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A Facile Synthesis of the Basic Steroidal Skeleton Using a Pauson−Khand Reaction as a Key Step

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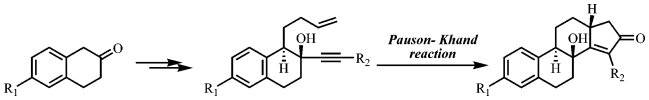
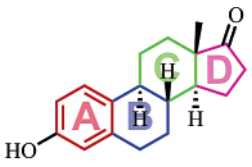


A high-yield synthesis of steroid-type molecules under mild reaction conditions is achieved in two steps involving nucleophilic addition of alkynyl cerium reagent to an easily enolizable carbonyl compound (β-tetralone) followed by an intramolecular Pauson−Khand reaction.

The Pauson−Khand reaction is a carbonylative coupling of alkyne and alkene in the presence of cobalt carbonyl complex giving a cyclopentenone framework.[1] It has received great attention due to its potential application in complex molecule synthesis and has been used as a key reaction in the synthesis of natural products, pharmaceuticals, and fine chemicals.[2] Despite its latent potential for the preparation of steroid framework from readily available materials, little attention has thus far been paid to the synthesis of steroid framework.[3]



Estrone (1)

Estrone (**1**) is a natural hormone having a steroid framework with an unsaturated A ring. Modification of estrone structure can bring about remarkable changes in the pharmacological activity of estrone, and its derivatives, bearing a variety of substituents, are also potential compounds exhibiting a range of biological activity. A variety of reaction processes exist for the construction of the steroid ring system;[4] however, most of these processes involve multistep synthetic transformations. Recently, a number of elegant transition-metal-catalyzed total syntheses have been reported.[5] Moreover, a few recent reports highlight the construction of the steroid ring system through tandem reaction processes.[6] To construct the steroid nucleus, they used cyclization of polyenes or polyynes, coupling, and ring expansion reactions.

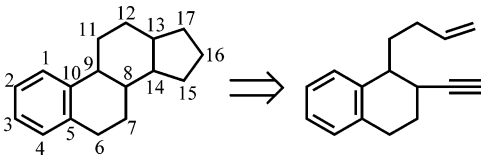
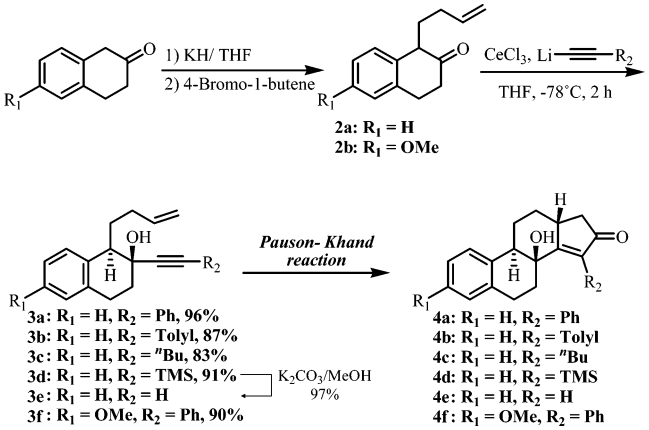


FIGURE 1. Synthetic strategy for a steroidal skeleton.

SCHEME 1. Scheme for the Synthesis of Steroid Analogues



Our ongoing project has been the development of a cycloaddition reaction in the synthesis of ring compounds using the Pauson−Khand reaction.[7] We report here on the generation of steroid-type ring skeletal compounds (**2**) starting from β-tetralone, using an intramolecular Pauson−Khand reaction as a key step (Figure 1).

We planned to use the Pauson−Khand reaction to make C and D rings. Thus, β-tetralone was chosen as a starting material to make A and B rings. We envisioned that a base treatment of β-tetralone followed by a reaction with 4-bromo-1-butene would lead to the introduction of a C=C double to an α-position of the carbonyl group and that a reaction of the resulting substituted tetralone with alkynylide would give an enyne.

(1) Pauson, P. L.; Khand, I. U.; Knox, G. R.; Watts, W. E. *J. Chem. Soc. D* **1971**, 36.

(2) For recent reviews, see: (a) Park, K. H.; Chung, Y. K. *Synlett* **2005**, 545. (b) Rodriguez Rivero, M.; Adrio, J.; Carretero, J. C. *Synlett* **2005**, 26. (c) Gibson, S. E.; Mainolfi, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 3022. (d) Bonaga, L. V. R.; Krafft, M. E. *Tetrahedron* **2004**, *60*, 9795. (e) Hanson, B. E. *Comments Inorg. Chem.* **2002**, *23*, 289. (f) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263.

(3) Krafft, M. E.; Dasse, O. A.; Shao, B. *Tetrahedron* **1998**, *54*, 7033.

(4) (a) Pattenden, G.; Gonzalez, M. A.; McCulloch, S.; Walter, A.; Woodhead, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12024 and references therein. (b) Nagyar, A.; Wolfling, J.; Kubas, M.; Seijo, J. A. C.; Sevvana, M.; Herbst-Imer, R.; Forgo, P.; Schneider, G. *Steroids* **2004**, *69*, 301. (c) Pattenden, G.; Reddy, L. K.; Walter, A. *Tetrahedron Lett.* **2004**, *45*, 4027. (d) Hu, Q. Y.; Rege, P. D.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 5984.

(5) (a) Sünnemann, H. W.; de Meijere, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 895. (b) Skoda-Földes, R.; Kollár, L. *Chem. Rev.* **2003**, *103*, 4095. (c) Wu, H. P.; Aumann, R.; Frolich, R.; Wibbeling, B. *Chem.−Eur. J.* **2002**, *8*, 910. (d) Aumann, R.; Meyer, A. G.; Frohlich, R. *J. Am. Chem. Soc.* **1996**, *118*, 10853. (e) Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1995**, *60*, 2962.

(6) (a) Petit, M.; Aubert, C.; Malacria, M. *Org. Lett.* **2004**, *6*, 3937. (b) Michellys, P. Y.; Marin, P.; Toupet, L.; Pellissier, H.; Santelli, M. *J. Org. Chem.* **2001**, *66*, 115. (c) Tietze, L. F.; Nöbel, T.; Spescha, M. *J. Am. Chem. Soc.* **1998**, *120*, 8971.

(7) (a) Park, K. H.; Son, S. U.; Chung, Y. K. *Adv. Synth. Catal.* **2005**, *347*, 854. (b) Kim, D. H.; Chung, Y. K. *Chem. Commun.* **2005**, 1634. (c) Park, K. H.; Son, S. U.; Chung, Y. K. *Org. Lett.* **2004**, *6*, 1183.

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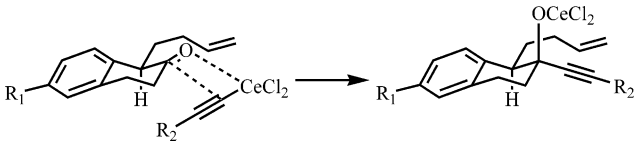


FIGURE 2. Diastereoselective addition of organocerium reagent.

Scheme 1 shows the synthetic pathway. In the synthesis of **3a**, the use of an alkynyllithium without $CeCl_3$ gave the expected product at a low yield (14%) because the proton at the α-position of the carbonyl group was easily removed by the lithium reagent (i.e., **2a** was enolized). However, when alkynyllithium was treated with $CeCl_3$,[8] the yield of **3a** was dramatically improved to 96%. The yield of **3** was slightly dependent upon the R_2 group: the yield was 87, 83, and 91% for tolyl, ^{n}Bu, and $SiMe_3$, respectively. In the synthesis of **3**, as the cerium reagent approached (Figure 2), a site selection was generated, resulting in a diastereoselective formation of **3**. Compound **3d** was easily transformed to **3e** in a high yield (97%). We also studied the preparation of **3f** starting from commercially available 6-methoxy-2-tetralone. The synthetic procedures were almost the same as the synthesis of **3a**−**3d** except for the use of 6-methoxy-2-tetralone instead of *β*-tetralone (Scheme 1). Nucleophilic addition of 1-butenyl group to 6-methoxy-2-tetralone followed by the addition of an alkynyl cerium reagent gave **3f** in 90% yield.

For a stoichiometric Pauson−Khand reaction, 1 equiv of $Co_2(CO)_8$ was added to a solution of **3a** in toluene to generate a cobalt−alkyne complex. After adding 5 equiv of 4-methylmorpholine *N*-oxide (NMO) to the solution, we stirred the resulting solution for 4 h to obtain the expected enone (**4a**) (Scheme 2).

The yield of **4** was highly dependent upon the R_2 group: the yield was 91, 77, 44, 19, and 23% for Ph, tolyl, ^{n}Bu, $SiMe_3$, and H, respectively. When other promoters such as DMSO, Me_3NO, or $CyNH_2$ were used instead of NMO, the yield of **4a** was 84, 73, and 46%, respectively. The stereochemistry of the steroid skeletal enone **4a** was confirmed by X-ray crystallography. Single crystals of **4a** suitable for an X-ray diffraction study were grown by a diffusion of diethyl ether into a dichloromethane solution of **4a** at low temperature.[9] The geometry of **4a**, along with the atomic numbering scheme used, is depicted in Figure 3, and bond distances and angles are given in the Supporting Information. The stereochemistries of the hydroxy group at C8, the hydrogen at C9, and the hydrogen at C13 were determined. Each substituent at each carbon shows the same relative stereochemistry as those observed in natural steroids.

Dehydration of **4a** in the presence of *p*-TsOH in a benzene solution gave the dehydration products **5** and its isomers, which

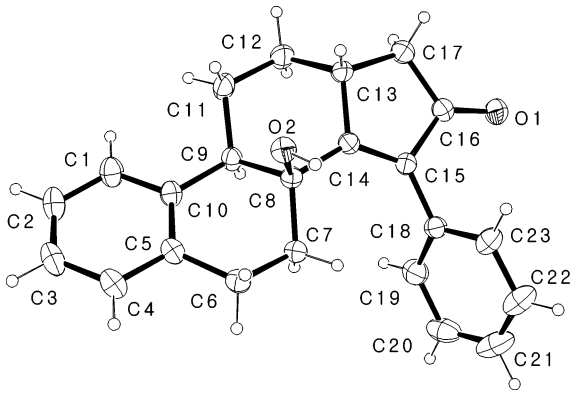


FIGURE 3. ORTEP drawing of **4a**.

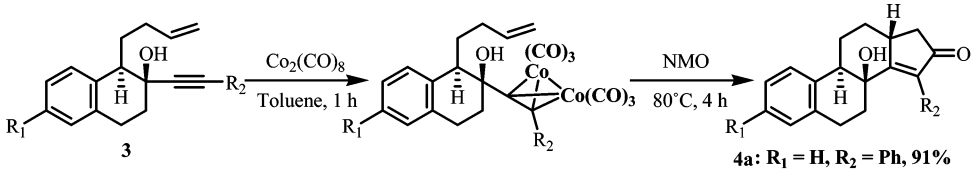
were assigned by NMR spectroscopy (Scheme 3). Because a fully conjugated **5** has a smaller R_f value than the others, **5** was easily obtained in 49% yield by column chromatography and the two other isomers were obtained in 32% yield.

Next, we investigated a catalytic intramolecular Pauson−Khand reaction of **3a**. When 5 mol % of $Co_2(CO)_8$ was used at 130 °C under 30 atm CO, instead of **4a** a mixture of **5** and its isomers were isolated at 24 and 16% yields, respectively. It seemed that an initially formed **4a** was dehydrated under high reaction temperatures and lengthy reaction time.

When 2.5 mol % of $[Rh(CO)_2Cl]_2$ was used as a catalyst in toluene under 1 atm of CO, **4a** was obtained as the sole product (Scheme 4), and the formation of **5** was not observed. The yield of the catalytic Pauson−Khand reaction was highly dependent upon the substituent on the alkyne. For example, **3d** was a less effective substrate under the current conditions. In addition to **4d**, a few minor products, a dehydrated and a desilylated compound, were also formed. Thus, the yield was rather low (29%). However, reasonable-to-high yields were obtained in other cases. The above result shows that the method developed in this study can be applicable to the synthesis of variously substituted steroid-like skeletons.

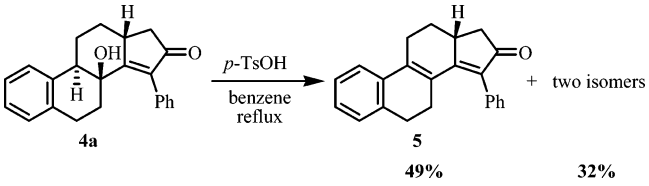
In conclusion, we have demonstrated a simple synthetic method for steroidal molecules starting from easily available *β*-tetralones using the Pauson−Khand reaction as a key reaction. The synthesized steroid has a diastereoselectivity derived from the enyne used, and the relative stereochemistry of the skeleton is the same as that of natural steroids. This work adds to the growing body of synthetic studies on steroids. Further applications of this methodology along with an asymmetric version and synthetic extensions are under active investigation in our laboratory.

SCHEME 2. Stoichiometric Pauson−Khand Reaction

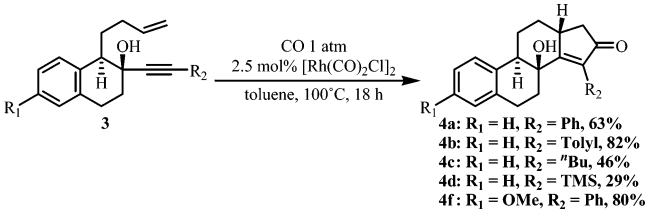


4a: R_1 = H, R_2 = Ph, 91%
4b: R_1 = H, R_2 = Tolyl, 77%
4c: R_1 = H, R_2 = ^{n}Bu, 44%
4d: R_1 = H, R_2 = TMS, 19%
4e: R_1 = H, R_2 = H, 23%
4f: R_1 = OMe, R_2 = Ph, 81%

SCHEME 3. Dehydration of 4a



SCHEME 4. Catalytic Pauson−Khand Reaction



Experimental Section

Preparation of 1-(But-3-enyl)-6-methoxy-3,4-dihydronaphthalen-2(1*H*)-one (2b) from 6-Methoxy-2-tetralone. The solution of 6-methoxy-2-tetralone (4.1 g, 23 mmol) in THF (25 mL) was treated with KH (0.92 g, 23 mmol) at 0 °C slowly and stirred during 2 h at room temperature. Then 4-bromo-1-butene (4.6 g, 35 mmol) was add to the solution at 0 °C slowly and stirred overnight at 60 °C. The THF solution was quenched with water, and **2b** was extracted with enough EA and dried with $MgSO_4$. Removal of the solvent followed by chromatography on a silica gel column eluting with hexane/ethyl acetate (v/v, 9/1) gave 2.6 g of **2b**. ^{1}H NMR ($CDCl_3$): δ 7.04 (d, J = 8.1 Hz, 1H), 6.80 (d, J = 2.5 Hz, 1H), 6.77 (s, 1H), 5.82−5.71 (m, 1H), 5.05 (dd, J = 1.4, 15.7 Hz, 1H), 4.98 (d, J = 9.5 Hz, 1H), 3.80 (s, 3H), 3.38 (t, J = 6.7 Hz, 1H), 3.13 (ddd, J = 5.8, 9.6, 15.5 Hz, 1H), 2.95 (dt, J = 5.8, 15.7 Hz 1H), 2.63 (dt, J = 5.5, 17.3 Hz, 1H), 2.49 (ddd, J = 6.4, 9.6, 17.3 Hz, 1H), 2.10−2.00 (m, 2H), 1.98−1.84 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 212.7, 158.4, 137.8, 129.1, 115.4, 113.4, 112.3, 55.3, 52.4, 37.6, 31.2, 30.9, 28.1; IR ν(C=O) 1706 cm^{-1}; HRMS for $C_{14}H_{16}O$: calcd 230.1307, obsd 230.1309.

Preparation of 1-(But-3-enyl)-2-(phenylethynyl)-1,2,3,4-tetrahydronaphthalen-2-ol (3a) from 1-(But-3-enyl)-2-tetralone (2a). To a suspension of dehydrated $CeCl_3$ (0.32 g, 1.3 mmol) in THF, the THF solution of lithium reagent generated by treatment of phenylacetylene (0.13 mL, 1.2 mmol) with *n*-BuLi (2.5 M in hexane, 0.48 mL) was added slowly at −78 °C. The solution was stirred for 0.5 h at that temperature and transferred to the THF solution of **2a** (0.20 g, 1.0 mmol) via cannula at −78 °C and stirred for an additional 2 h. Then the solution was quenched by addition of saturated aqueous NH_4Cl solution and filtered through a Celite pad covered with $MgSO_4$. Removal of the solvent followed by chromatography on a silica gel column eluting with hexane/ethyl acetate (v/v, 9/1) gave 0.29 g of **3a** (96%) ^{1}H NMR ($CDCl_3$): δ 7.05−7.02 (m, 5H), 6.96−6.92 (m, 4H), 5.72−5.63 (m, 1H), 4.94 (d, J = 17.0 Hz, 1H), 4.87 (d, J = 10.2 Hz, 1H), 2.92−2.79 (m, 3H), 2.13−2.01 (m, 4H), 1.96−1.90 (m, 1H), 1.63 (br, 1H), 1.38−1.27 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 139.2, 138.9, 134.6, 131.8, 129.5, 128.9, 128.3, 128.3, 126.4, 125.5, 122.7, 115.1, 92.9, 84.0, 70.4, 49.7, 32.8, 32.5, 31.3, 27.5; HRMS for $C_{22}H_{22}O$: calcd 302.1672, obsd 302.1669.

3b: ^{1}H NMR ($CDCl_3$): δ 7.12−7.10 (m, 6H), 7.03 (d, J = 8.0 Hz, 2H), 5.91−5.82 (m, 1H), 5.07 (dd, J = 1.7, 17.3 Hz, 1H), 5.00 (dd, J = 1.8, 10.3 Hz, 1H), 3.10−3.03 (m, 3H), 2.33−2.19 (m, 4H), 2.29 (s, 3H), 2.14−2.07 (m, 2H), 1.54−1.49 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 139.3, 139.0, 138.5, 134.7, 131.7, 129.6, 129.1, 128.9, 126.4, 125.5, 119.7, 115.1, 92.2, 84.1, 70.4, 49.8, 32.9, 32.6, 31.4, 27.5, 21.6; HRMS for $C_{23}H_{24}O$: calcd 316.1827, obsd 316.1829.

3c: ^{1}H NMR ($CDCl_3$): δ 7.07−7.03 (m, 4H), 5.85−5.72 (m, 1H), 5.00 (d, J = 17.2 Hz, 1H), 4.92 (d, J = 10.0 Hz, 1H), 2.97−2.88 (m, 3H), 2.21−2.06 (m, 4H), 2.00 (t, J = 6.8 Hz, 2H), 1.94−1.86 (m, 2H), 1.40−1.34 (m, 1H), 1.28−1.19 (m, 2H), 1.08 (qd, J = 7.0, 14.0 Hz, 2H), 0.72 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 139.6. 139.1, 134.7, 129.5, 128.8, 126.2, 125.3, 114.9, 84.5, 84.2, 69.9, 50.2, 32.8, 32.4, 31.3, 30.7, 27.6, 21.7, 18.3, 13.6; HRMS for $C_{20}H_{26}O$: calcd 282.1984, obsd 282.1979.

3d: ^{1}H NMR ($CDCl_3$): δ 7.07−7.06 (m, 4H), 5.88−5.75 (m, 1H), 5.03 (dd, J = 1.2, 17.3 Hz, 1H), 4.96 (d, J = 10.2 Hz, 1H), 2.95 (dd, J = 5.8, 8.0 Hz, 2H), 2.90−2.88 (m, 1H), 2.27−2.09 (m, 5H), 2.00−1.93 (m, 1H), 1.50−1.38 (m, 1H), −0.02 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 138.0, 134.6, 129.3, 128.6, 126.2, 125.3, 115.0, 109.7, 88.4, 70.0, 49.5, 32.7, 32.3, 30.0, 27.1, 0.178; HRMS for $C_{19}H_{26}OSi$: calcd 298.1753, obsd 298.1758.

Preparation of 1-(But-3-enyl)-2-ethynyl-1,2,3,4-tetrahydronaphthalen-2-ol (3e) from 1-(But-3-enyl)-2-((trimethylsilyl)ethynyl)-1,2,3,4-tetrahydronaphthalen-2-ol (3d). To the solution of compound **3d** (1.500 g, 5.025 mmol) and MeOH (10 mL), K_2CO_3 (2.100 g, 15.08 mmol) was added. The solution was stirred overnight and quenched by addition of saturated aqueous NH_4Cl. Removal of the solvent followed by chromatography on a silica gel column eluting with hexane/ethyl acetate (v/v, 5/1) gave 1.107 g of **3e** (97%). ^{1}H NMR ($CDCl_3$): δ 7.18−7.08 (m, 4H), 5.83 (tdd, J = 6.3 Hz, J = 10.2 Hz, J = 16.6 Hz, 1H), 5.06 (dd, J = 1.4 Hz, J = 17.3 Hz, 1H), 4.99 (d, J = 10.5 Hz, 1H), 3.13−2.95 (m, 3H), 2.32 (s, 1H), 2.28−2.10 (m, 5H), 2.05−1.98 (m, 1H), 2.00(s, 1H), 1.49−1.37 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 138.8, 138.7, 134.2, 129.4, 128.7, 126.4, 125.4, 115.0, 71.8, 69.7, 49.4, 32.5, 31.9, 31.1, 27.2; HRMS for $C_{16}H_{18}O$: calcd 226.1356, obsd 226.1358.

3f: ^{1}H NMR ($CDCl_3$): δ 7.23 (br, 5H), 7.03 (d, J = 8.4 Hz, 1H), 6.72−6.69 (dd, J = 2.5, 8.4 Hz, 1H), 6.66 (s, 1H), 5.90−5.81 (m, 1H), 5.07 (d, J = 17.0 Hz, 1H), 4.99 (d, J = 10.2 Hz, 1H), 3.77 (s, 3H), 3.13−2.94 (m, 3H), 2.30−2.04 (m, 6H), 1.52−1.39 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 157.9, 138.9, 135.7, 131.7, 131.3, 130.3, 128.2, 128.2, 122.7, 114.9, 113.3, 111.7, 92.9, 83.7, 70.4, 55.2, 48.9, 32.6, 32.2, 31.3, 27.6; HRMS for $C_{23}H_{24}O_2$: calcd 332.1776, obsd 332.1779.

Preparation of 8-Hydroxy-15-phenyl-7,8,11,12,13,17-hexahydro-6*H*-cyclopenta[*a*]phenanthren-16(9*H*)-one (4a) from 1-(But-3-enyl)-2-(phenylethynyl)-1,2,3,4-tetrahydronaphthalen-2-ol (3a).

Method A. A Stoichiometric Pauson−Khand Reaction Using $Co_2(CO)_8$. To a toluene solution of **3a** (0.20 g, 0.66 mmol), $Co_2(CO)_8$ (0.25 g, 0.73 mmol) was added, and the resulting solution was stirred for 1 h at room temperature. Then NMO (0.45 g, 3.3 mmol) was added to the solution, and the resulting solution was stirred at 80 °C for 4 h. After the solution was cooled to room temperature, the solvent was removed by evaporation. Chromatography of a residue on a silica gel column eluting with hexane/ethyl acetate (v/v, 9/1) gave 0.15 g of **4a** (69%). ^{1}H NMR ($CDCl_3$): δ 7.31−7.18 (m, 4H), 7.13−7.04 (m, 3H), 6.99−6.96 (m, 2H), 3.43−3.35 (m, 1H), 2.90−2.78 (m, 2H), 2.70 (dd, J = 6.7, 19.1 Hz, 1H), 2.59−2.51 (m, 1H), 2.42−2.35 (m, 2H), 2.10 (d, J = 19.1 Hz, 1H), 1.88 (qd, J = 3.1, 12.7 Hz, 1H), 1.82 (s, 1H), 1.65−1.61 (m, 2H), 1.35 (qd, J = 3.8, 12.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 208.6, 176.8, 138.4, 135.7, 135.0, 129.8, 129.2, 129.0, 128.1, 127.8, 127.0, 126.5, 126.5, 71.6, 47.5, 41.1, 37.1, 35.6, 33.1,

(8) (a) Fürstner, A.; Hannen, P. *Chem.−Eur. J.* **2006**, *12*, 3006. (b) Bartoli, G.; Bosco, M.; Di Martino, E.; Marcantoni, E.; Sambri, L. *Eur. J. Org. Chem.* **2001**, 2901. (c) Suzuki, M.; Kimura, Y.; Terashima, S. *Chem. Pharm. Bull.* **1986**, *34*, 1531. (d) Liu, H.-J.; Shia, K.-S.; Shang, X.; Zhu, B.-Y. *Tetrahedron* **1999**, *55*, 3803.

(9) Crystal data of **4a**: $C_{23}H_{22}O_2$, M = 330.41, orthorhombic, space group *Pc*21*b*, a = 8.5096(5) Å, b = 9.1160(3) Å, c = 22.3675(12) Å, V = 1735.13(15) Å^3, Z = 4, D_c = 1.265 mg m^{-3}, μ(Mo Kα) = 0.079 mm^{-1}, F(000) = 704, No. of data collected: 5985, No. of unique data: 3498, R = 0.0491, R_w = 0.1036. Data collected at 293(2) K with Mo Kα radiation (λ(Kα) = 0.7107 Å), $R(F) = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ with $F_o > 2.0\sigma(I)$, $R_w = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o)^2]^2\}^{1/2}$ with $F_o > 2.0\sigma(I)$.

25.3, 24.9; IR ν(C═O) 1698 cm^{-1}; HRMS for $C_{23}H_{22}O_2$: calcd 330.1620, obsd 330.1617.

Method B. A Catalytic Pauson−Khand Reaction Using [Rh(CO)$_2$Cl]$_2$. To a toluene solution of **3a** (0.20 g, 0.66 mmol), [Rh(CO)$_2$Cl]$_2$ (6.4 mg, 2.5 mol %) was added. The resulting solution was flushed with a balloon of CO gas. Then the solution was heated to 100 °C and stirred for 18 h at that temperature. After the solution was cooled to room temperature, the solvent was removed by evaporation. Chromatography of a residue on a silica gel column eluting with hexane/ethyl acetate (v/v, 9/1) gave 0.14 g of **4a** (63%).

4b: ^{1}H NMR ($CDCl_3$): δ 7.32−7.29 (m, 1H), 7.26−7.16 (m, 4H), 7.06 (d, J = 6.5 Hz, 2H), 7.07−7.05 (m, 1H), 3.49−3.40 (m, 1H), 2.94−2.87 (m, 2H), 2.76 (dd, J = 6.7, 19.1 Hz, 1H), 2.70−2.62 (m, 1H), 2.50−2.42 (m, 2H), 2.36 (s, 3H), 2.16 (dd, J = 1.7, 19.1 Hz, 1H), 1.96 (qd, J = 4.1, 13.7 Hz, 1H), 1.86 (s, 1H), 1.78−1.72 (m, 2H), 1.42 (qd, J = 4.0, 12.9 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 209.1, 176.7, 138.6, 137.7, 135.9, 135.3, 130.5, 129.8, 129.2, 129.0, 127.1, 126.7, 126.6, 71.8, 47.6, 41.3, 37.3, 35.7, 33.3, 25.5, 25.1, 21.5; IR ν(C═O) 1696 cm^{-1}; HRMS for $C_{24}H_{24}O_2$: calcd 344.1776, obsd 344.1776.

4c: ^{1}H NMR ($CDCl_3$): δ 7.11−7.08 (m, 1H), 6.99−6.96 (m, 3H), 3.09−2.93 (m, 1H), 2.74 (dd J = 5.8, 17.2 Hz, 1H), 2.63 (dd, J = 3.4, 12.1 Hz, 1H), 2.36 (dd, J = 6.7, 19.1 Hz, 1H), 2.30−2.28 (m, 1H), 2.22−2.13 (m, 5H), 1.76 (dd, J = 1.6, 19.1 Hz, 1H), 1.68 (qd, J = 3.4, 13.2 Hz, 1H), 1.50 (br, 1H), 1.15−0.94 (m, 6H), 0.69 (t, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 210.5, 174.3, 137.3, 136.1, 134.9, 129.0, 127.1, 126.5, 126.4, 71.9, 46.9, 40.7, 36.9, 35.5, 32.5, 32.1, 25.5, 25.1, 23.5, 23.1, 14.0; IR ν(C═O) 1693 cm^{-1}; HRMS for $C_{21}H_{26}O_2$: calcd 310.1933, obsd 310.1932.

4d: ^{1}H NMR ($CDCl_3$): δ 7.26−7.23 (m, 1H), 7.15−7.10 (m, 3H), 3.37 (ddd, J = 2.3, 5.4, 7.4 Hz, 1H), 3.10−3.04 (m, 1H), 2.92−2.84 (m, 1H), 2.76 (dd, J = 3.7, 12.3 Hz, 1H), 2.51 (dd, J = 7.1, 18.5 Hz, 1H), 2.35−2.28 (m, 2H), 2.26−2.21 (m, 1H), 1.98−1.82 (m, 2H), 1.76 (s, 1H), 1.29−1.15 (m, 2H), 0.23 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 214.0, 191.4, 136.3, 136.0, 134.9, 129.0, 127.1, 126.5, 126.4, 72.1, 47.2, 42.5, 39.8, 35.9, 33.9, 25.5, 25.1, 2.5; IR ν(C═O) 1686 cm^{-1}; HRMS for $C_{20}H_{26}O_2Si$: calcd 326.1702, obsd 326.1706.

4e: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32−7.30 (m, 1H), 7.24−7.18 (m, 3H), 5.99 (d, 1H, J = 1.3 Hz), 3.31 (td, 1H, J = 5.9 Hz, J = 12.2 Hz), 3.22−3.14 (m, 1H), 3.02−2.97 (m, 1H), 2.77 (dd, 1H, J = 3.1 Hz, J = 12.3 Hz), 2.68 (dd, 1H, J = 6.5 Hz, J = 18.9 Hz), 2.42 (tdd, 2H, J = 3.1 Hz, J = 6.3 Hz, J = 12.4 Hz), 2.26 (ddd, 1H, J = 1.9 Hz, J = 7.0 Hz, J = 13.4 Hz), 2.20−2.14 (m, 1H), 2.09 (dd, 1H, J = 1.9 Hz, J = 18.9 Hz), 1.96−1.88 (m, 1H), 1.84 (s, 1H), 1.36−1.28 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 209.3, 185.5, 135.4, 135.0, 129.1, 126.7, 126.7, 126.5, 125.3, 69.3, 46.9, 42.4, 38.0, 34.7, 31.3, 25.2, 24.0; IR ν(C═O) 1708 cm^{-1}; HRMS for $C_{17}H_{18}O_2$: calcd 254.1310, obsd 254.1307.

4f: ^{1}H NMR ($CDCl_3$): δ 7.31 (br, 3H), 7.23−7.12 (m, 2H), 7.01 (br, 1H), 6.75−6.72 (m, 1H), 6.56 (s, 1H), 3.74 (s, 3H), 3.50−3.39 (m, 1H), 2.93−2.78 (m, 2H), 2.75 (dd, J = 6.7, 19.2 Hz, 1H), 2.57 (d, J = 16.3 Hz, 1H), 2.46−2.36 (m, 2H), 2.15 (d, J = 19.1 Hz, 1H), 2.03−1.83 (m, 2H), 1.98 (s, 1H), 1.74−1.68 (m, 2H), 1.40 (qd, J = 4.0, 13.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 208.7, 176.9, 158.0, 138.4, 136.4, 133.5, 129.8, 129.2, 128.1, 128.0, 127.8, 113.4, 112.7, 71.6, 55.2, 47.0, 41.2, 37.1, 35.5, 33.1, 25.7, 25.1; IR ν(C═O) 1696 cm^{-1}; HRMS for $C_{24}H_{24}O_3$: calcd 360.1725, obsd 360.1721.

Synthesis of 15-Phenyl-6,7,11,12,13,17-hexahydrocyclopenta[*a*]phenanthren-16-one (5) from 8-Hydroxy-15-phenyl-7,8,11,12,13,17-hexahydro-6*H*-cyclopenta[*a*]phenanthren-16(9*H*)-one (4a). To a benzene solution of **4a** (0.10 g, 0.30 mmol), *p*-TsOH (1.1 mg, 2 mol %) was added, and the solution was refluxed for 16 h. After the solution was cooled to room temperature, the solvent was removed by evaporation. Chromatography of a residue on a silica gel column eluting with hexane/ethyl acetate (v/v, 10/1) gave **5** (46 mg, 49%) and the mixture of two kinds of double bond isomers (32 mg, 32%). ^{1}H NMR ($CDCl_3$): δ 7.42−7.40 (m, 1H), 7.35−7.29 (m, 3H), 7.23−7.21 (m, 4H), 7.10−7.07 (m, 1H), 3.03−2.91 (m, 2H), 2.88 (dd, J = 6.8, 18.2 Hz, 1H), 2.77−2.65 (m, 1H), 2.58 (m, 2H), 2.45−2.37 (m, 1H), 2.28−2.18 (m, 2H), 1.96−1.87 (m, 1H), 1.79 (double quartet, J = 5.8, 12.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): 206.8, 168.5, 140.4, 137.5, 135.9, 134.8, 133.6, 129.8, 129.7, 128.5, 127.9, 127.7, 127.4, 126.7, 124.1, 41.6, 37.6, 29.4, 28.3, 27.0, 25.6; IR ν(C═O) 1681 cm^{-1}; HRMS for $C_{23}H_{20}O$: calcd 312.1514, obsd 312.1517.

Method C. A Catalytic Pauson−Khand Reaction Using Co$_2$(CO)$_8$. Compound **3a** (0.17 g, 0.56 mmol) and $Co_2(CO)_8$ (19 mg, 10 mol %) were dissolved in 30 mL of dichloromethane in 100 mL of a high-pressure reactor. Then the reactor was charged with 30 atm of CO and then heated at 130 °C for 18 h. After the reactor was cooled to room temperature, the high pressure was released. Removal of the solvent followed by chromatography gave **5** (42 mg, 0.13 mmol) and its isomers (28 mg, 0.090 mmol) in 24 and 16% yields, respectively.

X-ray Crystallography. A single crystal was placed on an Enraf-Nonius CCD single-crystal X-ray diffractometer. The structures were solved by direct methods (SHELXS-97) and refined against all F^2 data (SHELXS-97). All non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were treated as idealized contributions. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as CCDC 290916.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all compounds and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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