palladium tetrafluoroborate (Strem). Tetravinyltin (Columbia Organics) and all other chemicals were reagent grade chemicals used as received. Flash chromatography was carried out on 230–400 mesh silica (EM reagents) following the procedure of Still.[18] All isolated products 1–5 gave satisfactory C,H analyses (±0.40%).

Preparation of 2-Carbomethoxy-3-vinylcyclopentanone (2a). Low halide methyllithium in ether (266 mL, 1.5 M, 0.40 mol) was added via syringe to a stirred solution of tetravinyltin (24.96 g, 0.11 mol) in anhydrous ether (500 mL) at 0 °C. After 15 min, the mixture was cooled to −78 °C, and copper(I) cyanide (18.02 g, 0.215 mol), was added all at once. The mixture was allowed to warm to −30 °C, at which temperature a solution of 1 (13.78 g, 0.08 mol) in ether (40 mL) was added dropwise. After an additional 30 min, half-saturated aqueous ammonium chloride (400 mL) was added dropwise as the temperature was allowed to rise, and the mixture was stirred an additional 1 h. The mixture was filtered, and the ether layer was separated. The aqueous layer was extracted with ether (2 × 200 mL). The combined organics were washed with water and dried ($MgSO_4$), and the solvent was removed at reduced pressure. Distillation of the residue afforded **2a** (10.4–11.4 g, 77–85%) as a colorless liquid: bp 58–62 °C (0.25 torr); ^{1}H NMR δ 1.72 (m, 1 H), 2.1–2.6 (m, 3 H), 3.05 (d, J = 11, 1 H), 3.1–3.3 (m, 1 H), 3.75 (s, 3 H), 5.09 (d, J = 11, 1 H), 5.16 (d, J = 17, 1 H), 5.75–5.85 (m, 1 H). IR (cm^{-1}) ν (C=O) 1762 s, 1662 m, 1618 m, ν (C=C) 1644 w.

2b. The isopropenyl derivative was prepared in an analogous manner from tetraisopropenyltin. It was isolated in 74% yield by flash chromatography with 25% (v/v) ethyl acetate in hexane as eluant: ^{1}H NMR δ 1.7–1.8 (m, 1 H), 1.78 (s, 3 H), 2.22–2.52 (m, 3 H), 3.19 (d + q, 2 H total) 3.73 (s, 3 H), 4.81 (s, 1 H), 4.83 (s, 1 H).

2-Carbomethoxy-3-vinylcyclopentene (3). Sodium borohydride (0.31 g, 8.2 mmol) was added gradually over 10 min to a solution of **2a** (5.00 g, 29.7 mmol) in ethanol (50 mL) at 0 °C. After 30 min the mixture was added to water (25 mL) and was extracted with ether (3 × 25 mL). After removal of solvent, flash chromatography afforded, in addition to recovered starting material (0.50 g, fractions 10–13), a pair of products, presumed to be the isomeric alcohols (3.59 g, 81% based on recovered **2a**, fractions 15–21). A portion of this material (3.03 g, 17.8 mmol) was dissolved in a mixture of methylene chloride (100 mL) and triethylamine (4.72 g, 46.6 mmol). To this solution at 0 °C was added dropwise methanesulfonyl chloride (2.67 g, 23.3 mmol) in methylene chloride (50 mL). The ice bath was removed, and the mixture was stirred 30 min, whereupon 1,8-diazabicyclo[5,4.0]-undec-7-ene (8.20 g, 53.9 mmol) was added and stirring continued for 3 h. Extraction with aqueous ammonium chloride and water followed by removal of solvent afforded **3** (2.43 g, 90%), which was 97% pure by GLC: ^{1}H NMR δ 1.78–1.87 (m, 1 H), 2.14–2.25 (m, 1 H), 2.36–2.59 (m, 2 H), 3.56 (m, 1 H), 3.72 (s, 3 H), 4.97 (d, J = 10, 1 H), 5.05 (d, J = 16, 1 H), 5.8–5.9 (m, 1 H), 6.82 (m, 1 H).

Preparation of 4. A solution of 9-borabicyclo[3.3.1]nonane (2.22 g, 18.2 mmol) in THF (35 mL) was added dropwise to a solution of **3** (2.64 g, 17.3 mmol) in THF (35 mL) at 0 °C. After 30 min at 0 °C the solution was stirred overnight at room temperature. Half-saturated aqueous sodium bicarbonate (60 mL) was added dropwise. After 30 min, the mixture was cooled to 0 °C, and 30% hydrogen peroxide (8.7 mL) was added dropwise. The ice bath was removed, and the reaction was stirred 5 h and was then poured into 500 mL H_2O, extracted with ether (3 × 100 mL), and dried ($MgSO_4$). Removal of solvent followed by flash chromatography with 25% (v/v) isopropyl alcohol in hexane afforded in fractions 8–15 a mixture of **4** and the corresponding methyl hydroxy ester. This was taken up in toluene (100 mL) and heated with toluenesulfonic acid (0.02 g) with azeotropic removal of solvent until the upper hydroxy ester spot by TLC disappeared. Neutralization with solid potassium carbonate and removal of solvent afforded **4** (1.63 g, 81%) as a colorless liquid: ^{1}H NMR δ 1.56–1.72 (m, 2 H), 2.12 (m, 1 H), 2.33–2.50 (m, 3 H), 2.99 (m, 1 H), 4.32 (dt, J = 3, 13, 1 H), 4.45 (ddd, J = 2, 5, 12, 1 H), 6.97 (m, 1 H).

Mitsugashiwalactone (5). Methyllithium in ether (23.3 mL, 1.8 M, 42 mmol) was added to a suspension of copper(I) iodide (4.0 g, 21 mmol) in ether (50 mL) at −25 °C. A solution of **4** (0.97 g, 7.0 mmol) in ether (25 mL) was added dropwise, and stirring was continued for 30 min at −25 °C. After being quenched with 10% aqueous acetic acid (50 mL) the mixture was added to water (100 mL) and extracted with ether (2 × 50 mL). Removal of the solvent from the dried ($MgSO_4$) mixture afforded the crude product, which was purified by flash chromatography with 35% (v/v) ethyl acetate in hexane. Fractions 14–19 afforded **5** (0.82 g, 76%) as a colorless liquid with NMR essentially identical with that reported[16] for the natural product: ^{1}H NMR δ 1.13–1.26 (m, 1 H), 1.18 (d, J = 7, 3 H), 1.27–1.38 (m, 1 H), 1.47–1.57 (m, 1 H), 1.86–1.94 (m, 1 H), 1.98–2.08 (m, 2 H), 2.15–2.27 (m, 1 H), 2.37 (t, J = 11, 1 H), 2.53–2.65 (m, 1 H), 4.21 (ddd, J = 3, 9, 11, 1 H), 4.32 (ddd, J = 3, 7, 11, 1 H); IR [film, cm^{-1} (% transmission)] 2953 (2.8), 2968 (10.4), 1736 (0.9), 1479 (25.4), 1459 (22.1), 1391 (11.8), 1257 (4.8) 1224 (21.5), 1202 (12.4), 1179 (6.8), 1141 (22.1), 1120 (27.1), 1074 (2.8).

Registry No. 1, 70353-99-0; **2a**, 75351-19-8; **2b**, 68151-48-4; **2** (R = butyl), 87682-82-4; (±)-**3**, 102979-48-6; (±)-**4**, 102979-49-7; (±)-4 (methyl hydroxy ester), 102979-50-0; (±)-**5**, 60363-05-5; $(H_2C{=}CH)_4Sn$, 1112-56-7; $(H_3C(CH_2)_{34}Sn$, 1461-25-2; $(H_2C{=}C(CH_3))_4Sn$, 64503-52-2.

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(19) **Note added in proof.** The IR spectrum of **5** was identical with that of material prepared by ref 16. We thank Professor T. Fujisawa for providing a copy of the IR spectrum.

Methyl 9,14-Didehydro-4,5-epoxy-3-methoxy-17-methyl-α-methylene-6-oxothebinan-8β-acetate[1]

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Hayakawa et al.[3] and we[4] have reported that thebaine and methyl propiolate form an adduct which on mild hydrolysis is transformed to the ketone **1** whose structure was secured by NMR spectroscopy and single-crystal X-ray analysis.

We reported earlier[4] that reduction of **1** with $NaBH_4$ gave the alcohol **2** characterized as the acetate, **3**, which on catalytic hydrogenation furnished the dihydro acetate **4**, (Scheme I). We now find that **4** is also obtained in modest yield by hydrogenation of **1** in acetic acid for 25 h followed by treatment with acetic anhydride in pyridine solution. If the reduction is carried out for a short time and the crude base dissolved in CH_3OH and the solution allowed to stand in air for about 2 days, a crystalline compound separates from solution which was shown to be **6** by means of single-crystal X-ray analysis (Figure 1).[5] In the NMR spectrum the signals at H-18 (δ 7.28) and H-5 (δ 5.06) of **1** were replaced by signals at δ 5.83 and 6.22 which were assigned to the vinylic protons at C-18 of compound **6**.

Recently, Theuns et al.[6] reported the isolation of the base **7** from *Papaver bracteatum* and commented that it may be an artifact since it was obtained by decomposition of one of the two thebaine *N*-oxides which are also present in the same plant. The acrylate ester **6** could arise by a process similar to the one suggested by Theuns et al. to

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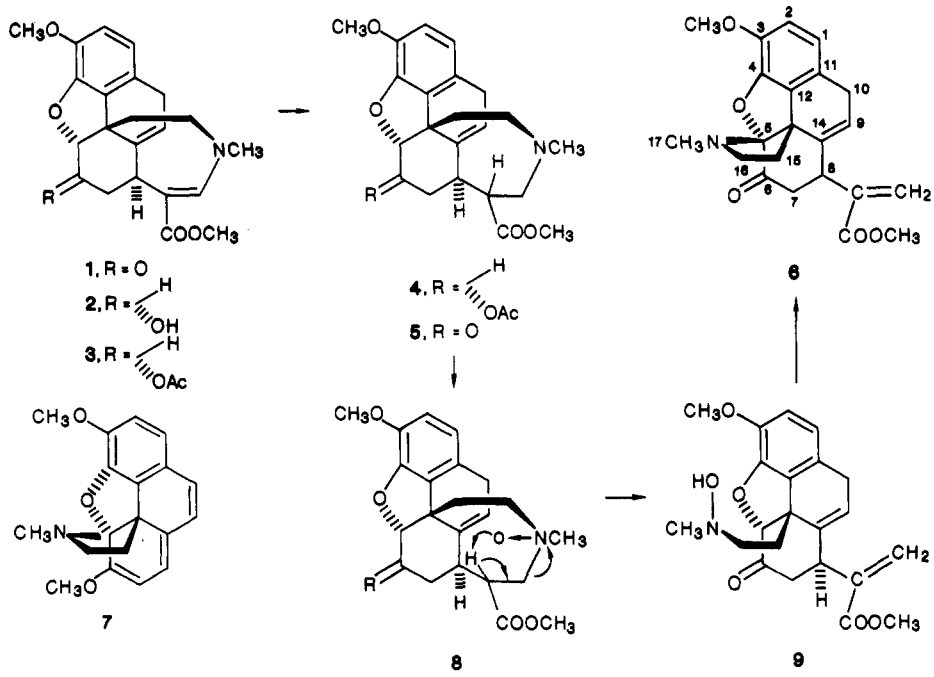
Scheme I



account for the formation of 7 from thebaine *N*-oxide. Short exposure to 1 to catalytic hydrogenation gives the dihydro ketone 5 which undergoes air oxidation to the *N*-oxide 8. Cope elimination followed by ring closure of the resulting hydroxylamine 9 at C-5 gives the thebinane derivative 6.

Experimental Section

Melting points were determined on a Laboratory Device Melt-Temp apparatus and are corrected. The ^1H NMR spectrum were run on a Varian XL-200 spectrometer in $CDCl_3$ using $(CH_3)_4Si$ as the standard. The mass spectrum were run on Hewlett-Packard 5987A GC–MS system and the IR spectrum on a Perkin-Elmer Model 298 infrared spectrometer. Microanalyses were performed by the Spang Microanalytical Laboratory, Eagle Harbor, MI.

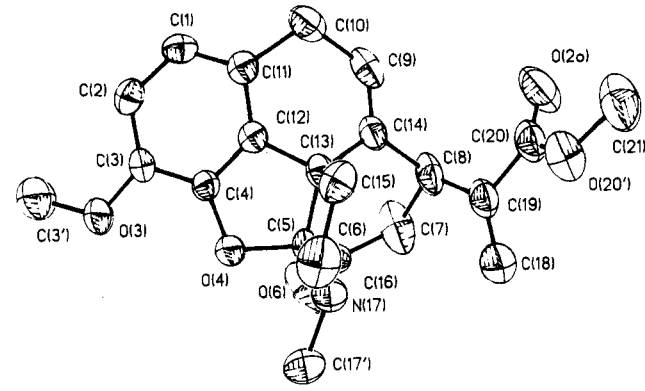


Figure 1. ORTEP drawing of 6.[5] The numbering of the carbon atoms corresponds to that in the text.

Preparation of the Acetate 4 from the Ketone 1. Catalytic reduction of 2.0 g (5 mmol) of ketone 1 in 200 mL of acetic acid in the presence of 60 mg of Adam's catalyst at an initial pressure of 50 psi for 25 h furnished a base, which was acetylated in acetic anhydride–pyridine. The solution was taken to dryness and taken up in $CHCl_3$. The solution was washed with dilute Na_2CO_3 solution and H_2O and dried over Na_2SO_4. The residue after removal of $CHCl_3$ was chromatographed on silica gel. The $CHCl_3$ eluants furnished a crystalline residue (600 mg; 26%), which after recrystallization from CH_3OH melted at 143–145 °C, identical in all respects with the sample prepared previously.[4]

Methyl 9,14-Didehydro-4,5-epoxy-3-methoxy-17-methyl-α-methylene-6-oxothebinan-8β-acetate (6). The ketone 1 (2 g, (5.2 mmol) was dissolved in 200 mL of acetic acid and hydrogenated in the presence of 60 mg of Adam's catalyst at an initial pressure of 50 psi for 10 min. The acetic acid was removed in vacuo, and the residue was dissolved in 20 mL of H_2O and filtered. The filtrate was neutralized with aqueous Na_2CO_3 solution. The material that separated was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried, and evaporated. The residue was dissolved in methanol, and the solution was allowed to stand uncovered for 48 h. The product 6 crystallized out, weight 0.8 g (40%). After crystallization from methanol it melted at 210–212 °C: NMR δ 2.62 (s, 3 H, NCH_3), 3.82 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.04 (t, 1 H, H-8), 5.82 (s, 1 H, H-18), 6.06 (d, 1 H, H-9), 6.38 (s, 1 H, H-18), 6.70 (s, 2 H, H-1, H-2); IR (KBr) 1710 cm^{-1} (C=O); UV_{max} 284 nm (log ε 4.26); MS, *m/e* 382 (M + 1).

(1) Dr. Joy E. Merritt, Senior Editor Nomenclature, Chemical Abstracts Service, suggested the following as the current CA index name: methyl [7a*R*-(4b*S**,7aα,10β)]-6,7,8,9,10,12-hexahydro-3-methoxy-7-methyl-α-methylene-8-oxo-5*H*-4,7a-epoxynaphth[1,2-*d*]indole-10-acetate. She also suggested the name used in the title (see ref 6). We prefer this name since the numbering corresponds to that employed in the morphinan ring system. We wish to thank Dr. Merritt for her assistance with the nomenclature.

(2) Present address: Department of Chemistry, GNDU, Amritsar, India.

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(5) Crystals of 6 were monoclinic plates 0.03 × 0.17 × 0.46 mm of space group $P2_1$ (no. 4); $Z = 2$. The unit cell parameters are: $a = 8.006$ (3) Å, $b = 6.583$ (2) Å, $c = 17.775$ (5) Å, $\beta = 90.54$ (3)°, $V = 936.9$ (5) Å^3. The calculated density is 1.35 g/cm^3. Data were collected on a Nicolet R3M diffractometer using Cu Kα radiation (graphite monochromator; λ = 1.541 78 Å) in a ω-scan mode (ω range: 2° + [$2\theta(K_{\alpha 1}) - 2\theta(K_{\alpha 2})$]; 2θ range: 3° to 100°). 1516 reflections were collected, of which 1024 were considered observed [$F > 3\sigma(F_0)$]. The programs of SHELXTL (Rev. 5.1) were used for data reduction and all other calculations. Direct-phase determination followed by three Fourier cycles allowed all 28 non-hydrogen atoms to be recognized. Atomic coordinates and anisotropic temperature factors were refined for all non-hydrogen atoms. Hydrogen atoms were included in the refinement in calculated positions with optimized isotropic temperature factors. The refinement converged at $R = 3.98\%$; $R_w = 4.10\%$. Tables with atomic coordinates, temperature factors, bond distances, and bond angles, and observed and calculated structure factors can be obtained from R.K.K.

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Anal. Calcd for $C_{22}H_{23}NO_5$ (381.4): C, 69.27; H, 6.07; N, 3.67. Found: C, 68.96; H, 6.11; N, 3.68.

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Registry No. 1, 78914-30-4; 4, 83967-59-3; 6, 103258-80-6.

Reaction of Benzeneselenenyl Halides with 3-Keto Steroids. A Novel Method for α-Bromination

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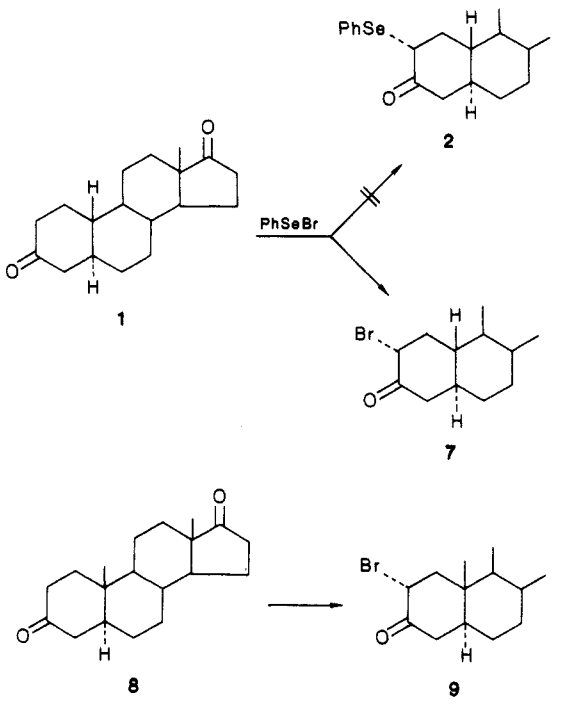
Recent studies on the introduction of the 1,2-double bond in 5α-estrane-3,17-dione (1) using benzeneselenenyl chloride[1] showed the formation of an unusual product which was identified as 2-chloro-5α-estr-1-ene-3,17-dione (5). It was proposed that compound 5 was formed by electrophilic attack of the chloro group in PhSeCl on 2-(phenylselenenyl)-5α-estrane-3,17-dione (2) to yield 2-chloro-2-(phenylselenenyl)-5α-estrane-3,17-dione (4) which undergoes 1,4-elimination following H_2O_2 oxidation as described by Sharpless et al.[2] It is interesting to note that the yield of 2-chloro-5α-estrenedione (5) is dependent on the amounts of PhSeCl used in the reaction mixture. Thus, as the molar ratio of PhSeCl increases the yield of compound 5 increases with a corresponding decrease in the formation of both 4-estrene-3,17-dione and 5α-estr-1-ene-3,17-dione (Table I).

To explore the reaction mechanism of formation of 2-chloro-5α-estrenedione (5), it was rationalized that compound 5 could be formed by either route a or route b as shown in Scheme I. When compounds 2 and 3 were reacted with PhSeCl, only compound 2 yielded 5, indicating that pathway a is involved in the formation of 5 from 1 using PhSeCl.

In an attempt to further extend these studies, it was presumed that reaction of 1 with PhSeBr would also follow the same reaction pathway leading to formation of 2-bromo-5α-estr-1-ene-3,17-dione (6). However, instead of introduction of the 1,2-double bond in 5α-estrane-3,17-dione (1), PhSeBr gave another compound which crystallized out of the reaction mixture and was shown by mass spectral analysis to be a monobromo estrane-3,17-dione. These observations led us to investigate the bromination of 3-keto 5α- and 5β-steroids by PhSeBr and to compare these products with bromo compounds obtained from brominations using bromine in acetic acid.

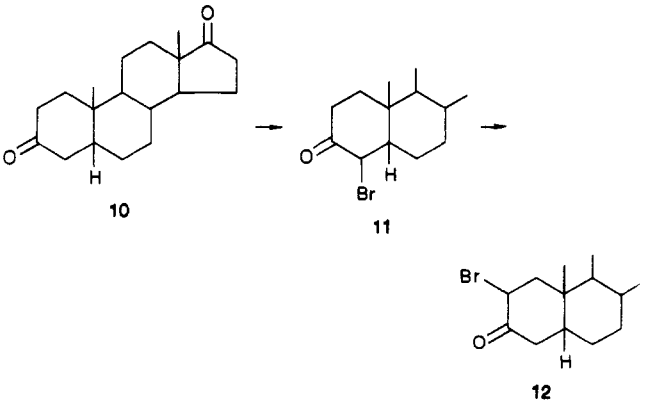
In a typical reaction, PhSeBr (404 mg) was added to 5α-estrane-3,17-dione (1) (390 mg) in ethyl acetate (15 mL), and the resulting solution was kept at room temperature for 1 h to afford, after purification by preparative thin-layer chromatography, compound 7 in yields ranging between 60% and 70%. This yield did not seem to increase even after a 96-h reaction time. Compound 7 was found to be identical with that obtained from bromination of 1 with Br_2/HOAc. Similarly, 5α-androstanedione (8) gave 2α-bromo-5α-androstane-3,17-dione (9) following reaction



of 8 with either PhSeBr or Br_2/HOAc.

It is interesting to note that in both the C-19 methyl and 19-nor 5α-series, the kinetically stable product is the 2α-bromo 5α-steroid, which suggests that steric hindrance due to the presence of the C-19 methyl group may be of secondary importance in determining the direction of attack by the brominium group as proposed by Corey[3,4] and later extended by Valls and Toromanoff.[5]

The above results on the bromination of 3-keto 5α-steroids are not unexpected since it is well documented that 3-keto 5α-steroids enolize primarily toward C-2.[6] However, in the case of 3-keto 5β-steroids, enolization toward C-4 predominates.[7] Thus, reaction of 5β-androstanedione (10) with Br_2/HOAc gave compound 11 which was found to be identical with an authentic sample of 4β-bromo-5β-androstanedione (11). Reaction of 10 with



PhSeBr for 1 h gave compound 11 in 65% yield, and its NMR spectrum showed a characteristic doublet centered at 4.94 ppm (J = 11.5 Hz), for C-4 proton and was identical with that of the product obtained from bromination of 10 with Br_2/HOAc. However, increasing the reaction time

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