Synthesis of the Putative Active Metabolites of the Cyclopenta[*a*]phenanthrenes. Synthesis of the *trans*-3,4-Dihydro 3,4-Diol and *syn*-3,4-Diol 1,2-Epoxide Derivatives of the Mutagen 15,16-Dihydrocyclopenta[*a*]phenanthren-17-one[1]

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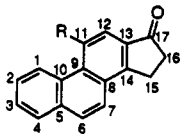
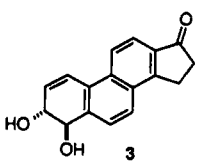
The first synthesis of the *trans*-dihydro diol and *syn*-diol epoxide derivatives of a biologically active cyclopenta[*a*]phenanthrene is described. The cyclopenta[*a*]phenanthrene skeleton is rapidly and efficiently assembled utilizing the Lewis acid-catalyzed Diels–Alder reaction of 1,2-dihydro-7-methoxy-4-vinylnaphthalene (**5**) with an α-heterosubstituted cyclopentenone, a "cyclopentynone" equivalent. It was found that the Diels–Alder reaction of α-(phenylselenenyl)- (**6a**) or α-bromocyclopentenone (**6b**) with **5** in the presence of 1.5 euqiv of $SnCl_4$ followed by elimination with hydrogen peroxide or DBU produced the key intermediate 15,16-dihydro-3-methoxycyclopenta[*a*]phenanthren-17-one (**10**) in 28% or 59% overall yield, respectively. The synthesis of the A-ring metabolites features the use of a unique methoxime protecting group for the 17-ketone. The deprotection of the 17-methoxime group of the highly acid-sensitive 3,4-*trans*-dihydro 3,4-diol bis(TBDMS) ether **15b** was achieved through the use of the low-valent titanium reagent produced upon reduction of $TiCl_3$·3THF by DIBAL-H (51%). Treatment of bis-(TBDMS) ether **16** with TBAF in THF provided the desired 3,4-*trans*-dihydro 3,4-diol (**3**) (83%), thus achieving the synthesis of **3** in 10 steps in 9.6% overall yield from **6b**. In addition, the bay-region *syn*-3,4-diol 1,2-epoxide (**4a**) was also synthesized from **3** in two steps [(1) NBA in 1:5 H_2O/DMSO, (2) NaOMe/THF] in 59% overall yield.

The cyclopenta[*a*]phenanthrenes are a family of compounds structurally related to steroids and phenanthrenes. Members of this group have been shown to exhibit mutagenic and carcinogenic activity.[2] For example, 15,16-dihydrocyclopenta[*a*]phenanthren-17-one (**1**) is mutagenic in bacterial[3a] and mammalian[3b] cell lines. The 11-methyl analogue (**2**) is a potent carcinogen on mouse skin, exhibiting activity comparable to benzo[*a*]pyrene.[4] These compounds represent a potential environmental hazard to humans: cyclopenta[*a*]phenanthrenes have been isolated from petroleum, coal, river and lake sediments, and, significantly, from the pyrolysis products of sterols present in edible oils.[5]



1 R = H
2 R = Me



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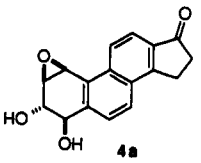
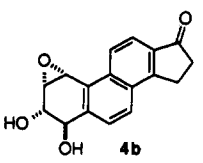


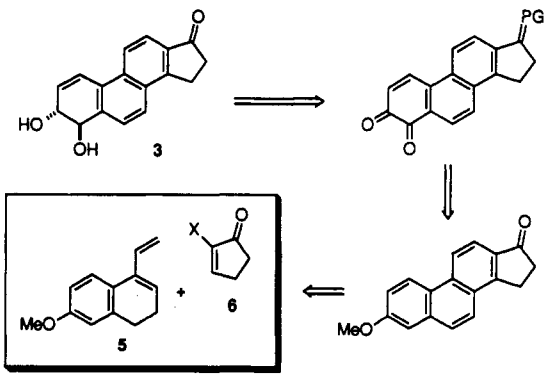
4a



4b

There is considerable evidence that the activity of these compounds arises from the metabolic activation of the hydrocarbon to the *trans*-3,4-dihydro 3,4-diol (**3**) and the corresponding bay-region diol epoxides (**4a**/**4b**).[6] Once

Scheme I



formed, these highly reactive electrophiles can then interact with cellular nucleophiles including DNA. However, progress in studies of the biological activity of these compounds has been hindered by the unavailability of synthetic samples of the putative active metabolites.

As a part of our efforts toward the development of a general synthetic route to the cyclopenta[*a*]phenanthrenes and their putative metabolites, we investigated the synthesis of metabolites of the unsubstituted 17-keto derivative of the cyclopenta[*a*]phenanthrenes. Herein we report the first synthesis of the *trans*-dihydro diol and *syn*-diol epoxide derivatives of a cyclopenta[*a*]phenanthrene, 3,4,15,16-tetrahydro-*trans*-3,4-dihydroxycyclopenta[*a*]-phenanthren-17-one (**3**), and *syn*-1,2-epoxy-1,2,3,4,15,16-hexahydro-*trans*-3,4-dihydroxycyclopenta[*a*]-phenanthren-17-one (**4a**), respectively. This synthesis features the rapid and efficient assembly of the cyclopenta[*a*]phenanthrene skeleton utilizing the highly regioselective Lewis acid-catalyzed Diels–Alder cycloaddition of 1,2-dihydro-7-methoxy-4-vinylnaphthalene (**5**) with an α-substituted cyclopentenone (Scheme I). The methoxy group then provides a handle for the regio- and stereoselective assembly of the *trans*-3,4-dihydro 3,4-diol moiety. However, it was anticipated from the outset of this research that the presence of a ketone functionality in the same molecule would present a considerable challenge to the efficient execution of the synthetic manipulations to-

(1) Presented at the 202nd American Chemical Society Meeting held in New York City on August 25–30, 1991. See: Koreeda, M.; Woski, S. A. Abstr. 118.

(2) Coombs, M. M.; Bhatt, T. S. *Cyclopenta[a]phenanthrenes*; Cambridge Monographs on Cancer Research: Cambridge, 1987.

(3) (a) Coombs, M. M.; Dixon, C.; Kissonerghis, A.-M. *Cancer Res.* **1976**, *36*, 4525. (b) Bhatt, T. S.; Coombs, M.; DiGiovanni, J.; Diamond, L. *Cancer Res.* **1983**, *43*, 984.

(4) Coombs, M. M.; Bhatt, T. S.; Young, S. *Br. J. Cancer* **1979**, *40*, 914.

(5) Coombs, M. M.; Bhatt, T. S. pp 239–241 in ref 1 and references cited therein.

(6) Coombs, M. M.; Kissonerghis, A.-M.; Allen, J. A.; Vose, C. W. *Cancer Res.* **1979**, *39*, 4160.

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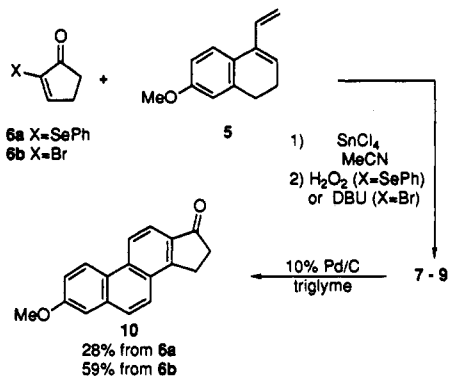
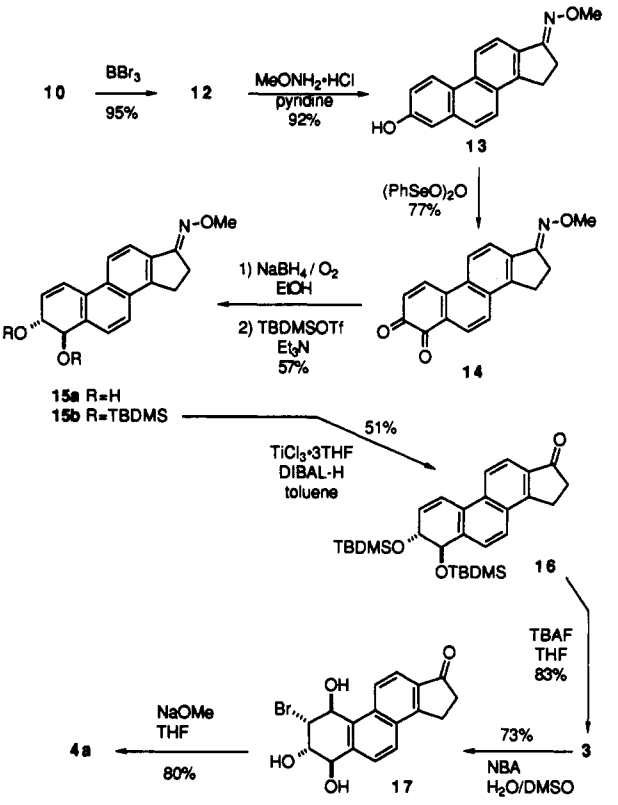
Scheme II



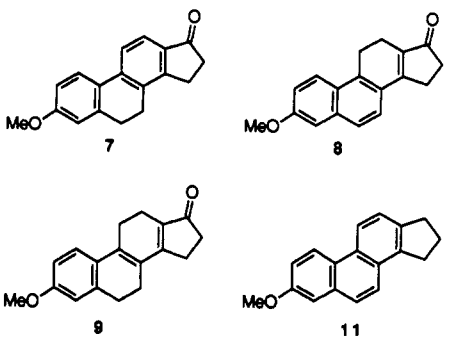
Scheme III



ward the diol and diol epoxide groups, requiring judicious choice of a protecting group for the ketone.

Diels–Alder reactions were utilized as the key synthetic step in early efforts toward the construction of the steroid/cyclopenta[a]phenanthrene skeleton.[7] However, these reactions proceeded in poor yield and with poor regioselectivity,[7] resulting in the development of a number of highly significant—but less direct—methodologies for steroid and cyclopenta[a]phenanthrene synthesis. Our strategy to overcome these difficulties was based upon the use of an α-heterosubstituted cyclopentenone as the dienophile in a Lewis acid-catalyzed cycloaddition reaction. Such captodative dienophiles have been reported to be highly reactive despite their added steric bulk.[8] The utilization of Lewis acid catalysis has been reported to impart both higher yields and excellent regioselectivities to these cycloaddition reactions.[8] The use of an α-hetero group provides an additional advantage: judicious choice of the hetero group can provide a species that can undergo a facile elimination after cycloaddition. Such a dienophile thus functions as a synthetic equivalent of cyclopentynone. The viability of this approach has been demonstrated in separate reports by Knapp[8m] and Liotta[8l] of the successful syntheses of indanone derivatives using the 2-phenyl sulfide and 2-phenyl selenide derivatives of cyclopentenone, respectively.

Our initial studies involved the utilization of Liotta's conditions: 2-(phenylselenenyl)-2-cyclopentenone (**6a**)[9] in the presence of $SnCl_4$ in acetonitrile.[8l] The requisite diene **5** is available from a one-pot three-step conversion of the commercially available 6-methoxy-1-tetralone.[10] Diene **5** underwent a rapid cycloaddition reaction with **6a** in the presence of $SnCl_4$ at low temperatures. Following the oxidative deselenenation of the crude mixture using hydrogen peroxide, 6,7,15,16-tetrahydro-3-methoxycyclopenta[a]phenanthren-17-one (**7**) was isolated in 38% yield[11] (Scheme II). Only the desired 17-keto regioisomer was detected. Dehydrogenation of **7** (10% Pd/C, triglyme, reflux)[12] produced the aromatized product **10** in 71% yield. The ^{1}H-NMR spectroscopic data for **10** were in accord with those reported by Lee and Harvey for the 17-keto isomer,[12,13] confirming our regiochemical assignment for cycloadduct **7**.



Having determined that this protocol produced the desired cycloadduct with complete control of the regiochemical outcome, we sought to determine whether the

(7) (a) Dane, E.; Eder, K. *Annalen* **1939**, *539*, 207. (b) Nazarov, I. N.; Kotlyaravskii, I. L. *Izv. Akad. Nauk SSSR Otdel. Khim. Nauk.* **1953**, 1100.

(8) For examples of Diels–Alder reactions with captodative dienophiles, see α-oxygen: (a) Wharton, P. S.; Aw, B. T. *J. Org. Chem.* **1966**, *31*, 3787. (b) Brodsky, L.; Agosta, W. C. *Ibid.* **1974**, *39*, 2928. (c) Quick, J.; Jenkins, R. *Ibid.* **1978**, *43*, 2275. (d) Tamariz, J.; Vogel, P. *Helv. Chim. Acta* **1981**, *64*, 188. (e) Ardecky, R.; Kerdesky, F. A. J.; Cava, M. P. *J. Org. Chem.* **1981**, *46*, 1483. (f) Sasaki, T.; Ishibashi, Y.; Ohno, M. *Tetrahedron Lett.* **1982**, *23*, 1693. (g) Aguilar, R.; Reyes, A.; Tamariz, J.; Birbaum, J.-L. *Ibid.* **1987**, *28*, 865. (h) Reyes, A.; Aguilar, R.; Muñoz, A. H.; Zwick, J.-C.; Rubio, M.; Escobar, J.-L.; Soriano, M.; Toscano, R.; Tamariz, J. *J. Org. Chem.* **1990**, *55*, 1024. α-Nitrogen: (i) Horikawa, H.; Nishitani, T.; Iwasaki, T.; Mushika, Y.; Inoue, I.; Miyoshi, M. *Tetrahedron Lett.* **1980**, *21*, 4101. (j) Boucher, J. L.; Stella, L. *Tetrahedron* **1985**, *41*, 4253. α-Selenium: (k) Uneyama, K.; Takano, K.; Torii, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2867. (l) Liotta, D.; Saindane, M., Barnum, C., Zima, G. *Tetrahedron* **1985**, *41*, 4881. α-Sulfur: (m) Knapp, S.; Lis, R.; Michna, P. *J. Org. Chem.* **1981**, *46*, 624. (n) Stella, L.; Boucher, J.-L. *Tetrahedron Lett.* **1982**, *23*, 953. (o) Boucher, J.-L.; Stella, L. *Ibid.* **1985**, *26*, 5041. (p) Boucher, J.-L.; Stella, L. *Bull. Chim. Soc. Fr.* **1985**, 276. (q) Boucher, J.-L.; Stella, L. *Tetrahedron* **1986**, *42*, 3871. (r) Boucher, J.-L.; Stella, L. *Ibid.* **1988**, *44*, 3595. (s) Boucher, J.-L.; Stella, L. *Ibid.* **1988**, *44*, 3607. (t) Merles, J.; Mattay, J. *Helv. Chim. Acta* **1988**, *71*, 742. (u) Watanabe, M.; Tsukazaki, M.; Hamada, Y.; Iwao, M.; Furukawa, S. *Chem. Pharm. Bull.* **1989**, *37*, 2948.

(9) Zima, G.; Liotta, D. *Synth. Commun.* **1979**, *9*, 697.

(10) Procedure is a modification of the method of Corey, E. J.; Estreicher, H. *Tetrahedron Lett.* **1981**, *22*, 603.

(11) This yield is unoptimized. The reaction mixture contained a trace amount of a second product which appears to be the 11,12,15,16-tetrahydro isomer **8**.

(12) Lee, H.; Harvey, R. G. *J. Org. Chem.* **1988**, *53*, 4253.

(13) The two regioisomers are easily distinguishable by the ^{1}H NMR chemical shift of H-7. The H-7 of the 17-ketone resonates at around δ 7.8, whereas the H-7 of the corresponding 15-ketone synthesized by another method resonates at δ 9.16. This dramatic downfield shift has also been reported by Lee and Harvey.[12]

phenyl selenide group could be replaced with a less toxic and less expensive congener. Although there are only a few examples of the use of α-halo enones as dienophiles in the Diels–Alder reaction,[14] we believed that 2-bromo-2-cyclopentenone (**6b**)[15] could be a useful replacement for **6a**. The reaction of **6b** with diene **4** in the presence of 1.5 equiv of $SnCl_4$, followed by dehydrohalogenation (DBU/benzene), produced a mixture of cycloadducts **7–9**, which upon dehydrogenation yielded the desired **10** as a single regioisomer. This cycloaddition was considerably slower than the reaction with **6a**; however, these reaction conditions were optimized to produce the cycloadducts **7–9** in ~85% crude yield. Dehydrogenation of this mixture produced the desired **10** in 59% overall yield from **6b**.

With the cyclopenta[*a*]phenanthrene skeleton in hand, the synthesis of the A-ring metabolites was undertaken (Scheme III). Although there is some precedent for the stereo- and regioselective transformation of the 3-methoxy group into the *trans*-dihydro diol,[16] the presence of the ketone functionality presented a novel challenge. Protection of the ketone as the ketal was not possible due to the extreme instability of the ketal derivative. Other common protecting groups were unsuitable for the planned transformations; however, the methoxime group was reported to be stable to the oxidation method to be employed (vide infra),[17] and this proved to be the protecting group of choice. Thus, cleavage of methyl ether **10** using BBr_3 produced the corresponding phenol **12** in excellent yield (95%). Treatment of **12** with methoxyamine hydrochloride in pyridine produced the desired methoxime **13** in 92% yield.

The stereoselective transformation of **13** into the *trans*-3,4-dihydro 3,4-diol was accomplished in two steps. The oxidation of **13** utilizing the method of Barton[18] (benzeneseleninic anhydride[19]) produced *o*-quinone **14** in 77% yield as a bright red solid. Quinone **14** was stereoselectively reduced to the corresponding *trans*-dihydro diol **15a** using $NaBH_4$ in ethanol with a steady stream of O_2 bubbling through the solution.[20] The product was isolated as the bis(TBDMS) ether (**15b**) following treatment of crude **15a** with TBDMS–OTf/Et_3N in benzene (57% yield from **14**).

Cleavage of the methoxime group in the presence of the sensitive dihydro diol moiety was accomplished by utilizing the reductive method of Corey and co-workers.[21] Thus, methoxime **15b** was treated with the low valent titanium reagent produced upon the reduction of $TiCl_3$·3THF[22] by DIBAL-H. The desired ketone **16** was isolated in satisfactory yield (51%, Scheme III). Cleavage of the silyl ethers with tetrabutylammonium fluoride produced the deisred **3** in 83% yield. The ^1H NMR spectral data for **3** corresponded to those reported for the metabolically derived compound.[23]

Efforts toward the synthesis of *anti*-diol epoxide **4b** by direct epoxidation of *trans*-dihydro diol **3**[24] with MCPBA were not successful, mainly due to the unexpected insolubility of this highly polar diol ketone in THF, dioxane, and methylene chloride, the solvents generally employed for the reaction. Treatment of **4b** with MCPBA in DMF resulted in the consumption of the starting material, but the highly sensitive product could not be isolated from this medium. In contrast, the *syn*-diol epoxide **4a** was smoothly obtainable in two steps in 59% overall yield from **3**. Thus, treatment of diol **3** with NBA in 5:1 DMSO/water regio- and stereoselectively produced homohydrin **17** in 73% yield. This THF-soluble bromohydrin was readily converted into *syn*-diol epoxide **4a** with NaOMe in THF.

The results presented above represent the first synthesis of the dihydro diol and diol epoxide derivatives of a cyclopenta[*a*]phenanthrene. In addition, this also represents the first synthesis of a dihydro diol and a diol epoxide of a molecule bearing a ketone functionality. The synthetic route described above is currently being applied to the syntheses of the putative active metabolites of other cyclopenta[*a*]phenanthren-17-ones, especially those of the carcinogenic analogues of **1**, including the 11-methyl (**2**), 7-methyl, and 7,11-dimethyl compounds. The availability of these compounds for further studies may allow for the definitive elucidation of the mechanism of action of these important compounds.

Experimental Section

1,2-Dihydro-7-methoxy-4-vinylnaphthalene (5). To a solution of vinylmagnesium bromide, produced from 6.90 g (284 mmol, 1.6 equiv) of freshly crushed magnesium turnings and 20.0 mL (30.3 g, 284 mmol, 1.6 equiv) of vinyl bromide in 250 mL of dry THF was added dropwise via cannula over 2 h a solution of 31.7 g (180 mmol) of 6-methoxy-1-tetralone in 175 mL of dry THF. The mixture was heated at reflux for 1 h and was then cooled to 0 °C. To the resulting solution was added 42 mL (62 g, 543 mmol, 3.0 equiv) of methanesulfonyl chloride. After 10 min, 150 mL (109 g, 1076 mmol, 6.0 equiv) of triethylamine was added slowly to the rapidly stirring mixture; during the addition of the triethylamine, a voluminous precipitate began to form. The mixture was stirred at 0 °C for 3 h. The reaction mixture was then poured into a separatory funnel containing 400 mL of water and was extracted with ethyl ether (3 × 400 mL). The combined organic extracts were washed with water (300 mL) and brine (300 mL) and were dried (Na_2SO_4). Filtration, concentration in vacuo by rotary evaporation, and purification by flash column chromatography (silica gel, CH_2Cl_2), afforded 13.7 g of **5** (41%) as a red-orange oil:[7] ^1H NMR (300 MHz, $CDCl_3$) δ 2.26 (ddd, 2H, $J_{2,1}$ = 8.0, 7.7 Hz, $J_{2,3}$ = 4.8 Hz, 2-H), 2.71 (dd, 2H, $J_{1,2}$ = 8.0, 7.7 Hz, 1-H), 3.78 (s, 3 H, OCH_3), 5.16 (dd, 1 H, $J_{2'a,1'}$ = 10.8 Hz, $J_{2'a,2'b}$ = 1.8 Hz, 2'a-H), 5.50 (dd, 1 H, $J_{2'b,1'}$ = 17.4 Hz, $J_{2'b,2'a}$ = 1.8 Hz, 2'b-H), 6.04 (t, 1 H, $J_{3,2}$ = 4.8 Hz, 3-H), 6.58 (ddquintets, 1 H, 1'-H), 6.68–6.72 (m, 2 H, 6-H and 8-H), 7.25 (d, 1 H, $J_{5,6}$ = 7.9 Hz, 5-H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 23.22 (t, 2-C), 28.77 (t, 1-C), 55.23 (q, OCH_3), 110.93 (d), 113.93 (d), 114.92 (t, 2'-C), 124.08 (d), 125.08 (d), 127.30 (s), 135.83 (d), 136.29 (s), 138.53 (s), 158.69 (s, 7-C); IR (neat) 1608, 1499, 1252 cm^{-1}.

6,7,15,16-Tetrahydro-3-methoxycyclopenta[a]phenanthren-17-one (7). A solution of 0.202 g (0.853 mmol) of 2-(phenylselenenyl)-2-cyclopentenone (**6a**)[9] and 9 mL of CH_3CN was cooled to −30 °C, and 0.15 mL (1.3 mmol, 1.5 equiv) of $SnCl_4$ was added via syringe. The resulting solution was stirred for 10 min. To this light-yellow solution was added dropwise by syringe a solution of 0.161 g (0.866 mmol, 1.01 equiv) of **5** in 2 mL of CH_3CN. The mixture was stirred at −30 °C for 40 min, and the reaction mixture was then poured into a separatory funnel con-

(14) (a) Ayyar, K. S.; Cookson, R. C.; Kagi, D. A. *J. Chem. Soc., Chem. Commun.* **1973**, 161; *J. Chem. Soc. Perkin Trans. 1* **1975**, 1727. (b) There are many examples of the use of α-haloacrylic acid derivatives as ketene equivalents. For a review, see: Ranganathan, S.; Ranganathan, D.; Mehrotra, A. K. *Synthesis* **1977**, 289.

(15) Chow, Y. L.; Bakker, B. H. *Can. J. Chem.* **1982**, *60*, 2268.

(16) (a) Sukumaran, K. B.; Harvey, R. G. *J. Org. Chem.* **1980**, *45*, 4407. (b) Jacobs, S. A.; Cortez, C.; Harvey, R. G. *Carcinogenesis* **1983**, *4*, 519.

(17) Barton, D. H. R.; Lester, D. J.; Ley, S. V. *J. Chem. Soc., Chem. Commun.* **1977**, 445.

(18) Barton, D. H. R.; Brewster, A. G.; Ley, S. V.; Rosenfeld, M. N. *J. Chem. Soc., Chem. Commun.* **1976**, 985.

(19) Ayrey, G.; Barnard, D.; Woodbridge, D. T. *J. Chem. Soc.* **1962**, 2089.

(20) Platt, K. L.; Oesch, F. *J. Org. Chem.* **1983**, *48*, 265. See also ref 16b.

(21) Corey, E. J.; Niimura, K.; Konishi, Y.; Hashimoto, S.; Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199.

(22) Manzer, L. E. *Inorg. Synth.* **1982**, *21*, 135.

(23) Hadfield, S. T.; Abbott, P. J.; Coombs, M. M.; Drake, A. F. *Carcinogenesis* **1984**, *5*, 1395.

(24) (a) Yagi, H.; Hernandez, O.; Jerina, D. M. *J. Am. Chem. Soc.* **1975**, *97*, 6881. (b) Yagi, H.; Thakker, D. R.; Hernandez, O.; Koreeda, M.; Jerina, D. M. *Ibid.* **1977**, *99*, 1604.

taining 15 mL of saturated aqueous $NaHCO_3$ and was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic extracts were concentrated in vacuo by rotary evaporation, and the residue was dissolved in 8 mL of CH_2Cl_2. To the resulting solution was added 1.8 mL of 30% aqueous H_2O_2 in six equal portions at 10-min intervals. The mixture was stirred for 1 h, and the resulting solution was poured into a separatory funnel containing 10 mL of water and 20 mL of CH_2Cl_2. The phases were equilibrated and separated, and the aqueous portion was washed with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL) and were dried ($MgSO_4$). Filtration, concentration in vacuo by rotary evaporation, and purification by flash column chromatography (silica gel, 19:1 CH_2Cl_2/EtOAc; then gradient elution) produced 0.085 g (38%) of **7** as a white crystalline solid: mp 141.5–142.5 °C (lit.[12] mp 141–142 °C). ^1H NMR (300 MHz, $CDCl_3$) δ 2.72 (br dd, 2 H, J = 6.0, 5.7 Hz, 16-H), 2.87 (br s, 4 H, 6-H and 7-H), 3.07 (br dd, 2 H, J = 6.0, 5.7 Hz, 15-H), 3.85 (s, 3 H, OCH_3), 6.81 (d, 1 H, $J_{4,2}$ = 2.7 Hz, 4-H), 6.87 (dd, 1 H, $J_{2,1}$ = 8.6 Hz, $J_{2,4}$ = 2.7 Hz, 2-H), 7.65 and 7.72 (AB q, $J_{A,B}$ = 8.3 Hz, 11-H and 12-H), 7.72 (d, 1 H, $J_{1,2}$ = 8.6 Hz, 1-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.93 (t), 24.53 (t), 28.75 (t), 36.56 (t), 55.33 (q, OCH_3), 112.68 (d), 113.74 (d), 122.07 (d), 122.77 (d), 126.22 (d), 126.63 (s), 133.32 (s), 135.25 (s), 139.55 (s), 140.25 (s), 153.15 (s), 160.10 (s), 206.49 (s, 17-C); IR (KBr) 1695, 1593, 1282, 1246 cm^{-1}.

15,16-Dihydro-3-methoxycyclopenta[*a*]phenanthren-17-one (10). A suspension of 85 mg of **7** and 5 mg of 10% Pd/C in 10 mL of triglyme was heated at reflux for 4 h. The resulting mixture was cooled, diluted with 50 mL of EtOAc, and filtered. The mixture was extracted with water (4 × 20 mL); the combined aqueous extracts were back-extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (30 mL) and were dried ($MgSO_4$). Filtration, concentration in vacuo by rotary evaporation, and purification by flash column chromatography (silica gel, 19:1 CH_2Cl_2/EtOAc) afforded 57 mg (71%) of **10** as a white solid: mp 212–213 °C (lit.[12] mp 212–213 °C). Additionally, 4 mg (5%) of 16,17-dihydro-3-methoxy-15*H*-cyclopenta[*a*]phenanthrene (**11**) was isolated as a white solid: mp 138–138.5 °C (lit.[12] mp 139–140 °C).

15,16-Dihydro-3-methoxycyclopenta[*a*]phenanthren-17-one (10): ^1H NMR (300 MHz, $CDCl_3$) δ 2.84 (br dd, 2 H, J = 5.7, 5.4 Hz, 16-H), 3.42 (br dd, 2 H, J = 5.7, 5.4 Hz, 15-H), 3.98 (s, 3 H, OCH_3), 7.27 (d, 1 H, $J_{4,2}$ = 2.7 Hz, 4-H), 7.30 (dd, 1 H, $J_{2,1}$ = 9.2 Hz, $J_{2,4}$ = 2.7 Hz, 2-H), 7.78 and 7.89 (AB q, 2 H, $J_{A,B}$ = 8.9 Hz, 6-H and 7-H), 7.88 (d, 1 H, $J_{12,11}$ = 8.6 Hz, 12-H), 8.53 (d, 1 H, $J_{11,12}$ = 8.6 Hz, 11-H), 8.59 (d, 1 H, $J_{1,2}$ = 9.2 Hz, 1-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.63 (t, 16-C), 36.46 (t, 15-C), 55.55 (q, OCH_3), 109.04 (d), 118.06 (d), 120.64 (d), 122.44 (d), 122.51 (d), 124.95 (s), 125.47 (d), 127.70 (d), 128.05 (s), 134.40 (s), 134.57 (s), 135.07 (s), 155.29 (s), 159.49 (s), 206.09 (s, 17-C); IR (KBr) 1695 (s), 1616, 1533, 1299, 1253, 1201, 805 cm^{-1}; UV (*p*-dioxane) λ (ε) 363 (2100), 345 (2900), 317 (15200), 289 (28500), 276 (77600), 267 nm (56400).

16,17-Dihydro-3-methoxy-15*H*-cyclopenta[*a*]phenanthrene (11): ^1H NMR (300 MHz $CDCl_3$) δ 2.24 (tt, 2 H, $J_{16,17}$ = 7.4 Hz, $J_{16,15}$ = 7.5 Hz, 16-H), 3.11 (t, 2 H, $J_{17,16}$ = 7.4 Hz, 17-H), 3.27 (t, 2 H, $J_{15,16}$ = 7.5 Hz, 15-H), 3.93 (s, 3 H, OCH_3), 7.21 (d, 1 H, $J_{4,2}$ = 2.7 Hz, 4-H), 7.24 (dd, 1 H, $J_{2,1}$ = 8.6 Hz, $J_{2,4}$ = 2.7 Hz, 2-H), 7.49 (d, 1 H, $J_{12,11}$ = 8.4 Hz, 12-H), 7.64 and 7.71 (AB q, 2 H, $J_{A,B}$ = 9.0 Hz, 6-H and 7-H), 8.39 (d, 1 H, $J_{11,12}$ = 8.4 Hz, 11-H), 8.53 (d, 1 H, $J_{1,2}$ = 8.6 Hz, 1-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.95 (t, 16-C), 31.50 (t, 17-C), 33.67 (t, 15-C), 55.49 (q, OCH_3), 108.87 (d), 117.20 (d), 120.85 (d), 123.57 (d), 124.32 (d), 124.56 (d), 125.54 (s), 126.55 (d), 127.91 (s), 129.19 (s), 133.00 (s), 140.87 (s), 141.19 (s), 158.08 (s, 3-C); IR (KBr) 3037, 3017, 1611, 1470 (s), 1250 (s), 1196 (s), 1131, 1027, 848 cm^{-1}.

15,16-Dihydro-3-methoxycyclopenta[*a*]phenanthren-17-one (10) [from 6b]. A solution of 6.08 g (37.7 mmol) of 2-bromo-2-cyclopentenone (**6b**)[15] in 350 mL of CH_3CN was cooled to 0 °C, and 6.60 mL (14.7 g, 56.4 mmol, 1.5 equiv) of $SnCl_4$ was added via syringe. The ice–water bath was removed, and the resulting solution was stirred at rt for 1 h. To this light-yellow solution was added via cannula over a period of 2 h a solution of 13.68 g (73.4 mmol, 2 equiv) of **5** in 50 mL of CH_3CN; during this addition the solution turned red-brown. The mixture was stirred for 4 h, and the reaction mixture was then poured into a separatory funnel containing 400 mL of water and was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (400 mL) and brine (400 mL) and were then dried ($MgSO_4$). Upon filtration and evaporation in vacuo by rotary evaporation, the residue was dissolved in 1000 mL of benzene. To the resulting solution was added 8.0 mL (8.1 g, 53.5 mmol, 1.4 equiv) of DBU. The solution was stirred for 12 h, during which time a yellow-white precipitate formed. The solution was poured into a separatory funnel containing 500 mL of 10% aqueous HCl. The phases were equilibrated and separated, and the organic portion was washed with water (3 × 200 mL) and then with brine (200 mL). The combined aqueous washes were extracted with $CHCl_3$ (3 × 200 mL). The combined organic extracts were dried ($MgSO_4$). Filtration, concentration in vacuo by rotary evaporation, and purification by flash column chromatography (silica gel, 19:1 CH_2Cl_2/EtOAc; then gradient elution) produced a mixture of **7**, **8**, and **9**. To this product mixture were added 4.31 g of 10% Pd/C and 500 mL of triglyme, and the mixture was heated at reflux for 36 h. Upon cooling to rt, the Pd/C was removed by suction filtration and washed with ethyl acetate (120 mL). The solvents were removed by vacuum distillation, producing a yellow solid. Purification by flash column chromatography (silica gel, 39:1 CH_2Cl_2/EtOAc, then gradient) afforded 5.82 g (59%) of **10**. Additionally, 0.680 g (7%) of 16,17-dihydro-3-methoxy-15*H*-cyclopenta[*a*]phenanthrene (**11**) was isolated.

15,16-Dihydro-3-hydroxycyclopenta[*a*]phenanthren-17-one (12). A solution of 1.14 g (4.33 mmol) of **10** in 100 mL of CH_2Cl_2 was cooled to −78 °C, and 13 mL (13 mmol, 3 equiv) of a BBr_3 solution (1.0 M in CH_2Cl_2) was added via syringe. The mixture was allowed to slowly warm to rt. After stirring overnight, the mixture was poured into a separatory funnel containing 200 mL of water. The resulting precipitate was filtered and washed with water and CH_2Cl_2, producing 1.02 g (95%) of **12** as a light brown solid: mp 260 °C dec; ^1H NMR (300 MHz, pyridine-d_5) δ 2.74 (br dd, 2 H, J = 5.7, 5.4 Hz, 16-H), 3.23 (br dd, 2 H, J = 5.7, 5.4 Hz, 15-H), 7.69 (dd, 1 H, $J_{2,1}$ = 9.0 Hz, $J_{2,4}$ = 2.5 Hz, 2-H), 7.76 (d, 1 H, $J_{4,2}$ = 2.5 Hz, 4-H), 7.86 and 7.92 (AB q, 2 H, $J_{A,B}$ = 9.0 Hz, 6-H and 7-H), 8.08 (d, 1 H, $J_{12,11}$ = 8.6 Hz, 12-H), 8.76 (d, 1 H, $J_{11,12}$ = 8.6 Hz, 11-H), 8.86 (d, 1 H, $J_{1,2}$ = 9.0 Hz, 1-H); ^{13}C NMR (90.6 MHz, pyridine-d_5) δ 24.71 (t, 16-C), 36.54 (t, 15-C), 112.54 (d), 119.31 (d), 120.62 (d), 122.73 (d), 122.86 (d), 124.19 (s), 126.32 (d), 127.89 (d), 128.07 (s), 134.45 (s), 135.04 (s), 136.01 (s), 155.74 (s), 159.08 (s), 205.68 (s, 17-C); IR (KBr) 3394 (br), 1675 (s), 1617, 1533, 1304, 1067, 797 cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{17}H_{12}O_2$ m/z 248.0837, found m/z 248.0828; MS (EI, 70 eV) m/z 248 (100, M^+), 219 (29, M^+ − CHO), 189 (14), 95 (9). Anal. Calcd for $C_{17}H_{12}O_2$: C, 82.24; H, 4.87. Found: C, 81.95; H, 4.76.

15,16-Dihydro-3-hydroxycyclopenta[*a*]phenanthren-17-one Methoxime (13). To 2.01 g (8.08 mmol) of **12** were added 0.851 g (10.2 mmol, 1.3 equiv) of methoxylamine hydrochloride and 60 mL of pyridine. The resulting solution was stirred for 18 h and was then poured into 200 mL of water. The resulting precipitate was washed with 10% aqueous HCl (50 mL) and then with water (100 mL). The filter cake was dried in vacuo and was recrystallized from ethanol/water, affording 2.07 g (92%) of **13** as a light yellow solid: mp 240 °C dec; ^1H NMR (360 MHz, acetone-d_6) δ 3.01 (br dd, 2 H, J = 6.7, 6.1 Hz, 16-H), 3.41 (br dd, 2 H, J = 6.7, 6.1 Hz, 15-H), 3.96 (s, 3 H, $NOCH_3$), 7.31 (dd, 1 H, $J_{2,1}$ = 9.0 Hz, $J_{2,4}$ = 2.4 Hz, 2-H), 7.35 (d, 1 H, $J_{4,2}$ = 2.4 Hz, 4-H), 7.77 and 7.81 (AB q, 2 H, $J_{A,B}$ = 9.0 Hz, 6-H and 7-H), 7.82 (d, 1 H, $J_{12,11}$ = 8.6 Hz, 12-H), 8.63 (d, 1 H, $J_{11,12}$ = 8.6 Hz, 11-H), 8.70 (d, 1 H, $J_{1,2}$ = 9.0 Hz, 1-H); ^{13}C NMR (90.6 MHz, acetone-d_6) δ 27.10 (t, 16-C), 27.98 (t, 15-C), 62.14 (q, $NOCH_3$), 112.38 (d), 118.69 (d), 120.16 (d), 122.86 (d), 123.87 (d), 125.18 (s), 125.94 (d), 127.95 (d), 128.53 (s), 132.76 (s), 134.00 (s), 135.17 (s), 147.47 (s), 157.44 (s), 163.35 (s, 17-C); IR (KBr) 3402 (br), 1618, 1468, 1255, 1197, 1043 (N-OMe), 859 cm^{-1}; MS (EI, 70 eV) m/z 277 (M^+, 100), 246 (M^+ − OMe, 26), 228 (M^+ − OMe − H_2O, 12), 139 (23), 101 (11), 94 (17); HRMS (EI, 70 eV) calcd for $C_{18}H_{15}NO_2$ m/z 277.1103, found m/z 277.1095. Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.00; H, 5.37; N, 4.93.

15,16-Dihydrocyclopenta[*a*]phenanthrene-3,4,17-trione 17-Methoxime (14). A partial solution of 1.82 g (6.6 mmol) of **13** in 400 mL of dry THF was treated with 8.05 g (22.4 mmol, 3.4 equiv) of benzeneseleninic anhydride. The resulting mixture

was heated at reflux for 4 h. The orange-red mixture was cooled and poured into a separatory funnel containing 300 mL of water and 300 mL of hexanes. The biphasic mixture was vacuum filtered; the solid was washed with water, saturated aqueous $NaHCO_3$, and then with hexanes. Drying in vacuo in a desiccator over anhydrous $CaCl_2$ afforded 1.47 g (77%) of the desired **14** as a red solid: ^1H NMR (360 MHz, THF-d_8) δ 3.02 (br dd, 2 H, J = 6.4, 6.2 Hz, 16-H), 3.39 (br dd, 2 H, J = 6.4, 6.2 Hz, 15-H), 3.97 (s, 3 H, $NOCH_3$), 6.50 (d, 1 H, $J_{2,1}$ = 10.6 Hz, 2-H), 7.86 (d, 1 H, $J_{12,11}$ = 9.0 Hz, 12-H), 8.05 and 8.15 (AB q, $J_{A,B}$ = 8.6 Hz, 6-H and 7-H), 8.42 (d, 1 H, $J_{11,12}$ = 9.0 Hz, 11-H), 8.50 (d, 1 H, $J_{1,2}$ = 10.6 Hz, 1-H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 26.42 (t), 27.53 (t), 62.42 (q), 121.68 (d), 123.35 (d), 125.32 (d), 127.13 (d), 128.07 (d), 130.07 (s), 130.87 (s), 132.47 (s), 134.52 (s), 137.37 (s), 139.62 (d), 146.72 (s), 162.09 (s), 179.28 (s), 180.56 (s); IR (KBr) 2918 (s), 2850 (s), 1691, 1668 (s), 1472, 1416, 1344, 1280, 1041 (s, N-OMe), 872 cm^{-1}; UV (*p*-dioxane) λ (ϵ) 391 (5500), 311 (28 400), 251 nm (35 000); MS (EI, 70 eV) m/z 291 (12, M^+), 263 (100, M^+ - CO), 232 (23, M^+ - CO - OCH_3), 88 (12); HRMS (EI, 70 eV) calcd for $C_{17}H_{12}O_2$ m/z 291.0895, found m/z 291.0898.

3,4,15,16-Tetrahydro-*trans*-3,4-bis[(*tert*-butyldimethylsilyl)oxy]cyclopenta[*a*]phenanthren-17-one Methoxime (15b). To a suspension of 0.447 g (1.53 mmol) of **14** in 500 mL of absolute EtOH was added 1.55 g (40.9 mmol, 26.6 equiv) of $NaBH_4$. The solution turned yellow and became homogeneous. The flask was fitted with a bubbler, and oxygen was passed through the stirred solution for 96 h. The addition of 300 mL of water, removal of the EtOH in vacuo by rotary evaporation, vacuum filtration, and drying in vacuo (2 mmHg) in a desiccator over anhydrous $CaCl_2$ produced a light yellow solid. This solid was suspended in 100 mL of dry benzene and cooled to 0 °C, and 5.0 mL of triethylamine and 1.5 mL (6.5 mmol, 2.1 equiv) of TBDMS triflate were added. The resulting solution was stirred for 4 h at rt and was poured into a separatory funnel containing 50 mL of water. The phases were equilibrated, and aqueous portion was washed with 50 mL of CH_2Cl_2. The combined organic extracts were washed successively with 10% aqueous HCl (2 × 100 mL), saturated aqueous $NaHCO_3$ (100 mL), and brine (100 mL). Drying (Na_2SO_4), concentration in vacuo by rotary evaporation, and purification by flash column chromatography (silica gel, 19:1 CH_2Cl_2/EtOAc) yielded 0.460 g (57%) of **15b** as a yellow oil. Crystallization from hexanes afforded the product as a white crystalline solid: mp 154.5–155 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 0.075 (s, 3 H, $OSiCH_3$), 0.10 (s, 3 H, $OSiCH_3$), 0.15 (s, 3 H, $OSiCH_3$), 0.22 (s, 3 H, $OSiCH_3$), 0.93 (s, 9 H, $OSiC(CH_3)_3$), 1.01 (s, 9 H, $OSiC(CH_3)_3$), 3.03 (br dd, 2 H, J = 6.3, 6.2 Hz, 16-H), 3.33 (br dd, 2 H, J = 6.3, 6.2 Hz, 15-H), 4.02 (s, 3 H, $NOCH_3$), 4.51 (ddd, 1 H, $J_{3,4}$ = 9.8 Hz, $J_{3,2}$ = 2.6 Hz, $J_{1,3}$ = 1.8 Hz, 3-H), 4.92 (d, 1 H, $J_{4,3}$ = 9.8 Hz, 4-H), 6.16 (dd, 1 H, $J_{2,1}$ = 10.1 Hz, $J_{2,3}$ = 2.6 Hz, 2-H), 7.18 (dd, 1 H, $J_{1,2}$ = 10.1 Hz, $J_{1,3}$ = 1.8 Hz, 1-H), 7.75 (d, 1 H, $J_{12,11}$ = 8.9 Hz, 12 H), 7.73 and 7.77 (AB q, 2 H, $J_{A,B}$ = 8.5 Hz, 6-H and 7-H), 8.00 (d, 1 H, $J_{11,12}$ = 8.9 Hz, 11-H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ -4.49 (q, $OSi(CH_3)_2$), -3.86 (q, $OSiCH_3$), -3.60 (q, $OSiCH_3$), 18.35 (s, $OSiC(CH_3)_3$), 18.38 (s, $OSiC(CH_3)_3$), 26.16 (q, $OSiC(CH_3)_3$), 26.20 (q, $OSiC(CH_3)_3$), 26.50 (t, 16-C), 27.44 (t, 15-C), 62.03 (q, $NOCH_3$), 72.62 (d, 3-C), 75.42 (d, 4-C), 119.25 (d), 122.65 (d), 123.00 (d), 123.37 (d), 125.14 (d), 129.03 (s), 130.28 (s), 130.31 (s), 133.11 (s), 134.02 (d), 136.70 (s), 146.68 (s), 163.32 (s, 17-C); IR (KBr) 2957 (s), 2857 (s), 1259, 1251, 1044 (s, N-OMe), 887 (s), 854 (s), 837 (s), 776 (s) cm^{-1}; UV (EtOH) λ (ϵ) 359 (2700), 343 (5700), 320 (9200), 274 nm (59 500). Anal. Calcd for $C_{30}H_{45}NO_3Si_2$: C, 68.78; H, 8.66; N, 2.67. Found: C, 68.69; H, 8.75; N, 2.70.

3,4,15,16-Tetrahydro-*trans*-3,4-bis[(*tert*-butyldimethylsilyl)oxy]cyclopenta[*a*]phenanthren-17-one (16). A 10- × 180-mm test tube equipped for magnetic stirring and the maintenance of an inert atmosphere (argon balloon) was charged with 0.310 g (0.836 mmol, 9.56 equiv) of $TiCl_3$·3THF[22] and 3 mL of dry toluene. This suspension was cooled to 0 °C, and 0.8 mL (0.8 mmol, 9.2 equiv) of DIBAL-H (1 M in toluene) was added slowly, immediately forming a black suspension with the evolution of hydrogen gas. The mixture was stirred for 10 min and then was warmed to room temperature. After 30 min, a second portion of DIBAL-H (0.2 mL, 0.2 mmol, 2.3 equiv) was added. The mixture was stirred at rt for 1.5 h and then was centrifuged at 2000 rpm for 40 min. The dark brown supernatant was removed using a syringe; the pasty black solid was washed with 1 mL of toluene, taking care not to disturb the pellet. To the resulting solid was added 3 mL of toluene, and a uniform suspension was formed with the aid of sonication. This suspension was added in three equal portions at 30-min intervals to a solution of 45.8 g (0.0874 mmol) of **15b** in 2 mL of dry toluene under argon. The black mixture gradually became golden-brown. After the reaction mixture was stirred for 18 h, the reaction was quenched by the addition of 25 mL of 10% aqueous NaOAc. The resulting mixture was diluted with 50 mL of ether and was acidified by the addition of aqueous citric acid. The phases were equilibrated and separated, and the aqueous portion was extracted with ether (4 × 50 mL). The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ (100 mL), water (200 mL), and brine (200 mL). Drying (Na_2SO_4), filtration, concentration in vacuo by rotary evaporation, and purification by flash column chromatography (silica gel, 19:1 CH_2Cl_2/EtOAc) yielded 22.3 g (52%) of **16** as a white solid: mp 148–149 °C (hexanes); ^1H NMR (360 MHz, $CDCl_3$) δ 0.086 (s, 3 H, $OSiCH_3$), 0.11 (s, 3 H, $OSiCH_3$), 0.15 (s, 3 H, $OSiCH_3$), 0.23 (s, 3 H, $OSiCH_3$), 0.94 (s, 9 H, $OSiC(CH_3)_3$), 1.01 (s, 9 H, $OSi(CH_3)_3$), 2.84 (br dd, 2 H, J = 5.5, 5.4 Hz, 16-H), 3.42–3.44 (m, 2 H, 15-H), 4.52 (ddd, 1 H, $J_{3,4}$ = 9.7 Hz, $J_{3,2}$ = 2.5 Hz, $J_{3,1}$ = 1.6 Hz, 3-H), 4.94 (d, 1 H, $J_{4,3}$ = 9.7 Hz, 4-H), 6.20 (dd, 1 H, $J_{2,1}$ = 10.2 Hz, $J_{2,3}$ = 2.5 Hz, 2-H), 7.19 (dd, 1 H, $J_{1,2}$ = 10.2 Hz, $J_{1,3}$ = 1.6 Hz, 1-H), 7.75 (d, 1 H, $J_{12,11}$ = 8.9 Hz, 12-H), 7.83 and 7.98 (AB q, 2 H, $J_{A,B}$ = 8.4 Hz, 6-H and 7-H), 8.08 (d, 1 H, $J_{11,12}$ = 8.9 Hz, 11-H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ -4.45 (q, $OSiCH_3$), -4.43 (q, $OSiCH_3$), -3.60 (q, $OSiCH_3$), 18.38 (s, $OSiC(CH_3)_3$), 18.42 (s, $OSiC(CH_3)_3$), 24.57 (t, 16-C), 26.18 (q, $OSiC(CH_3)_3$), 26.21 (q, $OSiC(CH_3)_3$), 36.25 (t, 15-C), 72.43 (d, 3-C), 75.46 (d, 4-C), 119.68 (d), 122.44 (d), 123.46 (d), 123.48 (d), 125.69 (d), 129.44 (s), 130.49 (s), 132.26 (s), 134.37 (s), 134.57 (d), 139.29 (s), 156.68 (s), 206.42 (s, 17-C); IR (KBr) 2957, 2855, 1704 (s, C=O), 1257 (s), 1128 (s), 889 (s), 840 (s), 776 (s); MS (EI, 70 eV) m/z 494 (15, M^+), 437 (71, M^+ - ^{t}Bu), 379 (14), 363 (11), 305 (12), 275 (51), 232 (16), 203 (17), 202 (12), 147 (67), 73 (100), 57 (15), 41 (15); HRMS (EI, 70 eV) calcd for $C_{29}H_{42}O_3Si_2$ m/z 494.2673, found m/z 494.2664.

3,4,15,16-Tetrahydro-*trans*-3,4-dihydroxycyclopenta[*a*]phenanthren-17-one (3). A solution of 18.3 mg (0.037 mmol) of **16** in 0.5 mL of dry THF was cooled to 0 °C, and 0.15 mL (0.15 mmol, 4.1 equiv) of 1.0 M tetrabutylammonium fluoride in THF was added via syringe. After 5 min the solution was warmed to rt and was stirred for 1.5 h. The resulting mixture was quenched by the addition of 2 mL of saturated aqueous $NaHCO_3$. The resulting brown precipitate was vacuum filtered, washed with water, and dried in vacuo in a desiccator over anhydrous $CaCl_2$, producing 8 mg (83%) of the desired dihydro diol **3** as a light brown solid. ^1H NMR (360 MHz, DMSO-d_6) δ 2.78 (br dd, 2 H, J = 5.3, 5.3 Hz, 16-H), 3.42 (br s, 15-H), 4.35 (br d, 1 H, $J_{3,4}$ = 11.1 Hz, 3-H), 4.74 (dd, 1 H, $J_{4,3}$ = 11.1 Hz, J = 5.4 Hz, 4-H), 5.36 (d, 1 H, J = 4.5 Hz, 3-OH), 5.77 (d, 1 H, J = 5.4 Hz, 4-OH), 6.19 (dd, 1 H, $J_{2,1}$ = 10.1 Hz, $J_{2,3}$ = 2.2 Hz, 2-H), 7.28 (dd, 1 H, $J_{1,2}$ = 10.1 Hz, $J_{1,3}$ = 2.2 Hz, 1-H), 7.62 (d, 1 H, $J_{12,11}$ = 9.0 Hz, 12-H), 7.94 and 8.09 (AB q, 2 H, $J_{A,B}$ = 8.5 Hz, 6-H and 7-H), 8.24 (d, 1 H, $J_{11,12}$ = 9.0 Hz, 11-H); ^{13}C NMR (90.6 MHz, DMSO-d_6) δ 24.12 (t, 16-C), 35.75 (t, 15-C), 71.45 (d, 3-C), 74.12 (d, 4-C), 118.82 (d), 121.54 (d), 123.32 (d), 123.75 (d), 124.96 (d), 128.36 (s), 129.66 (s), 131.31 (s), 133.44 (s), 134.81 (d), 139.56 (s), 156.80 (s), 205.80 (s, 17-C); MS (EI, 70 eV) m/z 266 (42, M^+), 248 (36, M^+ - H_2O), 235 (12), 220 (100, M^+ - H_2O - CO), 207 (13), 194 (25), 191 (37, M^+ - H_2O-CO-CHO), 189 (30, M^+ - H_2O-CO-CHO-2H), 178 (66), 176 (13), 165 (50), 152 (32), 94 (27); HRMS (EI, 70 eV) calcd for $C_{17}H_{14}O_3$ m/z 266.0943, found m/z 266.0944.

(±)-2α-Bromo-1,2,3,4,15,16-hexahydro-1β,3α,4β-trihydroxycyclopenta[*a*]phenanthren-17-one (17). A cooled (0 °C) solution of 11.4 mg (0.043 mmol) of *trans*-dihydro diol **3** in 2.5 mL of DMSO and 0.5 mL of water was treated with 8.1 mg (0.059 mmol, 1.4 equiv) of *N*-bromoacetamide (NBA). The mixture was stirred at 0 °C for 3 h and then poured into a separatory funnel containing 20 mL of ethyl acetate. The resulting solution was washed with water (2 × 20 mL) and then with brine (50 mL), and the combined aqueous washes were back-extracted with ethyl acetate (4 × 40 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo by rotary evaporation. The resulting pale yellow solid was washed with 15

mL of water. The resulting white solid was collected by filtration and was dried under reduced pressure (4 mmHg), producing 11.5 mg (74%) of the bromohydrin 17: ^{1}H NMR (360 MHz, acetone-d_6) δ 3.06 (dd, 2 H, $J_{15,16}$ = 5.5, 5.5 Hz, 15-H), 4.31 (br dd, 1 H, $J_{3,4}$ = 8.6, $J_{2,3}$ = 2.9 Hz, 3-H), 4.72 (br s, 1 H, OH), 4.78 (dd, 1 H, $J_{2,1}$ = 3.1, $J_{2,3}$ = 2.9 Hz, 2-H), 4.90 (m, 1 H, 4-H), 4.95 (br s, 1 H, OH), 5.43 (br s, 1 H, OH), 5.78 (br d, 1 H, $J_{1,2}$ = 3.1, 1-H), 7.71 (d, 1 H, $J_{12,11}$ = 8.8 Hz, 12-H), 7.98 (d, 1 H, $J_{7,6}$ = 8.6 Hz, 7-H), 8.18 (d, 1 H, $J_{6,7}$ = 8.6 Hz, 6-H), 8.30 (d, 1 H, $J_{11,12}$ = 8.8 Hz, 11-H) [note that 16-H's are obscured by the water peak at δ 2.80]; MS (CI, NH_3) m/z 382 and 380 ($[M + NH_4]^+$, 13), 365 and 363 ($[M + H]^+$, 24), 300 (48), 285 (70), 267 (95), 249 (100), 233 (19); HRMS (CI, NH_3) calcd for $C_{17}H_{15}O_4{}^{79}BrH$ ($[M + H]^+$) m/z 363.0232, found m/z 363.0210.

***syn*-1,2-Epoxy-1,2,3,4,15,16-hexahydro-*trans*-3,4-dihydroxycyclopenta[*a*]phenanthren-17-one (4a).** A 5-mL, round-bottomed flask equipped for magnetic stirring was charged with 9.8 mg (0.027 mmol) of bromohydrin 17 and 1 mL of dry THF. To this solution was added, under nitrogen, 7.5 mL (0.033 mmol) of 4.37 M sodium methoxide in methanol at rt, which resulted in the immediate formation of light brown precipitates. The resulting mixture was stirred at rt for 1 h and was poured into a separatory funnel containing 25 mL of ethyl acetate. This mixture was washed with water (2 × 10 mL) and then with brine (20 mL) and was dried (Na_2SO_4). Filtration and concentration in vacuo by rotary evaporation afforded 6.1 mg (80%) of *syn*-diol epoxide **4a** as a pale yellow solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.80 (br dd, 2 H, $J_{16,15}$ = 5.3, 4.9 Hz, 16-H), 3.45 (br dd, 2 H, $J_{15,16}$ = 5.3, 4.9 Hz, 15-H), 3.73 (br d, 1 H, $J_{2,1}$ = 4.1 Hz, 2-H), 3.78 (ddd, 1 H, $J_{3,4}$ = 6.9 Hz, $J_{3,OH}$ = 5.1 Hz, $J_{3,2}$ = 1.6 Hz, 3-H), 4.67 (d, 1 H, $J_{1,2}$ = 4.1 Hz, 1-H), 4.71 (dd, 1 H, $J_{4,3}$ = 6.9 Hz, $J_{4,OH}$ = 6.8 Hz, 4-H), 5.36 (d, 1 H, $J_{OH,4}$ = 6.8 Hz, 4-OH), 5.72 (d, 1 H, $J_{OH,3}$ = 5.1 Hz, 3-OH), 7.73 (d, 1 H, $J_{12,11}$ = 8.8 Hz, 12-H), 7.84 (d, 1 H, $J_{7,6}$ = 8.5 Hz, 7-H), 8.22 (d, 1 H, $J_{6,7}$ = 8.5 Hz, 6-H), 8.35 (d, 1 H, $J_{11,12}$ = 8.8 Hz, 11-H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 24.12 (16-C), 35.85 (15-C), 46.66 (2-C), 58.35 (1-C), 70.02 (3-C), 71.75 (4-C), 119.68, 123.51, 125.47, 126.99, 128.67, 129.54, 133.94, 135.38, 141.02, 156.78, 205.75 (17-C); MS (EI, 70 eV) m/z 282 (M^+, 58), 264 ($M^+ - H_2O$, 100), 236 ($M^+ - H_2O - CO$, 72), 235 ($M^+ - H_2O - CO - H$, 72), 223 (21), 207 (29), 194 (31), 189 (23), 178 (20), 165 (52), 152 (37), 97 (23), 95 (20), 80 (23), 71 (27), 69 (29), 57 (43) 43 (45); HRMS (EI, 70 eV) calcd for $C_{17}H_{14}O_4$ m/z 282.0892, found m/z 282.0909.

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Note Added in Proof. Since submission of the manuscript in August, 1991, a paper describing the synthesis of **3** appeared. See: Young, R. J.; Cortez, C.; Luna, E.; Lee, H.; Harvey, R. G. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 23.

Registry No. **3**, 143290-36-2; **4a**, 143216-77-7; **5**, 2811-50-9; **6a**, 71996-27-5; **6b**, 10481-34-2; **7**, 17521-83-4; **8**, 143216-78-8; **9**, 21070-86-0; **10**, 792-07-4; **11**, 98656-35-0; **12**, 24684-50-2; **13**, 143216-79-9; **14**, 143216-80-2; **15a**, 143216-81-3; **15b**, 143216-82-4; **16**, 143216-83-5; **17**, 143216-84-6; TBDMSOTf, 69739-34-0; vinylmagnesium bromide, 1826-67-1; 6-methoxy-1-tetralone, 1078-19-9.

Supplementary Material Available: ^{1}H NMR spectra of **3**, **4a**, **14**, **16**, and **17** and ^{13}C NMR spectra of **3**, **4a**, **14**, and **16** (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Diels-Alder Reactions of Dihydropyridinones: Synthetic Entry to the Manzamine A Tricyclic Core†

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For the construction of the tricyclic core of manzamine A (1), the Diels-Alder reactions of some dihydropyridinones were surveyed. The N-protecting group of the dihydropyridinone played an important role in achieving a successful Diels-Alder reaction. In view of its electron-withdrawing character as well as its thermal stability, the *p*-toluenesulfonyl protecting group was found to be best in our synthesis. An effective method for the preparation of 3-alkyldihydropyridinones via the Michael addition to dehydroalanine derivatives has also been devised. By the utilization of a high-pressure Diels-Alder reaction of the *N*-tosyl-3-alkyldihydropyridinone (**17**) with the Danishefsky diene, a facile construction of the central pyrroloisoquinoline skeleton (**21**) was successfully achieved.

Introduction

The manzamine family of marine alkaloids (manzamine A-F) was isolated from several Okinawan marine sponges by Higa,[1] and later Nakamura[2] also isolated the same compounds as keramamines. The first isolated congener, manzamine A[1a] (keramamine A[2], **1**), has been the subject of recent synthetic investigations owing to its unique molecular structure and remarkable biological properties including antitumor[1] and antibacterial activity,[2] while the simplest manzamine, manzamine C,[1b] and related analogues have already been synthesized in this laboratory.[3] Quite recently, the new and biogenetically related alkaloid

† This paper is dedicated to the late Professor Emeritus Shigehiko Sugasawa, Univeristy of Tokyo.

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(1) (a) Sakai, R.; T. Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.* **1986**, *108*, 6404. (b) Sakai, R.; Kohmoto, S.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *Tetrahedron Lett.* **1987**, *28*, 5493. (c) Ichiba, T.; Sakai, R.; Kohmoto, S.; Sausy, G.; Higa, T. *Ibid.* **1988**, *29*, 3083.

(2) Nakamura, H.; Deng, S.; Kobayashi, J.; Ohizumi, Y.; Tomotake, Y.; Matsuzaki, Y.; Hirata, Y. *Tetrahedron Lett.* **1987**, *28*, 621.

(3) (a) Torisawa, Y.; Hashimoto, A.; Nakagawa, M.; Hino, T. *Tetrahedron Lett.* **1989**, *30*, 6549. (b) Torisawa, Y.; Hashimoto, A.; Nakagawa, M.; Seki, H.; Hara, R.; Hino, T.; *Tetrahedron* **1991**, *47*, 8078.

0022-3263/92/1957-5741$03.00/0