Hydrophenanthrene Construction by Aryl Radical Cyclization. Synthesis of 2,3,4,4a,9,10-Hexahydro-7-methoxy-4a-methylphenanthren-2-one

Arthur G. Schultz* and Aihua Wang

Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12180-3590

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Hydrophenanthrenes have served as key intermediates for the synthesis of a wide range of steroids, steroidal alkaloids, diterpenes, and triterpenes. The exceedingly versatile 2,3,4,4a,9,10-hexahydro-7-methoxy-4a-methylphenanthren-2-one (**6**) has been utilized in syntheses of racemic 5α-pregnan-3β-ol-20-one,[1a] conessine,[1b] latifoline,[1b] phyllocladene,[1c] kaurene,[1d] atisirene,[1d] and hibaene,[1e] and (+)-α-onocerin.[1f]

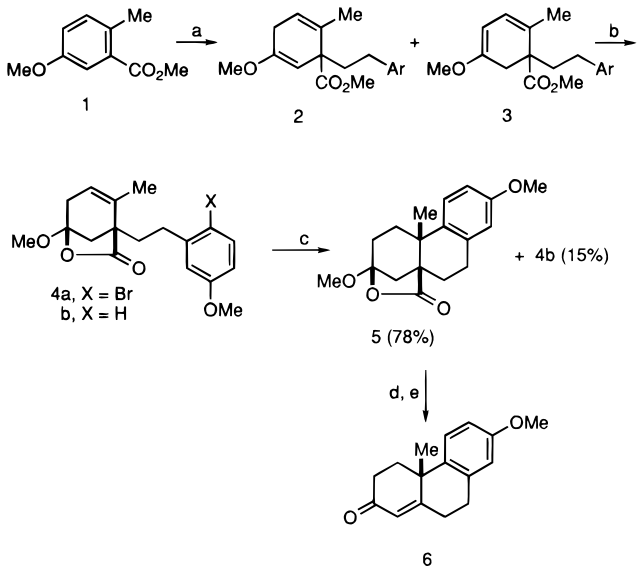
The classical procedure for preparation of the phenanthren-2-one ring system is based on the Robinson annulation of 1-alkyl-2-tetralones with methyl vinyl ketone or related Michael acceptors.[2] An enantioselective Robinson annulation, described by d'Angelo and co-workers,[3] provides high enantiomeric excess (80−92% ee), although 8-substituted-2-tetralones offer no regioselectivity in the Michael addition step. A conceptually different method for preparation of phenanthren-2-ones by intramolecular Friedel−Crafts alkylation of a 4-aryl-3-vinyl-2-cyclohexen-1-one has been described.[4] This procedure fails to give **6** and the 5-methoxy analogues of **6** because of the directing effects of the methoxy substituent on electrophilic aromatic substitution reactions. A 14-step enantioselective synthesis of the 1-methyl analogue of **6** has been reported;[5] however, the d'Angelo procedure has been found to be well suited to the large-scale asymmetric synthesis of this phenanthren-2-one.[6]

The preparation of **6** from 6-methoxy-1-tetralone in 7.9% yield was reported by Howell and Taylor in 1958.[7] Subsequent refinements by Stork and co-workers[1f] have increased the chemical efficiency to 56%.[1c] Asymmetric syntheses of **6** with 44% ee[8a] and 63% ee[8b] also have been described. Herein we report an alternative preparation of **6** from methyl 3-methoxy-6-methylbenzoate (**1**) by way of the radical cyclization **4a** → **5**.

Results and Discussion

The synthesis of 2,3,4,4a,9,10-hexahydro-7-methoxy-4a-methylphenanthren-2-one (**6**) is shown in Scheme 1.

Scheme 1[a]



[a] Reaction conditions: (a) K, LiBr, NH_3, *t*-BuOH (1 equiv) −78 °C; piperylene; 2-(2-bromo-5-methoxyphenyl)-1-iodoethane (1.1 equiv); (b) LiOH, MeOH, H_2O, reflux; SiO_2, CH_2Cl_2; (c) AIBN, Bu_3SnH, PhH, reflux; (d) K_2CO_3, MeOH, H_2O, reflux; (e) $Pb(OAc)_4$, $Cu(OAc)_2 \cdot H_2O$, PhH, pyridine, reflux.

Birch reduction−alkylation of methyl 3-methoxy-6-methylbenzoate (**1**)[9] with 2-(2-bromo-5-methoxyphenyl)-1-iodoethane[10] gave a mixture of isomeric 1,4- and 1,3-cyclohexadienes **2** and **3** in 96% yield. Without separation of isomers, **2** and **3** were converted to a single pseudoester **4a** in 91% yield by saponification with LiOH followed by acid-catalyzed cyclization of the resulting diene carboxylic acid. Treatment of **4a** with AIBN and Bu_3SnH in refluxing benzene solution gave a 5:1 mixture of the cis fused octahydrophenanthrene **5** and the uncyclized product of reduction **4b** in 93% isolated yield. The conversion of **5** to **6** was accomplished in 69% overall yield by saponification of **5** to keto acid **8b** and oxidative decarboxylation[11] of **8b** with $Pb(OAc)_4$ and $Cu(OAc)_2$.

The radical cyclization of **4a** to **5** is remarkable in that a quaternary center is generated at C(4a) by way of a 6-exo-trig pathway.[12] Chemo- and regioselectivity of the aryl radical generated from **4a** is the result of an absence of competing pathways for intramolecular 1,5-hydrogen atom transfer[13] and the lactone bridge which provides a conformational lock as shown in the qualitative transition state structure for the radical cyclization (Figure 1). Axial addition of the aryl radical to the C(1)-carbon atom can occur only with the observed facial selectivity to give a chair cyclohexyl radical, while addition to the less sterically congested C(2)-carbon atom by the 7-endo-trig pathway, which has precedent in the radical cyclization of methyl 1-(4′-bromobutyl)cyclohexa-2,5-diene-1-carboxylate,[12] is impossible because of the pseudoequatorial orientation of the arylethyl substituent enforced by the lactone ring fusion.

(1) (a) Nagata, W.; Terasawa, T.; Aoki, T. *Tetrahedron Lett.* **1963**, 865−868. (b) Nagata, W.; Terasawa, T.; Aoki, T. *Tetrahedron Lett.* **1963**, 869−871. (c) Church, R. F.; Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1966**, *31*, 2526−2530. (d) Bell, R. A.; Ireland, R. E.; Partyka, R. A. *J. Org. Chem.* **1966**, *31*, 2530−2536. (e) Bell, R. A.; Ireland, R. E.; Mander, L. N. *J. Org. Chem.* **1966**, *31*, 2536−2542. (f) Stork, G.; Meisels, A.; Davies, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 3419−3425.

(2) (a) Jung, M. E. *Tetrahedron* **1976**, *32*, 3−31. (b) Gawley, R. E. *Synthesis* **1976**, 777−794.

(3) (a) Volpe, T.; Revial, G.; Pfau, M.; d'Angelo, J. *Tetrahedron Lett.* **1987**, *28*, 2367−2370. (b) d'Angelo, J.; Revial, G.; Volpe, T.; Pfau, M. *Tetrahedron Lett.* **1988**, *29*, 4427−4430.

(4) (a) Majetich, G.; Liu, S.; Siesel, D. *Tetrahedron Lett.* **1995**, *36*, 4749−4752. (b) Majetich, G.; Siesel, D. *Synlett* **1995**, 559−560.

(5) Kondo, K.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 4322−4323.

(6) Chiu, C. K.-F.; Govindan, S. V.; Fuchs, P. L. *J. Org. Chem.* **1994**, *59*, 311−323.

(7) Howell, F. H.; Taylor, D. A. H. *J. Chem. Soc.* **1958**, 1248−1254.

(8) (a) Sone, T.; Terashima, S.; Yamada, S.-I. *Chem. Pharm. Bull.* **1976**, *24*, 1273−1287. (b) Nerinckx, W.; Vandewalle, M. *Tetrahedron Asymmetry* **1990**, *1*, 265−276.

(9) Prepared in 73% overall yield from 2-methylbenzoic acid; see: Hartmann, R. W.; Heindl, A.; Schönenberger, H. *J. Med. Chem.* **1984**, *27*, 577−585.

(10) Prepared in 93% overall yield from 3-methoxyphenylacetic acid; see: Snyder, L.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 7507−7515.

(11) McMurry, J. E.; Blaszczak, L. C. *J. Org. Chem.* **1974**, *39*, 2217−2222.

(12) Beckwith, A. L. J.; Roberts, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 5893−5901.

(13) Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051−6059 and references cited therein.

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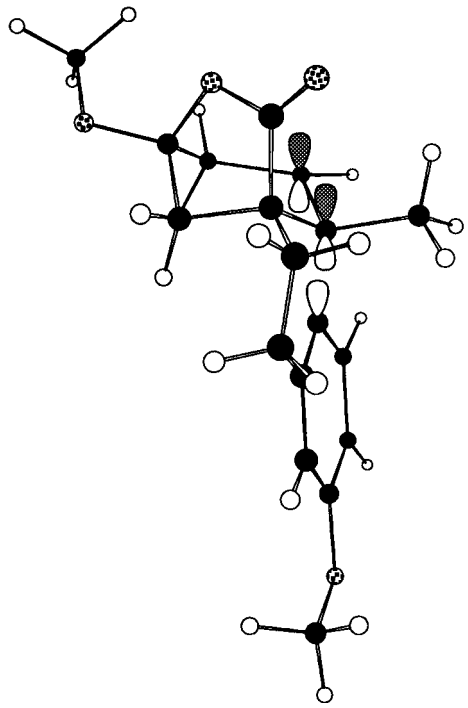
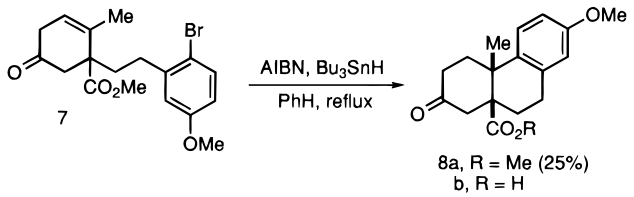


Figure 1. Qualitative transition state structure for cyclization of the aryl radical generated from **4a**.

The importance of the lactone fusion in **4a** was demonstrated with enone **7** which was prepared by acid-catalyzed hydrolysis of the mixture of **2** and **3**. Treatment of **7** with AIBN and Bu_3SnH in refluxing benzene solution gave only a 25% yield of octahydrophenanthrene **8a** along with the uncyclized product of reduction **7** (Br = H) and minor amounts of other uncharacterized reaction products.



Conclusion

The chemical efficiency for preparation of **6** from **1** (47% overall yield) is competitive with that for the classical Robinson annulation procedure. It is expected that the radical cyclization of **4a** to **5** will serve as a prototype for preparation of other C(4a)-substituted phenanthren-2-ones to be utilized for the syntheses of hasubanan[14] and new morphinane alkaloids.[15] The asymmetric variant of the Birch reduction−alkylation[16] of **1** should provide C(4a)-substituted phenanthren-2-ones with high enantiomeric excess.

Experimental Section

6-[2-(2-Bromo-5-methoxyphenyl)ethyl]-6-carbomethoxy-4-methoxy-1-methyl-1,4-cyclohexadiene (2) and 6-[2-(2-Bromo-5-methoxyphenyl)ethyl]-6-carbomethoxy-4-methoxy-1-methyl-1,3-cyclohexadiene (3). A 250 mL three-necked round bottom flask equipped with a dry ice/acetone cooled condenser fitted with a drying tube was charged with a solution of methyl 3-methoxy-6-methylbenzoate (1.23 g, 6.81 mmol), *tert*-butyl alcohol (0.64 mL, 6.8 mmol), lithium bromide (1.00 g, 11.5 mmol), and dry THF (25 mL). The mixture was cooled to −78 °C, and about 150 mL of NH_3 was condensed into the reaction flask through a drying tube. Potassium metal (0.62 g, 16 mmol) was added in small chunks at −78 °C. The resulting blue coloration changed to yellow after ∼10 min. 2-(2-Bromo-5-methoxyphenyl)-1-iodoethane (2.63 g, 7.71 mmol) in THF was added at −78 °C via a syringe. After stirring for 30 min at −78 °C, the dry ice/acetone bath was removed and stirring was continued for another 30 min. NH_3 was then allowed to evaporate. The residue was partitioned between CH_2Cl_2 and brine, and the organic layer was dried (Na_2SO_4) and concentrated. Flash chromatography on silica gel gave a mixture of **2** and **3** as a slightly yellow oil (2.57 g, 6.51 mmol, 96%). **2**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (d, 1 H, J = 8.8 Hz), 6.73 (d, 1 H, J = 3.0 Hz), ∼6.61 (dd, 1 H, overlapping), 5.69 (m, 1 H), 4.51 (m, 1 H), 3.77 (s, 3 H), 3.67 (s, 3 H), 3.60 (s, 3 H), 2.80 (m, 2 H), 2.57 (td, 1 H, overlapping), 2.34 (td, 1 H, J = 5.0, 13.0 Hz), 2.15 (td, 1 H, J = 5.1, 12.9 Hz), 1.96 (td, 1 H, J = 4.4, 13.2 Hz), 1.75 (s, 3 H).

3: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (d, 1 H, J = 8.5 Hz), 6.76 (d, 1 H, J = 3.2 Hz), 6.62 (dd, 1 H, overlapping), 5.76 (d, 1 H, J = 6.4 Hz), 4.86 (d, 1 H, J = 6.4 Hz), 3.77 (s, 3 H), 3.73 (s, 3 H), 3.59 (s, 3 H), 3.02 (d, 1 H, J = 16.4 Hz), 2.74 (td, 1 H, J = 4.4, 13.0 Hz), 2.57 (td, 1 H, J = 4.4, 13.0 Hz), 2.43 (d, 1 H, J = 16.3 Hz), 2.08 (td, 1 H, J = 4.4, 13.2 Hz), 1.87 (td, 1 H, J = 4.4, 13.2 Hz), 1.79 (s, 3 H). CIMS of the mixture of **2** and **3**, m/z (relative intensity) 395 (M^+ + 1, 100), 397 (M^+ + 1, 95).

6-[2-(2-Bromo-5-methoxyphenyl)ethyl]-4-methoxy-1-methyl-1-cyclohexene-6,4-carbolactone (4a). To a solution of the mixture of **2** and **3** (3.10 g, 7.85 mmol) in 32 mL of MeOH and 8 mL of H_2O was added $LiOH·H_2O$ (0.66 g, 16 mmol). The solution was refluxed for 19 h. After MeOH was evaporated under reduced pressure, CH_2Cl_2 and brine were added. The solution was acidified with concd HCl at 4 °C until acidic to pH paper. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4 and K_2CO_3) and concentrated. The diene acid, obtained as a white solid (3.12 g, mp 132−133 °C) was dissolved in 60 mL of CH_2Cl_2, and silica gel (18 g) was added. After the mixture was stirred at room temperature under N_2 for 1.5 h, the silica gel was filtered and rinsed with Et_2O and EtOAc. The filtrate was concentrated and chromatographed on silica gel to provide **4a** as a clear oil (2.72 g, 7.14 mmol, 91%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 (d, 1 H, J = 8.8 Hz), 6.84 (d, 1 H, J = 3.1 Hz), 6.66 (dd, 1 H, J = 3.2, 8.8 Hz), 5.58 (m, 1 H), 3.79 (s, 3 H), 3.54 (s, 3 H), 2.74 (td, 1 H, J = 4.9, 12.7 Hz), 2.67 (dm, 1 H, J = 18.0 Hz), 2.61 (td, 1 H, J = 4.9, 12.7 Hz), 2.55 (dm, 1 H, J = 17.9 Hz), 2.43 (dd, 1 H, J = 1.2, 11.0 Hz), 2.14−2.03 (m, 2 H), 2.01 (d, 1 H, J = 11.0 Hz), 1.84 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.7, 159.1, 141.6, 136.9, 133.3, 123.3, 115.8, 114.5, 113.6, 107.7, 55.4, 52.4, 51.0, 40.0, 35.9, 32.0, 29.6, 18.8; IR (film) 2932, 1764 cm^{-1}; CIMS, m/z (relative intensity) 381 (M^+ + 1, 100), 383 (M^+ + 1, 96). Anal. Calcd for $C_{18}H_{21}BrO_4$: C, 56.71; H, 5.55. Found: C, 56.64; H, 5.53.

2,7-Dimethoxy-4a-methyl-1,1a,2,3,4,4a,9,10-octahydrophenanthren-1a,2-carbolactone (5). A 250 mL round bottom flask equipped with a rubber septum-sealed condenser was charged with a solution of **4a** (0.600 g, 1.57 mmol), Bu_3SnH (0.50 mL, 1.9 mmol), AIBN (0.026 g, 0.16 mmol), and dry benzene (160 mL). The stirred solution was purged with N_2 for 20 min via a long needle that extended below the solution; another needle that pierced the rubber septum functioned as a gas outlet. The solution was then heated to reflux for 1.5 h. More AIBN (0.026 g, 0.16 mmol) was added, and the solution was refluxed for another 1.5 h. Bu_3SnBr was removed by the DBU workup procedure.[17] After evaporation of benzene, Et_2O was added followed by DBU (0.30 mL, 2.0 mmol). The solution was agitated, and a white solid precipitated. The solution was then transferred to a short column (SiO_2). Elution with hexane removed excess unreacted Bu_3SnH; the product was eluted with Et_2O, concentrated, and flash chromatographed on silica gel to

(14) Matsui, M. In *The Alkaloids*; Brossi, A., Ed., Academic: New York, 1988, Vol. 33, Chapter 5.
(15) Kashiwaba, N.; Morooka, S.; Kimura, M.; Murakoshi, Y.; Toda, J; Sano, T. *Chem. Pharm. Bull.* **1994**, *42*, 2452−2454.
(16) Schultz, A. G. *Acc. Chem. Res.* **1990**, *23*, 207−213.
(17) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140−3157.

give an inseparable mixture of **5** and the uncyclized product of reduction (**4b**) in 5:1 ratio as a white solid (0.441 g, 1.46 mmol, 93%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24 (d, 1 H, J = 8.5 Hz), 6.72 (dd, 1 H, J = 2.7, 8.5 Hz), 6.67 (d, 1 H, J = 2.6 Hz), 3.78 (s, 3 H), 3.41 (s, 3 H), 3.01 (dd, 1 H, J = 8.8, 18.0 Hz), 2.84−2.76 (m, 1 H), 2.60−2.52 (m, 2 H), 2.13−2.07 (m, 2 H), 1.74−1.57 (m, 4 H), 1.16 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.4, 158.0, 136.2, 132.8, 124.9, 114.9, 111.7, 109.0, 55.2, 53.4, 50.8, 41.0, 39.0, 31.2, 30.2, 28.4, 25.7, 23.5; IR (film) 2930, 1764 cm^{-1}; CIMS m/z (relative intensity) 303 (M^+ + 1, 100). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.43; H, 7.39.

1a-Carboxy-7-methoxy-4a-methyl-1,1a,2,3,4,4a,9,10-octahydrophenanthren-2-one (8b). A solution of **5** and **4b** (0.273 g, 0.904 mmol) and K_2CO_3 (0.375 g, 2.72 mmol) in 10 mL of MeOH and 2 mL of H_2O was refluxed for 3.5 h. After evaporation of MeOH, CH_2Cl_2 and brine were added. Concentrated HCl was added until the solution was acidic to pH paper. The aqueous solution was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated to provide **8b** as a white solid contaminated with the carboxylic acid derived from **4b** (0.265 g, 0.920 mmol, 100%): mp 221−222 °C dec. ^{1}H NMR (DMSO-d_6, 500 MHz) 12.8 (s(b), 1 H), 7.38 (d, 1 H, J = 8.6 Hz), 6.78 (d, 1 H, J = 8.3 Hz), 6.67 (m, 1 H), 3.71 (s, 3 H), 2.87−2.73 (m, 2 H), 2.45−2.43 (m, 1 H), 2.34−2.30 (m, 1 H), 2.24−2.08 (m, 3 H), 1.95−1.89 (m, 1 H), 1.62 (dd, 1 H, J = 6.6, 14.4 Hz), 1.17 (s, 3 H); ^{13}C NMR (DMSO-d_6, 125 MHz), 208.4, 176.8, 157.4, 136.0, 132.9, 126.9, 113.8, 113.4, 55.1, 51.1, 44.1, 38.3, 37.3, 33.4, 29.6, 25.7, 25.5; IR (CH_2Cl_2) 3037, 2970, 1760, 1707, 1421, 1258 cm^{-1}; CIMS, m/z (relative intensity) 289 (M^+ + 1, 100), 243 (57). HRMS (CI) Calcd for $C_{17}H_{21}O_4$ (M^+ + 1) 289.1440, found 289.1432.

2,3,4,4a,9,10-Hexahydro-7-methoxy-4a-methylphenanthren-2-one (6). A solution of **8b** (0.048 g, 0.17 mmol), Cu(OAc)$_2$·H_2O (0.005 g, 0.02 mmol), pyridine (0.055 mL, 0.47 mmol), and dry benzene was purged with N_2 for 15 min. After the addition of $Pb(OAc)_4$ (0.120 g, 0.271 mmol) the solution was stirred at room temperature in the dark for 1 h and then refluxed for 1 h. By that time a yellow solid formed. A few drops of MeOH were added at room temperature, and the solution was filtered through a pad of silica gel under vacuum. Chromatography on silica gel gave **6** as a clear oil (0.028 g, 0.11 mmol, 69%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.21 (d, 1 H, J = 8.8 Hz), 6.81 (dd, 1 H, J = 2.7, 8.8 Hz), 6.62 (d, 1 H, J = 2.5 Hz), 5.89 (m, 1 H), 3.79 (s, 3 H), 2.98 (ddd, 1 H, J = 2.5, 5.9, 15.9 Hz), 2.88 (m, 1 H), 2.74−2.66 (m, 2 H), 2.55−2.48 (m, 2 H), 2.35 (ddd, 1 H, J = 2.2, 5.2, 13.5 Hz), 2.04 (td, 1 H, J = 4.7, 14.0 Hz), 1.54 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.0, 170.0, 157.6, 136.04, 136.00, 127.2, 124.2, 113.3, 112.8, 55.2, 38.6, 37.1, 34.8, 31.3, 31.1, 27.7; IR (film) 2916, 1665, 1247 cm^{-1}; CIMS m/z (relative intensity) 243 (M^+ + 1, 100). HRMS (CI) Calcd for $C_{16}H_{19}O_2$ (M^+ + 1) 243.1385, found 243.1386.

5-[2-(2-Bromo-5-methoxyphenyl)ethyl]-5-carbomethoxy-4-methyl-3-cyclohexen-1-one (7). A mixture of **2** and **3** (0.35 g, 0.89 mmol) in 8 mL of MeOH was treated with one drop of concd HCl and then stirred at room temperature for 4.5 h. MeOH was evaporated at room temperature under vacuum, and the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. Flash chromatography on silica gel provided **7** as a clear oil (0.274 g, 0.719 mmol, 81%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (d, 1 H, J = 8.7 Hz), 6.77 (d, 1 H, J = 2.9 Hz), 6.64 (dd, 1 H, J = 2.9, 8.7 Hz), 5.69 (m, 1 H), 3.78 (s, 3 H), 3.70 (s, 3 H), 2.99 (d, 1 H, J = 15.4 Hz), 2.93 (m, 2 H), 2.67 (td, 1 H, J = 4.4, 12.7 Hz), 2.53 (d, 1 H, J = 14.9 Hz), 2.52 (1 H, overlapping), 2.22 (td, 1 H, J = 4.4, 13.4 Hz), 1.91 (td, 1 H, J = 4.4, 13.4 Hz), 1.84 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) 207.5, 173.5, 159.1, 141.7, 134.8, 133.3, 123.2, 116.0, 114.5, 113.4, 55.4, 52.7, 52.4, 46.0, 38.9, 35.6, 31.5, 19.4; IR (film) 2932, 1720, 1240 cm^{-1}; CIMS m/z (relative intensity) 381 (M^+ + 1, 100), 383 (M^+ + 1, 84), 321 (22), 323 (24). HRMS (CI) Calcd for $C_{18}H_{22}BrO_4$ (M^+ + 1) 381.0701, found 381.0692.

1a-Carbomethoxy-7-methoxy-4a-methyl-1,1a,2,3,4,4a,9,-10-octahydrophenanthren-2-one (8a). A solution of **7** (0.256 g, 0.672 mmol), Bu_3SnH (0.215 mL, 0.807 mmol), AIBN (0.011 g, 0.067 mmol), and dry benzene (70 mL) was purged with N_2 for 15 min. After the solution was refluxed for 1 h, AIBN (0.011 g, 0.067 mmol) was added. After another 2 h, more AIBN (0.011 g, 0.067 mmol) was added, and the solution was refluxed overnight. The workup procedure described for preparation of **5** was utilized. The residue was purified by flash chromatography on silica gel to give **8a** as a yellow oil (0.050 g, 0.17 mmol, 25%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31 (d, 1 H, J = 8.8 Hz), 6.80 (dd, 1 H, J = 2.7, 8.8 Hz), 6.65 (d, 1 H, J = 2.7 Hz), 3.79 (s, 3 H), 3.73 (s, 3 H), 2.95 (dd, 1 H, J = 7.3, 18.1 Hz), 2.87−2.79 (m, 1 H), 2.57 (m, 1 H), 2.48−2.44 (m, 1 H), 2.34−2.29 (m, 3 H), 2.21−2.08 (m, 2 H), 1.71 (ddd, 1 H, J = 1.6, 7.1, 14.4 Hz), 1.22 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) 209.2, 175.5, 157.8, 135.5, 132.4, 126.5, 113.7, 113.5, 55.1, 52.1, 51.9, 44.0, 38.8, 37.4, 33.8, 29.6, 25.8, 25.6; IR (film) 2937, 1715, 1202 cm^{-1}; CIMS m/z (relative intensity) 303 (M^+ + 1, 100), 243 (18). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.36; H, 7.32.

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