**. Extension of the carbon chain was accomplished by one-pot Julia olefination of the aldehyde using benzothiazolyl sulfone **15**, which was prepared from 3-methyl-1,3-butanediol in five steps (Scheme 5). Triethylsilyl (TES) protection of **15** was necessary for complete conversion of the starting aldehydes in the olefination reactions. Reduction of olefin **16** was

unsuccessfully attempted by hydrogenation using Pd/C in ethyl acetate, which resulted in simultaneous ring-opening of the cyclopropane. Accordingly, several catalysts were tested for the chemoselective hydrogenation. Reduction with Pd/Fib or Pd/C(en) gave a cyclopropane ring-opened product with the intact carbon-carbon double bond. No reaction occurred using Pd/MS5A<sup>13</sup> or Pd/BN<sup>14</sup> in methanol. In the reaction with Rh/alumina in ethyl acetate, the double bond was reduced without ring-opening of the cyclopropane, but the aromatic A-ring was also reduced to a cyclohexane ring. Although these efforts using heterogeneous catalysts were unfruitful, chemoselective reduction of the olefin was achieved by diimide reduction,<sup>15</sup> which was followed by removal of the TES group to give (20*S*)-**17**. The final deprotection of the methyl group was troublesome. Treatment with BBr<sub>3</sub> or reagents such as TMSI, NaSEt, or AlMe<sub>3</sub>/NaI<sup>16</sup> gave a complex mixture, probably due to instability of the spirocyclopropane. Nevertheless, the deprotection was accomplished by using *n*-BuLi/PPh<sub>2</sub>H<sup>17</sup> to give the final product (20*S*)-**18** in 76% yield. (20*R*)-**18** was also synthesized by the similar procedure. It is worth noting that treatment of (20*R*)-**10** with Red-Al gave a considerable amount of byproducts. Reduction with sodium borohydride in DMSO at 130 °C gave (20*R*)-**12** in 53% yield with less byproduct formation.<sup>12</sup>

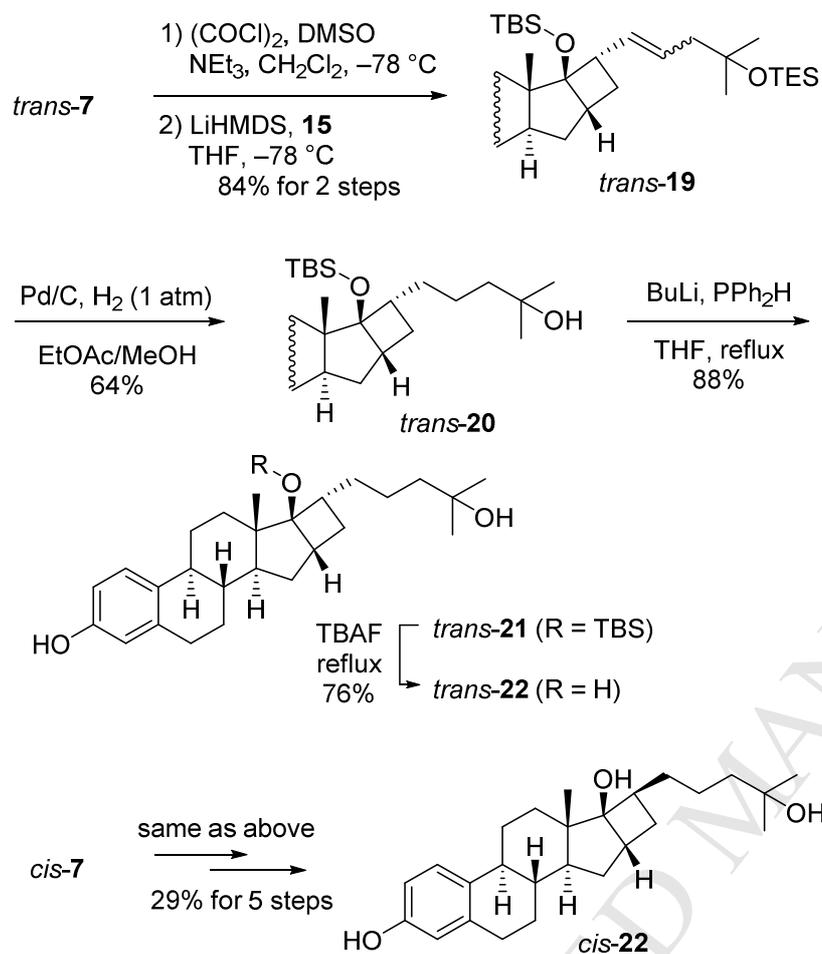
**Scheme 4.** Installation of a Side Chain and Completion of the Synthesis of (20*S*)- and (20*R*)-**18**

Scheme 5. Preparation of Benzothiazolyl Sulfone **15**



Installation of the side chain onto the cyclobutane ring was also accomplished using a similar strategy (Scheme 6). Swern oxidation followed by one-pot Julia olefination of *trans*- and *cis*-**7** afforded cyclobutanes *trans*- and *cis*-**19**, respectively. Reduction of the resulting olefin and removal of the TES group were carried out in one-pot by hydrogenation with palladium on carbon. Cleavage of the methyl and TBS groups completed the synthesis of *trans*- and *cis*-**22**, and the structures were verified by X-ray crystallography.

**Scheme 6.** Installation of a Side Chain and Completion of the Synthesis of *trans*- and *cis*-**22**



### 3. Conclusion

We have demonstrated the synthesis of four cholestane-type steroidal compounds bearing a cyclobutane or a spirocyclopropane skeleton. The described route features a diastereo-switchable [2+2] cycloaddition reaction and a stereospecific ring-contraction to construct small rings in a stereo-divergent manner. The diastereoselectivity in the [2+2] cycloaddition was inverted under kinetic or thermodynamic conditions. A carbon side chain was installed on the small rings using a one-pot Julia olefination followed by reduction of

the resulting olefin. This strategy provides a facile route to access a new class of steroid derivatives bearing a small ring. Biological evaluation of the synthetic steroids is currently underway.

## 4. Experimental Section

### 4.1. General Remarks

All non-aqueous reactions were carried out under a positive atmosphere of argon in dried glassware. Dehydrated solvents were purchased for the reactions and used without further desiccation. Reagents were purchased and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck TLC silica gel 60 F<sub>254</sub>. Column chromatography was performed using Fuji Silysia BW-200 silica gel. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-ECA 500 instrument. The <sup>1</sup>H chemical shifts were calibrated with internal tetramethylsilane (TMS, 0 ppm) in deuterated organic solvents. The <sup>13</sup>C chemical shifts are reported relative to CDCl<sub>3</sub> (77.0 ppm), DMSO-*d*<sub>6</sub> (39.5 ppm), acetone-*d*<sub>6</sub> (206.7 and 30.4 ppm), MeOH-*d*<sub>4</sub> (49.0 ppm) or THF-*d*<sub>8</sub> (67.4 and 25.3 ppm). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Low-resolution mass spectra (LRMS) were recorded on a SHIMADZU GCMS-QP2010 SE spectrometer (EI) or a JEOL MS700 spectrometer (FAB).

High-resolution mass spectra (HRMS) were recorded on a JEOL MS700 spectrometer (FAB) or a SHIMADZU LCMS-IT-TOF fitted with an ESI. IR experiments were recorded on a SHIMADZU IRAffinity-1 spectrometer. The wave numbers of maximum absorption peaks of IR spectroscopy are presented in  $\text{cm}^{-1}$ . All melting points were determined using a Yamato MP-21 melting point apparatus and are uncorrected. Optical rotations were obtained on a JASCO P-1030 polarimeter. X-ray diffraction data were recorded on a RIGAKU R-AXIS RAPID system. Compounds **1**,<sup>9</sup> *cis*-**3a**,<sup>9</sup> *trans*-**3b**,<sup>9</sup> *cis*-**3b**,<sup>9</sup> **4a**<sup>9</sup> and dipotassium azodicarboxylate<sup>18</sup> were prepared according to previous procedures.

## 4.2 Experimental Procedures

### 4.2.1. *Synthesis* of

((6*bS*,8*aS*,8*bR*,9*S*,10*aS*,11*aS*,11*bR*)-8*b*-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-8*a*-methyl-2,6*b*,7,8,8*a*,8*b*,9,10,10*a*,11,11*a*,11*b*-dodecahydro-1*H*-cyclobuta[3,4]cyclopenta[1,2-*a*]phenanthren-9-yl)methanol (*trans*-**7**). To a solution of a mixture of *trans*- and *cis*-**3b** (21.0 g, 33.8 mmol, 9:1) in toluene (135 mL) was added a 3.6 M solution of Red-Al in toluene (24 mL, 86 mmol) at 0 °C under argon. After being stirred for 3 h, the reaction mixture was quenched with saturated aqueous Rochell salt, and stirred vigorously for 30 min. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, and dried over

Na<sub>2</sub>SO<sub>4</sub>. Concentration under reduced pressure gave a white solid, which was purified by column chromatography (hexane/EtOAc 9:1) to afford *trans*-**7** (12.4 g, 80%) as a white solid along with *cis*-**7** (1.39 g, 9%). Analytical sample was obtained by recrystallization from hexane/EtOAc as white blocks; Found: C, 73.38; H, 9.93. C<sub>28</sub>H<sub>44</sub>O<sub>3</sub>Si requires C, 73.63; H, 9.71%; Mp 189–191 °C; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +14.2 (*c* 1.00, CHCl<sub>3</sub>);  $\nu_{\max}$  (CHCl<sub>3</sub>) 3494 (br), 2949, 2855, 1250 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 7.21 (d, *J* = 8.6 Hz, 1H), 6.72 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.64 (d, *J* = 2.6 Hz, 1H), 4.01 (ddd, *J* = 10.0, 10.0, 6.0 Hz, 1H), 3.86 (ddd, *J* = 9.7, 9.7, 5.8 Hz, 1H), 3.78 (s, 3H), 2.89–2.77 (m, 3H), 2.58–2.51 (m, 1H), 2.36 (ddd, *J* = 12.0, 12.0, 9.8 Hz, 1H), 2.30–2.22 (m, 2H), 1.98–1.89 (m, 1H), 1.81–1.71 (m, 2H), 1.62–1.34 (m, 6H), 1.22 (br s, 1H), 0.97 (ddd, *J* = 12.9, 8.6, 4.9 Hz, 1H), 0.90 (s, 9H), 0.74 (s, 3H), 0.22 (s, 3H), 0.13 (s, 3H);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 157.4, 138.0, 132.6, 126.4, 113.8, 111.5, 90.4, 62.7, 55.2, 50.6, 48.3, 47.5, 43.9, 41.6, 38.9, 33.2, 31.9, 29.9, 27.9, 26.5, 25.8, 24.6, 18.2, 17.2, -2.7, -3.1; *m/z* (EI) 456 (M), 441 (M-Me).

#### 4.2.2. *Synthesis of*

((6*bS*,8*aS*,8*bR*,9*R*,10*aS*,11*aS*,11*bR*)-8*b*-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-8*a*-methyl-2,6*b*,7,8,8*a*,8*b*,9,10,10*a*,11,11*a*,11*b*-dodecahydro-1*H*-cyclobuta[3,4]cyclopenta[1,2-*a*]phenanthren-9-yl)methanol (*cis*-**7**). To a solution of *cis*-**3b** (8.04 g, 13.0 mmol) in toluene (65 mL) was added 3.6 M Red-Al in toluene (9.0 mL, 32

mmol) at 0 °C under argon. After being stirred for 3 h, the reaction mixture was quenched with saturated aqueous Rochell salt, and stirred vigorously for 30 min. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration under reduced pressure gave a white solid, which was purified by column chromatography (hexane/EtOAc 9:1) to afford *cis*-**7** (5.17g, 87%) as a white solid. Analytical sample was obtained by recrystallization from hexane/EtOAc as white blocks; Found: C, 73.36; H, 9.91. C<sub>28</sub>H<sub>44</sub>O<sub>3</sub>Si requires C, 73.63; H, 9.71%; Mp 204–205 °C;  $[\alpha]_D^{20} +29.2$  (c 1.00, CHCl<sub>3</sub>);  $\nu_{\max}$  (CHCl<sub>3</sub>) 3500 (br), 2929, 2856, 1253 cm<sup>-1</sup>;  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 7.22 (d, *J* = 8.6 Hz, 1H), 6.72 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.64 (d, *J* = 2.6 Hz, 1H), 3.83 (ddd, *J* = 10.9, 10.9, 2.3 Hz, 1H), 3.78 (s, 3H), 3.49 (ddd, *J* = 10.9, 10.9, 5.8 Hz, 1H), 2.89–2.86 (m, 2H), 2.78–2.67 (m, 1H), 2.66–2.59 (m, 1H), 2.41–2.31 (m, 1H), 2.25 (ddd, *J* = 10.9, 10.9, 3.4 Hz, 1H), 1.94–1.83 (m, 2H), 1.81 (dd, *J* = 10.9, 1.7 Hz, 1H), 1.71–1.59 (m, 3H), 1.53–1.40 (m, 5H), 1.29 (ddd, *J* = 12.4, 9.2, 2.9 Hz, 1H), 0.94 (s, 9H), 0.73 (s, 3H), 0.30 (s, 3H), 0.16 (s, 3H);  $\delta_C$  (125 MHz, CDCl<sub>3</sub>) 157.4, 137.9, 132.7, 126.4, 113.8, 111.4, 90.7, 63.8, 55.2, 47.9, 46.4, 44.1, 39.3, 38.9, 38.4, 31.9, 29.8, 29.7, 27.7, 26.1, 26.0, 24.2, 18.4, 14.5, -1.2, -2.3; *m/z* (FAB) 457 (M+H).

4.2.3.

Synthesis

of

(6*bS*,8*aS*,8*bR*,9*S*,10*aS*,11*aS*,11*bR*)-9-(hydroxymethyl)-4-methoxy-8*a*-methyl-1,2,6*b*,7,8,8*a*,9,10,10*a*,11,11*a*,11*b*-dodecahydro-8*bH*-cyclobuta[3,4]cyclopenta[1,2-*a*]phenanthren-8*b*-ol (*trans*-**8**). A mixture of *trans*-**7** (7.74 g, 16.9 mmol) and a 1.0 M solution of TBAF in THF (51 mL, 51 mmol) was heated under reflux for 46 h. After cooling to room temperature, the resulting mixture was diluted with CHCl<sub>3</sub>, and washed with water. The aqueous layer was extracted with CHCl<sub>3</sub>, dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration *in vacuo* and purification by column chromatography (EtOAc) gave *trans*-**8** (4.30 g, 75%) as a pale yellow solid. Analytical sample was obtained by recrystallization from EtOAc as a white needle; Found: C, 77.16; H, 8.83. C<sub>22</sub>H<sub>30</sub>O<sub>3</sub> requires C, 76.88; H, 9.00%; Mp 199–201 °C; [α]<sub>D</sub><sup>20</sup> +25.2 (*c* 1.00, THF); ν<sub>max</sub> (CHCl<sub>3</sub>) 3287 (br), 2974, 2924, 2859, 1709, 1636, 1501, 1350, 1254, 1184 cm<sup>-1</sup>; δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 7.21 (d, *J* = 8.9 Hz, 1H), 6.72 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.64 (d, *J* = 2.3 Hz, 1H), 4.04 (dd, *J* = 8.9, 8.9 Hz, 1H), 3.84 (dd, *J* = 8.6, 8.6 Hz, 1H), 3.78 (s, 3H), 2.89–2.76 (m, 3H), 2.42–2.25 (m, 4H), 1.96–1.91 (m, 2H), 1.88 (ddd, *J* = 11.5, 11.5, 5.7 Hz, 1H), 1.79 (ddd, *J* = 12.0, 3.6, 3.3 Hz, 1H), 1.72 (ddd, *J* = 12.7, 12.7, 3.9 Hz, 1H), 1.57–1.36 (m, 6H), 1.03–0.95 (m, 1H), 0.84 (s, 3H); δ<sub>C</sub> (125 MHz, DMSO-*d*<sub>6</sub>) 157.0, 137.5, 132.2, 126.2, 113.4, 111.5, 87.2, 60.9, 54.8, 50.2, 47.9, 46.7, 43.4, 41.1, 38.6, 32.7, 31.6, 29.4, 27.4, 26.2, 25.0, 16.4; *m/z* (EI) 342 (M), 324 (M–H<sub>2</sub>O), 309 (M–H<sub>2</sub>O–Me).

4.2.4.

Synthesis

of

(6*b*S,8*a*S,8*b*R,9*R*,10*a*S,11*a*S,11*b*R)-9-(hydroxymethyl)-4-methoxy-8*a*-methyl-1,2,6*b*,7,8,8*a*,9,10,10*a*,11,11*a*,11*b*-dodecahydro-8*b*H-cyclobuta[3,4]cyclopenta[1,2-*a*]phenanthren-8*b*-ol (*cis*-8). A mixture of *cis*-7 (34.4 g, 75.4 mmol) and a 1.0 M solution of TBAF in THF (226 mL, 226 mmol) was stirred at room temperature for 20 h. The resulting mixture was diluted with CHCl<sub>3</sub>, and washed with water. The aqueous layer was extracted with CHCl<sub>3</sub>, dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration *in vacuo* and purification by column chromatography (hexane/EtOAc 3:2) gave *cis*-8 (15.0 g, 83%) as a white solid. Analytical sample was obtained by recrystallization from EtOAc as a white needle; Found: C, 77.43; H, 8.89. C<sub>22</sub>H<sub>30</sub>O<sub>3</sub> requires C, 77.16; H, 8.83%; Mp 203–205 °C (dec.); [ $\alpha$ ]<sub>D</sub><sup>20</sup> +36.5 (*c* 1.00, CHCl<sub>3</sub>);  $\nu_{\max}$  (KBr) 3264 (br), 2932, 2920, 2859, 1609, 1499, 1236 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 7.23 (d, *J* = 8.6 Hz, 1H), 6.73 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.64 (d, *J* = 2.6 Hz, 1H), 3.85–3.74 (m, 2H), 3.78 (s, 3H), 2.93–2.82 (m, 2H), 2.62–2.55 (m, 1H), 2.50 (s, 1H), 2.41–2.32 (m, 2H), 2.28–2.20 (m, 2H), 2.17–2.09 (m, 1H), 1.97–1.89 (m, 1H), 1.69 (ddd, *J* = 11.2, 11.2, 5.5 Hz, 1H), 1.56–1.36 (m, 7H), 1.27 (ddd, *J* = 12.6, 9.5, 3.5 Hz, 1H), 0.80 (s, 3H);  $\delta_{\text{C}}$  (125 MHz, DMSO-*d*<sub>6</sub>) 157.0, 137.4, 132.3, 126.2, 113.4, 111.4, 86.6, 62.3, 54.9, 48.6, 45.4, 43.6, 40.4, 38.3, 37.9, 31.5, 29.4, 29.3, 27.3, 25.8, 24.9, 13.9; *m/z* (EI) 342 (M), 324 (M–H<sub>2</sub>O).

4.2.5.

Synthesis

of

((6*bS*,8*aS*,8*bR*,9*S*,10*aS*,11*aS*,11*bR*)-8*b*-hydroxy-4-methoxy-8*a*-methyl-2,6*b*,7,8,8*a*,8*b*,9,10,10*a*,11,11*a*,11*b*-do decahydro-1*H*-cyclobuta[3,4]cyclopenta[1,2-*a*]phenanthren-9-yl)methyl benzoate (*trans*-**9**). To a suspension of *trans*-**8** (3.10 g, 9.05 mmol) and DMAP (112 mg, 0.917 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (36 ml) were added triethylamine (2.5 mL, 18 mmol) and benzoyl chloride (1.3 mL, 11 mmol). After being stirred for 2 h at room temperature, the reaction mixture was quenched with saturated aqueous NaHCO<sub>3</sub>. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, and dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to give a brown solid. The residue was purified by column chromatography (hexane/EtOAc 4:1 to 1:1) to yield *trans*-**9** (3.85 g, 95%) as a white solid. Analytical sample was obtained by recrystallization from hexane/EtOAc as a white crystal; Found: C, 77.84; H, 7.67. C<sub>29</sub>H<sub>34</sub>O<sub>4</sub> requires C, 78.00; H, 7.67%; Mp 168–169 °C; [α]<sub>D</sub><sup>20</sup> +23.3 (*c* 1.00, CHCl<sub>3</sub>); ν<sub>max</sub> (CHCl<sub>3</sub>) 3491 (br), 2936, 2866, 1713, 1609, 1501, 1450, 1273, 1219 cm<sup>-1</sup>; δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 8.04 (dd, *J* = 7.9, 1.3 Hz, 2H), 7.56 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.44 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 1H), 6.70 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.63 (d, *J* = 2.6 Hz, 1H), 4.63 (dd, *J* = 11.2, 7.7 Hz, 1H), 4.58 (dd, *J* = 10.9, 8.9 Hz, 1H), 3.78 (s, 3H), 3.10–3.03 (m, 1H), 2.93–2.83 (m, 2H), 2.49–2.41 (m, 2H), 2.33–2.27 (m, 2H), 1.96–1.91 (m, 2H), 1.85–1.80 (m, 1H), 1.71 (ddd, *J* = 12.4, 12.4, 2.3 Hz, 1H), 1.62–1.56 (m, 2H), 1.52–1.38 (m, 3H), 1.18–1.10 (m, 1H), 0.86 (s, 3H); δ<sub>C</sub>

(125 MHz, CDCl<sub>3</sub>) 166.6, 157.4, 137.8, 132.9, 132.4, 130.2, 129.5, 128.3, 126.3, 113.7, 111.4, 88.5, 64.4, 55.1, 48.7, 47.2, 45.7, 43.6, 42.2, 38.9, 32.7, 31.6, 29.8, 27.7, 26.3, 24.1, 16.1; *m/z* (EI) 446 (M), 428 (M-H<sub>2</sub>O).

#### 4.2.6. *Synthesis of*

*((6bS,8aS,8bR,9R,10aS,11aS,11bR)-8b-hydroxy-4-methoxy-8a-methyl-2,6b,7,8,8a,8b,9,10,10a,11,11a,11b-decahydro-1H-cyclobuta[3,4]cyclopenta[1,2-a]phenanthren-9-yl)methyl benzoate (cis-9)*. To a suspension of *cis-8* (5.32 g, 15.5 mmol) and DMAP (191 mg, 1.56 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (62 mL) were added triethylamine (4.3 mL, 31 mmol) and benzoyl chloride (2.2 mL, 19 mmol). After being stirred for 3 h at room temperature, the reaction mixture was quenched with saturated aqueous NaHCO<sub>3</sub>. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, and dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to give a brown solid. The residue was purified by column chromatography (hexane/EtOAc 4:1) to yield *cis-9* (6.25 g, 90%) as a white solid. Analytical sample was obtained by recrystallization from hexane/EtOAc as a white crystal; Found C, 77.91; H, 7.81. C<sub>29</sub>H<sub>34</sub>O<sub>4</sub> requires C, 78.00; H, 7.67%; Mp 126–128 °C; [α]<sub>D</sub><sup>20</sup> +38.6 (*c* 1.00, CHCl<sub>3</sub>); ν<sub>max</sub> (CHCl<sub>3</sub>) 3464 (br), 2932, 2862, 1713, 1605, 1501, 1450, 1277 cm<sup>-1</sup>; δ<sub>H</sub> (500 MHz CDCl<sub>3</sub>) 8.03 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.58 (tt, *J* = 7.5, 1.4 Hz, 1H), 7.45 (dd, *J* = 8.0, 8.0 Hz,

2H), 7.15 (d,  $J = 8.6$  Hz, 1H), 6.68 (dd,  $J = 8.6, 2.9$  Hz, 1H), 6.63 (d,  $J = 2.9$  Hz, 1H), 4.75 (dd,  $J = 11.5, 9.8$  Hz, 1H), 4.24 (dd,  $J = 11.2, 4.0$  Hz, 1H), 3.76 (s, 3H), 2.92–2.77 (m, 3H), 2.43–2.38 (m, 1H), 2.26–2.16 (m, 2H), 2.10–2.02 (m, 1H), 1.95–1.88 (m, 1H), 1.75–1.67 (m, 1H), 1.60 (ddd,  $J = 12.3, 12.3, 8.3$  Hz, 1H), 1.55–1.34 (m, 7H), 0.80 (s, 3H);  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 167.1, 157.4, 137.9, 133.0, 132.5, 130.1, 129.5, 128.4, 126.2, 113.7, 111.3, 87.1, 65.2, 55.1, 49.7, 46.0, 44.0, 40.0, 38.6, 35.3, 31.4, 29.8, 29.6, 27.6, 26.0, 24.4, 13.8;  $m/z$  (EI) 446 (M).

4.2.7. *Synthesis of*  
*((2'S,8S,9S,13S,14S,16S,17R)-16-chloro-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[a]phenanthrene-17,1'-cyclopropan]-2'-yl)methyl benzoate ((20S)-10)*. To a solution of *cis-9* (6.15 g, 13.8 mmol) in dichloroethane (69 mL) were added triethylamine (3.8 mL, 28 mmol) and thionyl chloride (2.0 mL, 28 mmol) under argon. After being stirred at 50 °C for 2 h, the reaction was quenched with saturated aqueous  $\text{NaHCO}_3$ . The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/diethyl ether 10:1) to afford (20S)-10 (5.60 g, 87%, dr 4:1) as a white solid. The diastereomers were partially separated upon careful column chromatography to obtain an analytical sample.

Data for the major diastereomer: Mp 177–179 °C;  $[\alpha]_D^{20} +54.7$  (*c* 1.00, CHCl<sub>3</sub>);  $\nu_{\max}$  (CHCl<sub>3</sub>) 2932, 2859, 1717, 1609, 1501, 1450, 1258, 1177, 1111 cm<sup>-1</sup>;  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 8.09 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.56 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.45 (dd, *J* = 8.1, 8.1 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.64 (d, *J* = 2.6 Hz, 1H), 4.74 (dd, *J* = 11.7, 6.0 Hz, 1H), 4.44 (dd, *J* = 11.5, 8.6 Hz, 1H), 4.32 (dd, *J* = 8.3, 5.2 Hz, 1H), 3.78 (s, 3H), 2.94–2.82 (m, 2H), 2.78 (ddd, *J* = Hz, 13.5, 8.0, 8.0 Hz, 1H), 2.34–2.26 (m, 1H), 2.25–2.17 (m, 1H), 2.00 (ddd, *J* = 13.5, 13.5, 5.4 Hz, 1H), 1.93–1.85 (m, 1H), 1.58–1.35 (m, 5H), 1.31–1.22 (m, 2H), 1.17 (s, 3H), 1.08 (ddd, *J* = 12.9, 12.9, 4.1 Hz, 1H), 0.49 (dd, *J* = 5.7, 5.7 Hz, 1H);  $\delta_C$  (125 MHz, CDCl<sub>3</sub>) 166.7, 157.5, 137.8, 132.8, 132.2, 130.6, 129.6, 128.3, 126.2, 113.8, 111.6, 67.0, 66.8, 55.2, 52.5, 43.8, 43.7, 42.4, 39.6, 39.0, 32.8, 29.7, 27.6, 25.7, 19.3, 18.9, 17.7; *m/z* (EI) 464 (M), 429 (M–Cl), 342 (M–BzOH), 307 (M–Cl–BzOH); HRMS (ESI):  $[M+Na]^+$ , found 487.2018. C<sub>29</sub>H<sub>33</sub>ClO<sub>3</sub>Na requires 487.2010.

4.2.8. *Synthesis* of  
 ((2'R,8S,9S,13S,14S,16S,17R)-16-chloro-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,1'-cyclopropan]-2'-yl)methyl benzoate ((20R)-**10**) and  
 2-chloro-2-((6bS,8aS,8bS,9aS,10aS,10bS)-4-methoxy-8a-methyl-1,6b,7,8,8a,9,9a,10,10a,10b-decahydrocyclopropa[3,4]cyclopenta[1,2-*a*]phenanthren-8b(2H)-yl)ethyl benzoate (**11**). To a solution of *trans*-**9** (1.51 g,

3.38 mmol) in dichloroethane (17 mL) were added triethylamine (0.93 mL, 6.7 mmol) and thionyl chloride (0.49 mL, 6.8 mmol) under argon. After being stirred at 50 °C for 2 h, the reaction was quenched with saturated aqueous NaHCO<sub>3</sub>. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/diethyl ether 10:1) to afford (2*R*)-**10** (1.03 g, 66%, dr 7:3) as a white solid and **11** (173 mg, 11%) as a pale yellow oil. The diastereomers were partially separated upon careful column chromatography to obtain an analytical sample. Data for the major diastereomer: Mp 60–63 °C; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +29.3 (*c* 1.00, CHCl<sub>3</sub>);  $\nu_{\max}$  (CHCl<sub>3</sub>) 2936, 1717, 1609, 1501, 1450, 1273, 1111 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 8.09 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 6.9 Hz, 1H), 7.46 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 1H), 6.72 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.64 (d, *J* = 2.3 Hz, 1H), 4.51 (dd, *J* = 11.2, 8.3 Hz, 1H), 4.40 (dd, *J* = 11.5, 7.5 Hz, 1H), 3.96 (dd, *J* = 8.0, 6.3 Hz, 1H), 3.78 (s, 3H), 2.94–2.82 (m, 2H), 2.70–2.63 (m, 1H), 2.34–2.21 (m, 2H), 1.98–1.82 (m, 3H), 1.65 (ddd, *J* = 11.8, 3.2, 3.2 Hz, 1H), 1.58–1.36 (m, 5H), 1.17 (s, 3H), 1.13 (dd, *J* = 5.2, 5.2 Hz, 1H), 0.79 (dd, *J* = 9.5, 4.9 Hz, 1H);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 166.6, 157.5, 137.7, 132.9, 132.1, 130.3, 129.6, 128.3, 126.2, 113.7, 111.5, 69.5, 64.8, 55.2, 53.3, 43.6, 43.3, 41.9, 38.5, 38.3, 36.7, 29.6, 27.5, 25.9, 22.7, 19.2, 17.5; *m/z* (EI) 464 (M), 429 (M–Cl), 342 (M–BzOH), 307 (M–Cl–BzOH); HRMS (ESI): [M+Na]<sup>+</sup>, found 487.2011. C<sub>29</sub>H<sub>33</sub>ClO<sub>3</sub>Na requires 487.2010. Data for compound **11**:  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 8.05 (d, *J* =

7.8 Hz, 2H), 7.58 (t,  $J = 7.5$  Hz, 1H), 7.46 (dd,  $J = 7.8, 7.8$  Hz, 2H), 7.18 (d,  $J = 8.6$  Hz, 1H), 6.71 (dd,  $J = 8.6, 2.9$  Hz, 1H), 6.62 (d,  $J = 2.6$  Hz, 1H), 4.93 (dd,  $J = 7.2, 7.2$  Hz, 1H), 4.29 (dd,  $J = 11.5, 7.8$  Hz, 1H), 4.23 (dd,  $J = 11.5, 6.1$  Hz, 1H), 3.77 (s, 3H), 2.91–2.80 (m, 2H), 2.36–2.29 (m, 1H), 2.21–2.08 (m, 2H), 1.87–1.80 (m, 1H), 1.72–1.64 (m, 2H), 1.55–1.48 (m, 3H), 1.41 (ddd,  $J = 11.8, 11.8, 4.0$  Hz, 1H), 1.37–1.30 (m, 1H), 1.14 (d,  $J = 6.3, 4.0$  Hz, 1H), 1.10–1.04 (m, 1H), 1.01 (s, 3H), 0.68 (dd,  $J = 8.3, 6.9$  Hz, 1H);  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 166.0, 157.5, 137.8, 133.3, 132.7, 129.72, 129.68, 128.5, 126.1, 113.8, 111.4, 66.2, 60.4, 55.2, 45.9, 44.3, 42.9, 39.0, 37.4, 35.0, 29.7, 27.9, 26.6, 26.3, 24.6, 17.7, 10.5;  $m/z$  (FAB) 464 (M), 429 (M–Cl), 307 (M–Cl–BzOH); HRMS (ESI):  $[\text{M}+\text{Na}]^+$ , found 487.2021,  $\text{C}_{29}\text{H}_{33}\text{ClO}_3\text{Na}$  requires 487.2010.

4.2.9. *Synthesis of*  
*((2'S,8S,9S,13S,14S,17S)-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[a]phenanthrene-17,1'-cyclopropan]-2'-yl)methanol ((20S)-12)*. To a solution of compound (20S)-**10** (2.09 g, 4.50 mmol) in toluene (23 mL) was added a 3.6 M Red-Al solution in toluene (6.3 mL, 23 mmol) under argon at 0 °C. After being stirred at room temperature for 6 h, the reaction was quenched with saturated aqueous Rochell salt. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure to give a yellow oil. The crude

material was purified by column chromatography (hexane/diethyl ether 7:3) to afford (20*S*)-**12** (1.17 g, 79%) as a white solid; Found: C, 80.68; H, 9.54. C<sub>22</sub>H<sub>30</sub>O<sub>2</sub> requires C, 80.94; H, 9.26%; Mp 112–113°C; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +27.1 (*c* 1.00, CHCl<sub>3</sub>);  $\nu_{\max}$  (CHCl<sub>3</sub>) 3410 (br), 3009, 2932, 2866, 1609, 1501, 1450, 1219 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 7.19 (d, *J* = 8.6 Hz, 1H), 6.70 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.63 (d, *J* = 2.3 Hz, 1H), 3.77 (s, 3H), 3.64 (br m, 1H), 3.53 (br m, 1H), 2.91–2.82 (m, 2H), 2.28–2.18 (m, 2H), 2.10–2.03 (m, 1H), 1.94–1.87 (m, 2H), 1.50–1.39 (m, 6H), 1.25–1.18 (m, 2H), 1.11 (ddd, *J* = 12.6, 12.6, 4.0 Hz, 1H), 0.99–0.92 (m, 2H), 0.81 (s, 3H);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 157.4, 138.0, 132.8, 126.2, 113.7, 111.4, 65.1, 55.1, 53.3, 43.9, 41.4, 39.5, 36.3, 33.2, 29.9, 29.0, 27.8, 26.1, 24.6, 19.8, 17.2, 16.2; *m/z* (EI) 326 (M), 308 (M–H<sub>2</sub>O).

4.2.10. *Synthesis of*  
*((2'R,8S,9S,13S,14S,17S)-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,1'-cyclopropan]-2'-yl)methanol ((20*R*)-**12**). A mixture of (20*R*)-**10** (1.59 g, 3.42 mmol), NaBH<sub>4</sub> (776 mg, 20.5 mmol) and DMSO (14 mL) was stirred for 20 h at 130 °C. After cooling to room temperature, water was added to the mixture. The aqueous layer was extracted with hexane/EtOAc (4:1), and the combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was partially purified by column chromatography (hexane/diethyl ether 1:1) to give (20*R*)-**12** (584 mg, 53%)*

as a white gum;  $[\alpha]_D^{20} +19.6$  ( $c$  1.00,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 3383 (br), 2928, 2862, 1609, 1574, 1501, 1454, 1281, 1018  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.19 (d,  $J = 8.6$  Hz, 1H), 6.71 (dd,  $J = 8.3, 2.6$  Hz, 1H), 6.63 (d,  $J = 2.6$  Hz, 1H), 3.87 (dd,  $J = 10.9, 6.3$  Hz, 1H), 3.77 (s, 3H), 3.54 (dd,  $J = 10.9, 10.9$  Hz, 1H), 2.93–2.78 (m, 2H), 2.31–2.17 (m, 2H), 2.14–2.03 (m, 1H), 1.97–1.89 (m, 1H), 1.88–1.78 (m, 1H), 1.58–1.30 (m, 8H), 1.17–1.11 (m, 1H), 0.89 (s, 3H), 0.67 (dd,  $J = 4.6, 4.6$  Hz, 1H), 0.42 (dd,  $J = 8.3, 4.3$  Hz, 1H);  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 157.3, 137.9, 132.6, 126.2, 113.7, 111.4, 63.1, 55.1, 54.5, 43.5, 41.4, 39.1, 36.6, 35.8, 29.8, 27.6, 26.4, 25.0, 24.6, 17.1 (two signals missing);  $m/z$  (EI) 326 (M); HRMS (ESI):  $[\text{M}+\text{Na}]^+$ , found 349.2145.  $\text{C}_{22}\text{H}_{30}\text{O}_2\text{Na}$  requires 349.2138.

4.2.11. *Synthesis of (2'S,8S,9S,13S,14S,17S)-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,1'-cyclopropane]-2'-carbaldehyde ((20S)-13).* To a solution of oxalyl chloride (0.32 mL, 3.7 mmol) in  $\text{CH}_2\text{Cl}_2$  (4.0 mL) was dropwise added a solution of DMSO (0.40 mL, 5.6 mmol) in  $\text{CH}_2\text{Cl}_2$  (5.0 mL) at  $-78$  °C. After being stirred for 5 min, a solution of (20S)-12 (601 mg, 1.84 mmol) in  $\text{CH}_2\text{Cl}_2$  (9.0 mL) was dropwise added. After being stirred for 10 min at  $-78$  °C, triethylamine (1.5 mL, 10.8 mmol) was added. After being stirred for 20 min, the resulting mixture was allowed to warm to ambient temperature, diluted

with  $\text{CHCl}_3$ , and quenched with saturated aqueous  $\text{NH}_4\text{Cl}$ . The aqueous layer was extracted with  $\text{CHCl}_3$ , and the combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The crude material was purified by column chromatography (hexane/EtOAc 10:1) to afford (2*S*)-**13** (490 mg, 82%) as a white solid. Analytical sample was obtained by recrystallization from hexane/EtOAc as a white needle; Found C, 81.17; H, 8.55.  $\text{C}_{22}\text{H}_{28}\text{O}_2$  requires C, 81.44; H, 8.70%; Mp 148–149 °C (dec.);  $[\alpha]_{\text{D}}^{20} +47.7$  ( $c$  1.00,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 2932, 2913, 2866, 1701, 1609, 1501, 1238, 1172, 1042  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 9.12 (d,  $J = 6.3$  Hz, 1H), 7.19 (d,  $J = 8.6$  Hz, 1H), 6.71 (dd,  $J = 8.6, 2.6$  Hz, 1H), 6.63 (d,  $J = 2.3$  Hz, 1H), 3.77 (s, 3H), 2.97–2.83 (m, 2H), 2.33–2.17 (m, 3H), 2.00–1.93 (m, 2H), 1.79–1.70 (m, 2H), 1.52–1.39 (m, 6H), 1.26 (ddd,  $J = 12.1, 3.4, 3.4$  Hz, 1H), 1.18–1.15 (m, 2H), 0.83 (s, 3H);  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 201.8, 157.5, 137.9, 132.3, 126.2, 113.8, 111.4, 55.1, 52.4, 43.80, 43.78, 42.6, 39.3, 32.9, 31.0, 29.8, 29.5, 27.7, 25.9, 24.7, 21.0, 17.1;  $m/z$  (EI) 324 (M), 309 (M–Me), 291 (M–Me– $\text{H}_2\text{O}$ ).

4.2.12.

Synthesis

of

(2'*R*,8*S*,9*S*,13*S*,14*S*,17*S*)-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,1'-cyclopropane]-2'-carbaldehyde ((20*R*)-**13**). To a solution of oxalyl chloride (0.37 mL, 4.3 mmol) in  $\text{CH}_2\text{Cl}_2$  (5.0 mL) was dropwise added a solution of DMSO (0.46 mL, 6.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (5.0 mL)

at  $-78\text{ }^{\circ}\text{C}$ . After being stirred for 5 min, a solution of (20*R*)-**12** (584 mg, 1.80 mmol) in  $\text{CH}_2\text{Cl}_2$  (12 mL) was dropwise added. After being stirred for 20 min at  $-78\text{ }^{\circ}\text{C}$ , triethylamine (1.8 mL, 13 mmol) was added. After being stirred for 10 min, the resulting mixture was allowed to warm to ambient temperature, diluted with  $\text{CHCl}_3$ , and quenched with saturated aqueous  $\text{NH}_4\text{Cl}$ . The aqueous layer was extracted with  $\text{CHCl}_3$ , and the combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The crude material was purified by column chromatography (hexane/EtOAc 10:1) to afford (20*R*)-**13** (471 mg, 81%) as a white solid; Found C, 81.50; H, 8.92.  $\text{C}_{22}\text{H}_{28}\text{O}_2$  requires C, 81.44; H, 8.70%; Mp  $128\text{--}129\text{ }^{\circ}\text{C}$ ;  $[\alpha]_{\text{D}}^{20} +42.7$  ( $c$  1.00,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 2932, 2866, 1694, 1609, 1501, 1161,  $1038\text{ cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 9.16 (d,  $J = 7.2\text{ Hz}$ , 1H), 7.19 (d,  $J = 8.6\text{ Hz}$ , 1H), 6.72 (dd,  $J = 8.5, 2.4\text{ Hz}$ , 1H), 6.64 (d,  $J = 2.0\text{ Hz}$ , 1H), 3.78 (s, 3H), 2.93–2.83 (m, 2H), 2.37–2.15 (m, 3H), 1.95–1.85 (m, 3H), 1.75 (dd,  $J = 5.2, 5.2\text{ Hz}$ , 1H), 1.62–1.37 (m, 8H), 1.10 (dd,  $J = 7.9, 5.0\text{ Hz}$ , 1H), 0.89 (s, 3H);  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 200.4, 157.5, 137.8, 132.2, 126.2, 113.8, 111.5, 55.2, 54.4, 44.9, 43.4, 42.0, 39.2, 36.3, 36.2, 35.4, 29.8, 27.5, 26.3, 24.4, 21.9, 18.0;  $m/z$  (EI) 324 (M), 309 (M–Me), 291 (M–Me– $\text{H}_2\text{O}$ ).

4.2.13. *Synthesis of 3-hydroxy-3-methylbutyl 4-methylbenzenesulfonate (14)*. To a stirred solution of 3-methyl-1,3-butanediol (4.19 g, 40.2 mmol) in pyridine (100 mL) was added tosyl chloride (9.15 g, 48.0

mmol) at 0 °C. After being stirred for 12 h at room temperature, the reaction mixture was quenched with water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub> and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated *in vacuo*, and azeotroped with toluene. The resulting pale yellow oil was purified by column chromatography (hexane/EtOAc 3:2 to 1:1) to afford **14** (7.62 g, 73%) as a colorless oil;  $\nu_{\max}$  (neat) 3518 (br), 2970, 1597, 1465, 1354, 1172 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 7.80 (d,  $J$  = 8.3 Hz, 2H), 7.35 (d,  $J$  = 8.1 Hz, 2H), 4.21 (t,  $J$  = 6.9 Hz, 2H), 2.45 (s, 3H), 1.86 (t,  $J$  = 6.9 Hz, 2H), 1.22 (s, 6H);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 144.7, 132.7, 129.7, 127.7, 69.3, 67.5, 41.5, 29.4, 21.4;  $m/z$  (FAB) 259 (M+H), 241 (M-OH).; HRMS (FAB): [M+H]<sup>+</sup>, found 259.0975. C<sub>12</sub>H<sub>19</sub>O<sub>4</sub>S requires 259.0999.

4.2.14. *Synthesis of 2-((3-methyl-3-((triethylsilyl)oxy)butyl)sulfonyl)benzo[d]thiazole (15)*. To a solution of **14** (7.62 g, 29.5 mmol) in acetone (98 mL) was added NaI (11.2 g, 74.7 mmol). The mixture was heated under reflux for 2 h. The resulting mixture was allowed to cool to room temperature, and concentrated *in vacuo*. The residue was dissolved in EtOAc, and washed with water. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure to give a brown oil (5.79 g). To a solution of the brown oil (5.79 g) in THF (90 mL) were

added triethylamine (5.6 mL, 41 mmol) and 2-mercaptobenzothiazole (5.67 g, 33.9 mmol). After being heated under reflux for 12 h, the reaction mixture was allowed to cool to room temperature, diluted with EtOAc, and washed with water. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration under reduced pressure gave a yellow oil (6.87 g). To a solution of the yellow oil (6.87 g) in CH<sub>2</sub>Cl<sub>2</sub> (135 mL) was added *m*CPBA (75%, 18.8 g, 81.7 mmol) at 0 °C. After being stirred for 6 h at room temperature, the reaction mixture was quenched with saturated aqueous NaHCO<sub>3</sub>. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was dissolved in CHCl<sub>3</sub>, and passed through a short pad of silica gel with hexane/EtOAc (1:1) to give a white solid. (7.67 g). To a solution of the white solid (7.67 g) in CH<sub>2</sub>Cl<sub>2</sub> (67 mL) were added triethylamine (7.5 mL, 54 mmol) and triethylsilyl trifluoromethanesulfonate (7.3 mL, 32 mmol) at 0 °C under argon. After being stirred for 7 h at room temperature, the reaction mixture was quenched with water. The aqueous layer was extracted with ether, and the combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to give a brown solid. The residue was purified by column chromatography (hexane/EtOAc 10:1) to afford **15** (8.49 g, 72%, 4 steps) as a white solid; Found C, 53.90; H, 7.31; N, 3.47. C<sub>18</sub>H<sub>29</sub>NO<sub>3</sub>S<sub>2</sub>Si requires C, 54.10; H, 7.31; N, 3.50%; Mp 57–59 °C;  $\nu_{\max}$  (neat) 2951, 2873, 1470, 1327, 1304, 1146 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 8.23 (dd, *J* = 8.2, 1.4 Hz, 1H),

8.02 (dd,  $J = 8.1, 1.4$  Hz, 1H), 7.65 (ddd,  $J = 8.2, 7.0, 1.4$  Hz, 1H), 7.60 (ddd,  $J = 7.8, 6.6, 1.5$  Hz, 1H), 3.65–3.62 (m, 2H), 1.95–1.92 (m, 2H), 1.23 (s, 6H), 0.87 (t,  $J = 8.0$  Hz, 9H), 0.51 (q,  $J = 8.0$  Hz, 6H);  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 65.6, 152.7, 136.7, 127.9, 127.5, 125.4, 122.2, 71.8, 51.2, 36.9, 29.7, 6.9, 6.5;  $m/z$  (FAB) 400 (M+H), 370 (M–Et), 268 (M–TES).

4.2.15. *Synthesis* of triethyl(((*E*)-5-((2'*R*,8*S*,9*S*,13*S*,14*S*,17*S*)-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,1'-cyclopropan]-2'-yl)-2-methylpent-4-en-2-yl)oxy)silane ((20*S*)-**16**). To a solution of **15** (352 mg, 1.08 mmol) in THF (6.0 mL) was added a 1.0 M solution of LiHMDS in toluene (1.6 mL, 1.6 mmol) at  $-78$  °C under argon. After being stirred for 30 min, a solution of (20*S*)-**13** (352 mg, 1.08 mmol) in THF (10 mL) was added, and stirred for 1 h. The reaction mixture was diluted with EtOAc, and quenched with saturated aqueous  $\text{NH}_4\text{Cl}$ . The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo* to give a yellow oil. The crude material was purified by column chromatography (hexane/diethyl ether 50:1) to afford an inseparable *E/Z* mixture of (20*S*)-**16** (470 mg, 86%, *E/Z* 9:1) as a colorless oil. The following data were collected as a 9:1 *E/Z* mixture;  $[\alpha]_{\text{D}}^{20} +23.3$  (c 1.00,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (neat) 2954, 2909, 2874, 1609, 1501, 1238,

1042, 1018  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.20 (d,  $J = 8.6$  Hz, 1H), 6.70 (dd,  $J = 8.6, 2.6$  Hz, 1H), 6.63 (d,  $J = 2.0$  Hz, 1H), 5.52 (dt,  $J = 15.2, 7.5$  Hz, 0.9H), 5.50 (dt,  $J = 10.9, 3.7$  Hz, 0.1H), 5.08 (dd,  $J = 15.2, 8.9$  Hz, 0.9H), 5.01 (dd,  $J = 10.3, 10.3$  Hz, 0.1H), 3.77 (s, 3H), 2.95–2.75 (m, 2H), 2.34–2.02 (m, 5H), 1.97–1.84 (m, 2H), 1.50–1.28 (m, 7H), 1.27–1.18 (m, 1.6H), 1.18 (s, 2.7H), 1.17 (s, 2.7H), 1.15–1.05 (m, 2H), 0.95 (t,  $J = 8.1$  Hz, 9H), 0.78 (s, 3H), 0.57 (q,  $J = 8.0$  Hz, 6H), 0.15 (dd,  $J = 5.5, 5.5$  Hz, 1H);  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 157.4, 138.1, 134.3, 132.9, 126.3, 125.5, 113.8, 111.4, 73.5, 55.2, 53.5, 48.4, 43.9, 41.9, 39.4, 38.0, 33.4, 29.9, 29.7, 29.6, 27.8, 26.1, 24.7, 20.9, 19.2, 16.7, 7.1, 6.8 (Signals of the minor isomer were not observed);  $m/z$  (EI) 508 (M), 493 (M–Me), 479 (M–Et), 450 (M–2Et), 376 (M–TESOH); HRMS (ESI):  $[\text{M}+\text{Na}]^+$ , found 531.3631.  $\text{C}_{33}\text{H}_{52}\text{O}_2\text{SiNa}$  requires 531.3629.

4.2.16. *Synthesis* of triethyl(((*E*)-5-((2*S*,8*S*,9*S*,13*S*,14*S*,17*S*)-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,1'-cyclopropan]-2'-yl)-2-methylpent-4-en-2-yl)oxy)silane ((20*R*)-**16**). To a solution of **15** (747 mg, 1.87 mmol) in THF (5 mL) was added a 1.0 M solution of LiHMDS in toluene (1.9 mL, 1.9 mmol) at  $-78$  °C under argon. After being stirred for 30 min, a solution of (20*R*)-**13** (463 mg, 1.43 mmol) in THF (10 mL) was added, and stirred for 1 h. The reaction mixture was diluted with EtOAc, and

quenched with saturated aqueous  $\text{NH}_4\text{Cl}$ . The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo* to give a yellow oil. The crude material was purified by column chromatography (hexane/diethyl ether 50:1) to afford an inseparable *E/Z* mixture of (20*R*)-**16** (667 mg, 92%, *E/Z* 4:1) as a colorless oil. The following data were collected as a 4:1 *E/Z* mixture;  $[\alpha]_{\text{D}}^{20} +28.6$  (*c* 1.00,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 2932, 2913, 2874, 1609, 1501, 1458, 1234, 1153, 1038, 1015  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.20 (d, *J* = 8.6 Hz, 1H), 6.71 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.63 (d, *J* = 2.3 Hz, 1H), 5.54 (dt, *J* = 15.2, 7.2 Hz, 0.8H), 5.43 (dt, *J* = 10.4, 7.8 Hz, 0.2H), 5.29–5.18 (m, 1H), 3.77 (s, 3H), 2.92–2.79 (m, 2H), 2.33–2.05 (m, 5H), 1.95–1.78 (m, 2H), 1.60–1.26 (m, 9H), 1.22 (s, 1.2H), 1.18 (s, 4.8H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.88 (s, 2.4H), 0.87 (s, 0.6H), 0.83–0.78 (m, 1H), 0.57 (q, *J* = 8.0 Hz, 6H), 0.54–0.51 (m, 1H);  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 57.4, 138.0, 133.3, 132.9, 126.3, 125.5, 113.7, 111.4, 73.7, 55.2, 54.6, 48.6, 43.6, 41.7, 39.1, 37.9, 36.2, 35.7, 29.9, 29.8, 29.5, 27.7, 26.4, 25.7, 24.8, 20.3, 16.0, 7.1, 6.8 (Signals of the minor isomer were not observed); *m/z* (EI) 508 (M), 493 (M–Me), 479 (M–Et), 450 (M–2Et), 376 (M–TESOH); HRMS (ESI):  $[\text{M}+\text{Na}]^+$ , found 531.3619.  $\text{C}_{33}\text{H}_{52}\text{O}_2\text{SiNa}$  requires 531.3629.

4.2.17.

Synthesis

of

5-((2'*S*,8*S*,9*S*,13*S*,14*S*,17*S*)-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]ph

*enanthere-17,1'-cyclopropan]-2'-yl)-2-methylpentan-2-ol ((20S)-17)*. To a suspension of (20S)-**16** (166 mg, 0.326 mmol, *E/Z* 9:1) and dipotassium azodicarboxylate (317 mg, 1.63 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) was added a 1 M solution of acetic acid in CH<sub>2</sub>Cl<sub>2</sub> (3.3 mL, 3.3 mmol) dropwise at reflux. Additional dipotassium azodicarboxylate (317 mg, 1.63 mmol) and a 1.0 M solution of acetic acid (3.3 mL, 3.3 mmol) were added after 3, 6, 22, 25, 28, 31, 34, 43 h, respectively. The reaction mixture was stirred under reflux for a total 46 h, and the resulting mixture was filtered through Celite. The eluent was concentrated under reduced pressure to give the spirocyclopropane (166 mg) as a pale yellow oil. To a solution of the spirocyclopropane (166 mg) in THF (2 mL) was added a 1.0 M solution of TBAF (1.7 mL, 1.7 mmol), and the solution was heated under reflux for 6 h. After cooling to room temperature, the resulting mixture was diluted with EtOAc, and washed with water. The aqueous layer was extracted with EtOAc, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to give a yellow oil. The crude material was purified by column chromatography (hexane/EtOAc 4:1) to give (20S)-**17** (92.3 mg, 71% for 2 steps) as a white solid; Mp 107–109 °C; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +21.1 (*c* 1.00, CHCl<sub>3</sub>);  $\nu_{\max}$  (CHCl<sub>3</sub>) 3333 (br), 2970, 2924, 2901, 1501, 1454, 1381, 1084, 1049 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 7.20 (d, *J* = 8.6 Hz, 1H), 6.70 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.63 (d, *J* = 2.0 Hz, 1H), 3.77 (s, 3H), 2.92–2.82 (m, 2H), 2.27–2.18 (m, 2H), 2.04–2.01 (m, 1H), 1.95–1.87 (m, 2H), 1.54–1.16 (m, 20H), 1.10 (ddd, *J* = 13.2, 13.2, 4.0 Hz, 1H), 0.85 (dd, *J* = 8.9, 4.3 Hz, 1H), 0.77 (s, 3H), 0.58–0.52 (m, 1H), –0.26 (dd, *J* = 4.9, 4.9 Hz, 1H);  $\delta_{\text{C}}$  (125

MHz, CDCl<sub>3</sub>) 157.3, 138.0, 132.9, 126.2, 113.7, 111.3, 70.9, 55.1, 53.6, 43.9, 43.8, 41.3, 39.4, 36.0, 33.3, 31.6, 29.9, 29.2, 29.1, 29.0, 27.8, 26.1, 24.9, 24.6, 17.4, 17.1, 17.0; *m/z* (EI) 396 (M), 378 (M–H<sub>2</sub>O), 363 (M–H<sub>2</sub>O–Me); HRMS (ESI): [M+H]<sup>+</sup>, found 397.3096. C<sub>27</sub>H<sub>41</sub>O<sub>2</sub> requires 397.3101.

4.2.18. *Synthesis* of

5-((2*R*,8*S*,9*S*,13*S*,14*S*,17*S*)-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,1'-cyclopropan]-2'-yl)-2-methylpentan-2-ol ((20*R*)-**17**). To a suspension of (20*R*)-**16** (483 mg, 0.949 mmol, *E/Z* 4:1) and dipotassium azodicarboxylate (922 mg, 4.75 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL) was added a 1.0 M solution of acetic acid in CH<sub>2</sub>Cl<sub>2</sub> (9.4 mL, 9.4 mmol) dropwise at reflux. Additional dipotassium azodicarboxylate (922 mg, 4.75 mmol) and a 1.0 M solution of acetic acid in CH<sub>2</sub>Cl<sub>2</sub> (9.4 mL, 9.4 mmol) were added after 3, 17, 29, 42, 47, 53, 67, 70, 74, 77 h, respectively. The reaction mixture was stirred under reflux for a total 89 h, and the resulting mixture was filtered through Celite. The eluent was concentrated under reduced pressure to give a pale yellow oil (402 mg, only about 50% conversion by <sup>1</sup>H NMR). Again, to a suspension of the pale yellow oil (402 mg) and dipotassium azodicarboxylate (768 mg, 3.95 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4.0 mL) was added a 1.0 M solution of acetic acid in CH<sub>2</sub>Cl<sub>2</sub> (8.0 mL, 8.0 mmol) dropwise at reflux. Additional dipotassium carboxylate (770 mg, 3.96 mmol) and a 1.0 M solution of acetic acid in CH<sub>2</sub>Cl<sub>2</sub> (8.0

ml, 8.0 mmol) were added after 5, 9, 12, 32, 36, 49, 58 h, respectively. The reaction mixture was stirred under reflux for a total 72 h, and the resulting white suspension was allowed to cool to room temperature, and diluted with water. The aqueous layer was extracted with  $\text{CHCl}_3$ , and washed with brine, dried over  $\text{Na}_2\text{SO}_4$ . Concentration under reduced pressure gave a pale yellow oil (390 mg). To a solution of the pale yellow oil (390 mg, 0.763 mmol) in THF (5.0 mL) was added a 1.0 M solution of TBAF in THF (2.3 mL, 2.3 mmol). After being refluxed for 13 h, the resulting mixture was allowed to cool to room temperature, and diluted with water. The aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , concentrated under reduced pressure to give a yellow oil. The residue was purified by column chromatography (hexane/EtOAc 5:1) to afford (20*R*)-**17** (284 mg, 75% for 2 steps) as a white solid. Mp 95–96 °C;  $[\alpha]_{\text{D}}^{20} +13.0$  (*c* 1.00,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 3333 (br), 2970, 2924, 2901, 1501, 1454, 1381, 1084, 1049  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.19 (d, *J* = 8.6 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.63 (d, *J* = 2.6 Hz, 1H), 3.77 (s, 3H), 2.92–2.80 (m, 2H), 2.29–2.16 (m, 2H), 2.04–1.98 (m, 1H), 1.94–1.89 (m, 1H), 1.84–1.73 (m, 2H), 1.56–1.24 (m, 13H), 1.22 (s, 6H), 1.13–1.05 (m, 1H), 0.91 (s, 3H), 0.72 (m, 1H), 0.42 (dd, *J* = 4.9, 4.9, Hz, 1H), 0.27 (dd, *J* = 8.6, 4.0 Hz, 1H);  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 157.4, 138.1, 132.9, 126.2, 113.7, 111.4, 71.1, 55.2, 54.7, 43.9, 43.7, 41.6, 39.1, 36.7, 36.2, 35.6, 29.92, 29.90, 29.3, 29.2, 27.7, 26.5, 25.4, 24.8, 22.6, 18.4, 16.2; *m/z* (EI) 396 (M), 378 (M–H<sub>2</sub>O), 363 (M–H<sub>2</sub>O–Me), 348 (M–H<sub>2</sub>O–2Me);

HRMS (ESI):  $[M+H]^+$ , found 397.3115.  $C_{27}H_{41}O_2$  requires 397.3101.

4.2.19. *Synthesis* of  
(2'S,8S,9S,13S,14S,17S)-2'-(4-hydroxy-4-methylpentyl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[a]phenanthrene-17,1'-cyclopropan]-3-ol ((20S)-**18**). To a solution of diphenylphosphine (0.12 mL, 0.69 mmol) in THF (1.0 mL) were added a 2.5 M solution of *n*-BuLi in hexane (0.27 mL, 0.68 mmol) and a solution of (20S)-**17** (52.0 mg, 0.132 mmol) in THF (1.0 mL). After the red solution was heated under reflux for 25 h, the resulting mixture was allowed to cool to room temperature. The mixture was diluted with EtOAc, washed with 10% HCl, saturated aqueous NaHCO<sub>3</sub> and brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration under reduced pressure gave a pale yellow oil, which was purified by column chromatography (hexane/EtOAc 7:3) to give (20S)-**18** (38.2 mg, 76%) as a white solid; Mp 80–83 °C;  $[\alpha]_D^{20} +9.85$  (*c* 0.50, CHCl<sub>3</sub>);  $\nu_{\max}$  (KBr) 3717 (br), 3292 (br), 2968, 2932, 2864, 1611, 1585, 1501, 1452, 1375, 1287, 1240 cm<sup>-1</sup>;  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 7.15 (d, *J* = 8.6 Hz, 1H), 6.62 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.56 (d, *J* = 2.3 Hz, 1H), 4.71 (br s, 1H), 2.90–2.77 (m, 2H), 2.30–2.13 (m, 2H), 2.09–1.99 (m, 1H), 1.97–1.83 (m, 2H), 1.55–1.21 (m, 19H), 1.16 (ddd, *J* = 12.3, 2.9, 2.9 Hz, 1H), 1.08 (ddd, *J* = 12.6, 12.6, 4.0 Hz, 1H), 0.85 (dd, *J* = 9.2, 4.3 Hz, 1H), 0.76 (s, 3H), 0.58–0.51 (m, 1H), –0.26 (dd, *J* = 4.9, 4.9 Hz, 1H);  $\delta_C$  (125 MHz, CDCl<sub>3</sub>) 153.4, 138.4,

132.9, 126.4, 115.2, 112.6, 71.5, 53.7, 44.0, 43.8, 41.4, 39.5, 36.0, 33.3, 31.6, 29.7, 29.2, 29.1, 29.0, 27.8, 26.2, 24.9, 24.6, 17.5, 17.11, 17.07;  $m/z$  (EI) 382 (M), 364 (M-H<sub>2</sub>O), 349 (M-H<sub>2</sub>O-Me); HRMS (ESI): [M+H]<sup>+</sup>, found 383.2931. C<sub>26</sub>H<sub>39</sub>O<sub>2</sub> requires 383.2945.

4.2.20. *Synthesis* of  
(2'*R*,8*S*,9*S*,13*S*,14*S*,17*S*)-2'-(4-hydroxy-4-methylpentyl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,1'-cyclopropan]-3-ol ((20*R*)-**18**). To a solution of diphenylphosphine (0.33 ml, 1.90 mmol) in THF (1 ml) were added a 2.5 M solution of *n*-BuLi in hexane (0.76 ml, 1.90 mmol) and a solution of (20*R*)-**17** (151 mg, 0.381 mmol) in THF (3 ml). After the red solution was heated under reflux for 21 h, the resulting mixture was allowed to cool to room temperature. The mixture was diluted with EtOAc, washed with 10% HCl, saturated aqueous NaHCO<sub>3</sub> and brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration under reduced pressure gave a pale yellow oil, which was purified by column chromatography (hexane/EtOAc 4:1 to 7:3) to give (20*R*)-**18** (133 mg, 91%) as a white solid; Mp 192–193 °C; [α]<sub>D</sub><sup>20</sup> +14.1 (*c* 1.00, THF); ν<sub>max</sub> (KBr) 3319 (br), 2968, 2857, 2816, 1614, 1585, 1504, 1440, 1375, 1283, 1213, 1148, 895 cm<sup>-1</sup>; δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 7.14 (d, *J* = 8.3 Hz, 1H), 6.62 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.56 (d, *J* = 2.3 Hz, 1H), 2.88–2.78 (m, 2H), 2.26–2.15 (m, 2H), 2.05–1.98 (m, 1H), 1.93–1.87 (m, 1H), 1.84–1.73 (m, 2H), 1.56–1.29 (m, 14H), 1.23 (s,

6H), 1.10–1.05 (m, 1H), 0.91 (s, 3H), 0.72 (m, 1H), 0.42 (dd,  $J = 4.3, 4.3$ , Hz, 1H), 0.27 (dd,  $J = 8.6, 4.0$  Hz, 1H);  $\delta_{\text{C}}$  (125 MHz, acetone- $d_6$ ) 156.5, 139.0, 132.7, 127.5, 116.5, 114.1, 70.7, 56.2, 45.4, 45.2, 43.0, 40.9, 38.2, 37.5, 37.0, 31.5, 31.0, 30.4, 29.1, 27.9, 26.8, 26.0, 24.1, 19.5, 17.3;  $m/z$  (EI) 382 (M), 364 (M–H<sub>2</sub>O), 349 (M–H<sub>2</sub>O–Me); HRMS (ESI):  $[M+Na]^+$ , found 405.2772. C<sub>26</sub>H<sub>38</sub>O<sub>2</sub>Na requires 405.2764.

4.2.21. *Synthesis* of *tert-butyl(((6bS,8aS,8bR,9S,10aS,11aS,11bR)-4-methoxy-8a-methyl-9-((E)-4-methyl-4-((triethylsilyl)oxy)pent-1-en-1-yl)-1,2,6b,7,8,8a,9,10,10a,11,11a,11b-dodecahydro-8bH-cyclobuta[3,4]cyclopenta[1,2-a]phenanthrene-8b-yl)oxy)dimethylsilane (trans-19)*. To a solution of oxalyl chloride (0.38 mL, 4.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL) was dropwise added a solution of DMSO (0.47 mL, 6.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6.0 mL) at –78 °C. After being stirred for 5 min, *trans-7* (1.00 g, 2.19 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (11 mL) was dropwise added. After being stirred for 40 min at –78 °C, triethylamine (1.8 mL, 13 mmol) was added. After being stirred for 20 min, the resulting mixture was allowed to warm to ambient temperature, diluted with CHCl<sub>3</sub>, and quenched with saturated aqueous NH<sub>4</sub>Cl. The aqueous layer was extracted with CHCl<sub>3</sub>, and the combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The residue was dissolved in CHCl<sub>3</sub> and passed through a short pad of silica gel with hexane/diethyl ether (10:1) to obtain a

crude aldehyde (936 mg) as a white solid, which was used directly in the next step without further purification. To a solution of **15** (1.07 g, 2.69 mmol) in THF (7 mL) was added a 1.0 M solution of LiHMDS in toluene (2.7 mL, 2.7 mmol) at  $-78\text{ }^{\circ}\text{C}$  under argon. After being stirred for 30 min, a solution of the above crude aldehyde (936 mg, 2.06 mmol) in THF (13 mL) was added, and stirred for 1 h. The reaction mixture was diluted with EtOAc, and quenched with saturated aqueous  $\text{NH}_4\text{Cl}$ . The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo* to give a yellow solid. The crude material was purified by column chromatography (hexane/diethyl ether 50:1) to afford an inseparable *E/Z* mixture of *trans*-**19** (1.18 g, 84% for 2 steps, *E/Z* 3:2) as a colorless oil. The following data were collected as a 3:2 *E/Z* mixture;  $[\alpha]_{\text{D}}^{20} +11.5$  (*c* 1.00,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 2955, 2928, 1501, 1458, 1254, 1238, 1045  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.22 (d,  $J = 8.6$  Hz, 0.4H), 7.21 (d,  $J = 8.6$  Hz, 0.6H), 6.71 (dd,  $J = 8.6, 2.9$  Hz, 1H), 6.63 (d,  $J = 2.9$  Hz, 1H), 5.86–5.77 (m, 1H), 5.49 (ddt,  $J = 10.9, 7.5, 0.9$  Hz, 0.4H), 5.43 (ddt,  $J = 15.5, 7.2, 1.4$  Hz, 0.6H), 3.77 (s, 3H), 3.44–3.36 (m, 0.4H), 3.26–3.18 (m, 0.6H), 2.93–2.81 (m, 2H), 2.60–2.54 (m, 0.4H), 2.51–2.42 (m, 1H), 2.38–2.28 (m, 1H), 2.27–2.13 (m, 4H), 2.06 (ddd,  $J = 3.8, 3.8, 3.2$  Hz, 0.6H), 1.97–1.90 (m, 1H), 1.89–1.78 (m, 1H), 1.60–1.33 (m, 6H), 1.20 (s, 1.2H), 1.18 (s, 1.2H), 1.17 (s, 3.6H), 1.08–0.89 (m, 19H), 0.70 (s, 1.8H), 0.69 (s, 1.2H), 0.57 (q,  $J = 8.1$  Hz, 2.4H), 0.56 (q,  $J = 8.0$  Hz, 3.6H), 0.27 (s, 1.2H), 0.21 (s, 1.8H), 0.133 (s, 1.8H), 0.127 (s, 1.2H);  $\delta_{\text{C}}$  (125 MHz,

CDCl<sub>3</sub>) 157.4, 157.3, 138.1, 138.0, 133.02, 133.0, 132.7, 132.6, 127.0, 126.5, 126.4, 125.6, 113.7, 111.41, 111.38, 92.0, 91.7, 73.6, 73.4, 55.2, 50.5, 48.47, 48.45, 48.3, 47.1, 47.0, 45.8, 44.0, 43.8, 43.3, 41.5, 41.0, 38.87, 38.85, 33.7, 33.6, 31.2, 30.0, 29.94, 29.91, 29.85, 29.7, 28.7, 27.89, 27.85, 26.42, 26.37, 26.0, 25.9, 25.8, 18.3, 17.01, 16.95, 7.1, 6.8, -2.4, -2.7, -3.1, -3.3 (some signals missing); *m/z* (EI) 638 (M), 623 (M-Me), 609 (M-Et), 581 (M-*t*Bu), 506 (M-TESOH); HRMS (ESI): [M+Na]<sup>+</sup>, found 661.4428. C<sub>39</sub>H<sub>66</sub>O<sub>3</sub>Si<sub>2</sub>Na requires 661.4442.

4.2.22.

*Synthesis* of

*tert-butyl(((6*bS*,8*aS*,8*bR*,9*R*,10*aS*,11*aS*,11*bR*)-4-methoxy-8*a*-methyl-9-((*E*)-4-methyl-4-((triethylsilyl)oxy)pent-1-en-1-yl)-1,2,6*b*,7,8,8*a*,9,10,10*a*,11,11*a*,11*b*-dodecahydro-8*bH*-cyclobuta[3,4]cyclopenta[1,2-*a*]phenanthrene-8*b*-yl)oxy)dimethylsilane (cis-19). To a solution of oxalyl chloride (0.49 mL, 5.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (7.0 mL) was dropwise added a solution of DMSO (0.61 mL, 8.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6.0 mL) at -78 °C. After being stirred for 5 min, a solution of *cis*-7 (1.30 g, 2.85 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was dropwise added. After being stirred for 40 min at -78 °C, triethylamine (2.4 mL, 17 mmol) was added. After being stirred for 20 min, the resulting mixture was allowed to warm to ambient temperature, diluted with CHCl<sub>3</sub>, and quenched with saturated aqueous NH<sub>4</sub>Cl. The aqueous layer was extracted with CHCl<sub>3</sub>, and the combined organic layers*

were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The residue was dissolved in  $\text{CHCl}_3$  and passed through a short pad of silica gel with hexane/EtOAc (20:1) to obtain a crude aldehyde (1.21 g) as a white solid, which was used directly in the next step without further purification. To a solution of **15** (1.39 g, 3.48 mmol) in THF (8.0 mL) was added a 1.0 M solution of LiHMDS in toluene (3.5 mL, 3.5 mmol) at  $-78\text{ }^\circ\text{C}$  under argon. After being stirred for 30 min, a solution of the above crude aldehyde (1.21 g, 2.66 mmol) in THF (19 mL) was added, and stirred for 1 h. The reaction mixture was diluted with EtOAc, and quenched with saturated aqueous  $\text{NH}_4\text{Cl}$ . The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo* to give a yellow oil. The crude material was purified by column chromatography (hexane/EtOAc 50:1) to afford an inseparable *E/Z* mixture of *cis*-**19** (1.29 g, 71% for 2 steps, *E/Z* 1:1) as a colorless oil. The following data were collected as a 1:1 *E/Z* mixture;  $[\alpha]_{\text{D}}^{20} +4.95$  (*c* 1.00,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 2951, 2928, 2878, 2855, 1501, 1462, 1234, 1153, 1099, 1045, 1018  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.23 (d,  $J = 8.9$  Hz, 1H), 6.72 (dd,  $J = 8.6, 2.3$  Hz, 1H), 6.64 (d,  $J = 2.3$  Hz, 1H), 5.74 (dt,  $J = 10.0, 7.9$  Hz, 0.5H), 5.43 (dd,  $J = 15.5, 6.1$  Hz, 0.5H), 5.45–5.32 (m, 1H), 3.78 (s, 3H), 3.27–3.21 (m, 0.5H), 3.11–3.04 (m, 0.5H), 2.96–2.82 (m, 2H), 2.60 (dd,  $J = 7.5, 7.5$  Hz, 0.5H), 2.54 (dd,  $J = 8.0, 8.0$  Hz, 0.5H), 2.35–2.05 (m, 5H), 1.99–1.90 (m, 1H), 1.74–1.64 (m, 1H), 1.62–1.38 (m, 8H), 1.20 (s, 1.5H), 1.19 (s, 1.5H), 1.18 (s, 1.5H), 1.16 (s, 1.5H), 0.95 (t,  $J = 8.0$  Hz, 9H),

0.92 (s, 4.5H), 0.90 (s, 4.5H), 0.70 (s, 1.5H), 0.69 (s, 1.5H), 0.574 (q,  $J = 7.7$  Hz, 3H), 0.569 (q,  $J = 8.1$  Hz, 3H), 0.26 (s, 1.5H), 0.22 (s, 1.5H), 0.10 (s, 1.5H), 0.08 (s, 1.5H);  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 157.4, 137.9, 134.1, 132.90, 132.87, 132.8, 126.3, 126.1, 125.3, 113.8, 111.4, 90.7, 90.5, 73.6, 73.5, 55.1, 48.4, 48.34, 48.32, 47.0, 46.9, 44.31, 44.27, 43.4, 40.8, 40.5, 40.3, 38.7, 38.6, 35.9, 32.1, 31.9, 30.4, 30.0, 29.9, 29.80, 29.76, 29.6, 29.5, 29.3, 28.3, 27.8, 26.14, 26.10, 18.64, 18.56, 14.6, 14.5, 7.11, 6.8, -1.46, -1.51, -2.4 ppm (some signals missing);  $m/z$  (EI) 638 (M), 609 (M-Et), 581 (M-*t*Bu), 506 (M-TESOH); HRMS (ESI):  $[\text{M}+\text{Na}]^+$ , found 661.4439.  $\text{C}_{39}\text{H}_{66}\text{O}_3\text{Si}_2\text{Na}$  requires 661.4442.

4.2.23.

Synthesis

of

5-((6*bS*,8*aS*,8*bS*,9*R*,10*aS*,11*aS*,11*bR*)-8*b*-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-8*a*-methyl-2,6*b*,7,8,8*a*,8*b*,9,10,10*a*,11,11*a*,11*b*-dodecahydro-1*H*-cyclobuta[3,4]cyclopenta[1,2-*a*]phenanthren-9-yl)-2-methylpentan-2-ol (*trans*-**20**). A mixture of *trans*-**19** (1.18 g, 1.85 mmol, *E/Z* 3:2), 10% Pd/C (200 mg) and EtOAc/MeOH (1:1, 18 mL) was stirred under  $\text{H}_2$  (1 atm) at room temperature for 10 h. The reaction mixture was filtered through Celite, and concentrated under reduced pressure to give a pale yellow oil, which was purified by column chromatography (hexane/diethyl ether 3:2) to afford *trans*-**20** (626 mg, 64%) as a white solid; Mp 52–55 °C;  $[\alpha]_{\text{D}}^{20} +9.64$  ( $c$  1.00,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 3422 (br), 2940, 2862, 1612, 1485, 1454, 1238, 1211, 1103  $\text{cm}^{-1}$ ;

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.22 (d,  $J = 8.6$  Hz, 1H), 6.71 (dd,  $J = 8.6, 2.6$  Hz, 1H), 6.67 (d,  $J = 2.3$  Hz, 1H), 3.78 (s, 3H), 2.90–2.82 (m, 2H), 2.59 (dddd,  $J = 12.6, 12.6, 8.0, 5.5$  Hz, 1H), 2.48–2.44 (m, 1H), 2.36–2.22 (m, 3H), 1.95–1.88 (m, 2H), 1.84–1.72 (m, 2H), 1.68–1.64 (m, 2H), 1.56–1.38 (m, 7H), 1.36–1.28 (m, 1H), 1.21 (s, 6H), 1.16–1.09 (m, 1H), 0.89 (s, 9H), 0.82 (ddd,  $J = 12.9, 8.6, 4.9$  Hz, 1H), 0.72 (s, 3H), 0.18 (s, 3H), 0.11 (s, 3H);  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 157.3, 138.1, 132.9, 126.4, 113.7, 111.4, 90.4, 71.0, 55.2, 48.8, 48.6, 47.5, 44.0, 43.9, 41.5, 39.0, 33.3, 31.9, 31.4, 30.0, 29.3, 29.2, 27.9, 27.4, 26.5, 25.9, 23.1, 18.3, 17.5, –2.7, –3.0;  $m/z$  (EI) 526 (M), 511 (M–Me), 411 (M–TBS); HRMS (ESI):  $[\text{M}+\text{Na}]^+$ , found 549.3752.  $\text{C}_{33}\text{H}_{54}\text{O}_3\text{SiNa}$  requires 549.3734.

4.2.24. *Synthesis of*  
*5-((6bS,8aS,8bS,9S,10aS,11aS,11bR)-8b-((tert-butyl dimethylsilyl)oxy)-4-methoxy-8a-methyl-2,6b,7,8,8a,8b,9,10,10a,11,11a,11b-dodecahydro-1H-cyclobuta[3,4]cyclopenta[1,2-a]phenanthren-9-yl)-2-methylpentan-2-ol (cis-20)*. A mixture of *cis-19* (1.29 g, 2.02 mmol, *E/Z* 1:1), 10% Pd/C (215 mg) and EtOAc/MeOH (1:1, 20 mL) was stirred under  $\text{H}_2$  (1 atm) at room temperature for 10 h. The reaction mixture was filtered through Celite, and concentrated under reduced pressure to give a white gum, which was purified by column chromatography (hexane/diethyl ether 3:2) to afford *cis-20* (847 mg, 80%) as a white solid; Mp 63–66 °C;

$[\alpha]_{\text{D}}^{20} +19.0$  ( $c$  1.00,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (neat) 3325 (br), 2970, 2928, 1612, 1500, 1254, 1092, 1045  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.22 (d,  $J = 8.6$  Hz, 1H), 6.72 (dd,  $J = 8.6, 2.6$  Hz, 1H), 6.64 (d,  $J = 2.6$  Hz, 1H), 3.78 (s, 3H), 2.89–2.83 (m, 2H), 2.54 (dd,  $J = 7.5, 7.5$  Hz, 1H), 2.38–2.30 (m, 2H), 2.23 (dd,  $J = 9.9, 9.9$  Hz, 1H), 1.93–1.83 (m, 2H), 1.68–1.21 (m, 15H), 1.20 (s, 6H), 0.91 (s, 9H), 0.69 (s, 3H), 0.24 (s, 3H), 0.11 (s, 3H);  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 157.4, 138.0, 132.9, 126.4, 113.8, 111.4, 90.2, 71.1, 55.2, 48.3, 46.6, 44.4, 44.3, 40.0, 38.6, 38.1, 32.0, 31.9, 29.9, 29.7, 29.5, 29.2, 29.0, 27.8, 26.2, 23.0, 18.6, 14.6, -1.2, -2.3;  $m/z$  (EI) 526 (M), 511 (M-Me), 411 (M-TBS); HRMS (ESI):  $[\text{M}+\text{Na}]^+$ , found 549.3737.  $\text{C}_{33}\text{H}_{54}\text{O}_3\text{SiNa}$  requires 549.3734.

4.2.25.

Synthesis

of

(6*bS*,8*aS*,8*bS*,9*R*,10*aS*,11*aS*,11*bR*)-8*b*-((*tert*-butyldimethylsilyl)oxy)-9-(4-hydroxy-4-methylpentyl)-8*a*-methyl-2,6*b*,7,8,8*a*,8*b*,9,10,10*a*,11,11*a*,11*b*-dodecahydro-1*H*-cyclobuta[3,4]cyclopenta[1,2-*a*]phenanthren-4-ol (*trans*-**21**). To a solution of diphenylphosphine (0.53 ml, 3.1 mmol) in THF (4.0 mL) were added a 2.5 M solution of *n*-BuLi in hexane (1.2 mL, 3.0 mmol) and a solution of *trans*-**20** (533 mg, 1.01 mmol) in THF (6.0 mL). The red solution was heated under reflux for 27 h, and the diphenyl phosphine (0.35 mL, 2.0 mmol) and a 2.5 M solution of *n*-BuLi in hexane (0.81 mL, 2.0 mmol) were added again to the mixture. After being stirred for additional 19 h under reflux, the resulting mixture was allowed to cool to room temperature.

The mixture was diluted with EtOAc, washed with 10% HCl, saturated aqueous NaHCO<sub>3</sub> and brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration under reduced pressure gave a pale yellow oil, which was purified by column chromatography (hexane/EtOAc 3:1) to give *trans*-**21** (458 mg, 88%) as a white solid. Analytical sample was obtained by recrystallization from EtOAc as a white powder; Found 74.70; H, 10.29. C<sub>32</sub>H<sub>52</sub>O<sub>3</sub>Si requires C, 74.94; H, 10.22%; Mp 178–179 °C; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +5.35 (*c* 1.00, CHCl<sub>3</sub>);  $\nu_{\max}$  (neat) 3329 (br), 2974, 2928, 2893, 1454, 1088, 1049 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 7.17 (d, *J* = 8.3 Hz, 1H), 6.63 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.57 (d, *J* = 2.6 Hz, 1H), 2.88–2.79 (m, 2H), 2.62–2.54 (m, 1H), 2.48–2.44 (m, 1H), 2.32 (ddd, *J* = 12.0, 12.0, 9.5 Hz, 1H), 2.26–2.20 (m, 2H), 1.94–1.88 (m, 2H), 1.84–1.72 (m, 2H), 1.67–1.60 (m, 2H), 1.57–1.25 (m, 9H), 1.21 (s, 6H), 1.16–1.09 (m, 1H), 0.89 (s, 9H), 0.82 (ddd, *J* = 12.2, 8.5, 5.2 Hz, 1H), 0.72 (s, 3H), 0.18 (s, 3H), 0.11 (s, 3H);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 153.4, 138.3, 132.7, 126.6, 115.2, 112.6, 90.4, 71.4, 48.8, 48.6, 47.5, 43.9, 41.5, 38.9, 33.3, 31.9, 31.4, 29.8, 29.2, 29.1, 27.8, 27.3, 26.5, 25.9, 23.1, 18.3, 17.5, 18.3, 17.5, -2.7, -3.0; *m/z* (EI) 512 (M), 453 (M-2Me-OH), 397 (M-TBS).

4.2.26.

Synthesis

of

(6*bS*,8*aS*,8*bS*,9*S*,10*aS*,11*aS*,11*bR*)-8*b*-((*tert*-butyldimethylsilyl)oxy)-9-(4-hydroxy-4-methylpentyl)-8*a*-methyl-2,6*b*,7,8,8*a*,8*b*,9,10,10*a*,11,11*a*,11*b*-dodecahydro-1*H*-cyclobuta[3,4]cyclopenta[1,2-*a*]phenanthren-4-ol

(*cis*-**21**). To a solution of diphenylphosphine (0.99 mL, 5.7 mmol) in THF (4.0 mL) were added a 2.5 M solution of *n*-BuLi in hexane (2.3 mL, 5.8 mmol) and a solution of *cis*-**20** (603 mg, 1.14 mmol) in THF (7.0 mL). After the red solution was heated under reflux for 20 h, the resulting mixture was allowed to cool to room temperature. The mixture was diluted with EtOAc, washed with 10% HCl, saturated aqueous NaHCO<sub>3</sub> and brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration under reduced pressure gave a pale yellow oil, which was purified by column chromatography (hexane/EtOAc 3:1) to give *cis*-**21** (455 mg, 78%) as a white solid. Analytical sample was obtained by recrystallization from EtOAc as a white powder; C, 74.79; H, 10.44. C<sub>32</sub>H<sub>52</sub>O<sub>3</sub>Si requires C, 74.94; H, 10.22%; Mp 205–206 °C; [α]<sub>D</sub><sup>20</sup> +21.5 (*c* 1.00, THF); ν<sub>max</sub> (neat) 3314 (br), 2974, 2882, 1088, 1045 cm<sup>-1</sup>; δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 7.17 (d, *J* = 8.3 Hz, 1H), 6.64 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.57 (d, *J* = 2.3 Hz, 1H), 4.56 (s, 1H), 2.85–2.82 (m, 2H), 2.54 (ddd, *J* = 8.4, 8.4, 1.6 Hz, 1H), 2.35–2.28 (m, 2H), 2.23–2.19 (m, 1H), 1.92–1.83 (m, 2H), 1.67–1.24 (m, 16H), 1.21 (s, 3H), 1.20 (s, 3H), 0.91 (s, 9H), 0.69 (s, 3H), 0.24 (s, 3H), 0.10 (s, 3H); δ<sub>C</sub> (125 MHz, THF-*d*<sub>8</sub>) 156.4, 138.1, 131.6, 126.7, 115.9, 113.6, 91.4, 69.7, 49.3, 47.6, 45.5, 45.4, 41.0, 40.0, 39.2, 33.3, 32.7, 30.7, 30.6, 30.1, 29.4, 28.9, 27.2, 26.7, 23.8, 19.4, 15.3, –1.0, –2.0; *m/z* (EI) 512 (M).

4.2.27.

Synthesis

of

(6*bS*,8*aS*,8*bS*,9*R*,10*aS*,11*aS*,11*bR*)-9-(4-hydroxy-4-methylpentyl)-8*a*-methyl-1,2,6*b*,7,8,8*a*,9,10,10*a*,11,11*a*,11*b*-dodecahydro-8*bH*-cyclobuta[3,4]cyclopenta[1,2-*a*]phenanthrene-4,8*b*-diol (*trans*-**22**). To a solution of *trans*-**21** (120 mg, 0.234 mmol) in THF (1.0 mL) was added a 1.0 M solution of TBAF in THF (1.2 mL, 1.2 mmol), and the solution was heated under reflux for 24 h. The resulting mixture was allowed to cool to room temperature, and purified by column chromatography (hexane/EtOAc 2:3) to give *trans*-**22** (71 mg, 76%) as a white solid; Mp 197–198 °C;  $[\alpha]_D^{20} +12.8$  (*c* 1.00, THF);  $\nu_{\max}$  (THF) 3348 (br), 1454, 1361, 1288, 1222, 1080  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz, MeOH-*d*<sub>4</sub>) 7.09 (d, *J* = 8.6 Hz, 1H), 6.54 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.48 (d, *J* = 1.7 Hz, 1H), 2.81–2.76 (m, 2H), 2.62–2.55 (m, 1H), 2.42–2.23 (m, 3H), 2.21 (ddd, *J* = 11.1, 11.1, 3.0 Hz, 1H), 2.02–1.91 (m, 3H), 1.80–1.65 (m, 3H), 1.56–1.33 (m, 9H), 1.161 (s, 3H), 1.158 (s, 3H), 0.86 (m, 1H), 0.80 (s, 3H);  $\delta_{\text{C}}$  (125 MHz, MeOH-*d*<sub>4</sub>) 155.9, 138.8, 132.6, 127.3, 116.0, 113.7, 89.2, 71.4, 50.0, 49.6, 48.9, 45.3, 44.8, 42.4, 40.6, 33.9, 33.4, 32.6, 30.8, 29.3, 29.1, 29.0, 28.3, 27.7, 24.1, 17.3; *m/z* (EI) 398 (M), 380 (M–H<sub>2</sub>O); HRMS (ESI): [M+Na]<sup>+</sup>, found 421.2720. C<sub>26</sub>H<sub>38</sub>O<sub>3</sub>Na requires 421.2713.

4.2.28.

Synthesis

of

(6*bS*,8*aS*,8*bS*,9*S*,10*aS*,11*aS*,11*bR*)-9-(4-hydroxy-4-methylpentyl)-8*a*-methyl-1,2,6*b*,7,8,8*a*,9,10,10*a*,11,11*a*,11*b*-dodecahydro-8*bH*-cyclobuta[3,4]cyclopenta[1,2-*a*]phenanthrene-4,8*b*-diol (*cis*-**22**). To a solution of *cis*-**21**

(138 mg, 0.269 mmol) in THF (1.0 mL) was added a 1.0 M solution of TBAF in THF (2.2 mL, 2.2 mmol), and the solution was heated under reflux for 55 h. After cooling to room temperature, the resulting mixture was diluted with EtOAc, and washed with water. The aqueous layer was extracted with EtOAc, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to give a yellow oil. The crude material was purified by column chromatography (hexane/EtOAc 1:1 to 2:3) to give *cis*-**22** (70.0 mg, 66%) as a white solid; Mp 222–223 °C (dec.);  $[\alpha]_D^{20} +66.9$  (*c* 1.00, THF);  $\nu_{\max}$  (THF) 3298 (br), 2932, 1616, 1582, 1454, 1369, 1069 cm<sup>-1</sup>;  $\delta_H$  (500 MHz, DMSO-*d*<sub>6</sub>) 8.98 (s, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 6.50 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.43 (d, *J* = 2.0 Hz, 1H), 4.46 (s, 1H), 4.02 (s, 1H), 2.78–2.65 (m, 2H), 2.29–2.09 (m, 4H), 1.85–1.61 (m, 3H), 1.50–1.13 (m, 14H), 1.04 (s, 6H), 0.67 (s, 3H);  $\delta_C$  (125 MHz, DMSO-*d*<sub>6</sub>) 154.9, 137.2, 130.6, 126.0, 114.9, 112.7, 86.3, 68.9, 48.8, 45.5, 44.2, 43.6, 40.2, 38.5, 36.4, 31.9, 31.5, 29.5, 29.4, 29.2, 28.8, 27.4, 25.9, 22.1, 14.1; *m/z* (EI) 398 (M), 380 (M–H<sub>2</sub>O), 365 (M–H<sub>2</sub>O–Me); HRMS (ESI): [M+H]<sup>+</sup>, found 399.2882. C<sub>26</sub>H<sub>39</sub>O<sub>3</sub> requires 399.2899.

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### Supplementary data

Copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for all new compounds as well as X-ray crystal structures of *trans*- and *cis*-**22**.

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