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Regiospecific and Stereoselective Alkylation of the Octahydronaphthal-8(9)-en-3-one Nucleus

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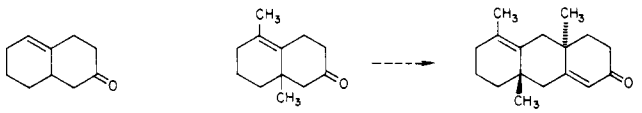
In order to evaluate the title ring system in the context of its ability to form an enolate ion regiospecifically and to undergo stereocontrolled alkylation, **2** was sequentially carbomethoxylated and methylated. Within the limits of spectroscopic analysis, only **6** was produced. In analogous fashion, the methyl homologue **7** underwent exclusive conversion to tricyclic enone **11** when subjected to base- and acid-catalyzed Robinson annulation conditions, as well as to a Wichterle sequence. All stereochemical assignments have been made with reference to an X-ray crystal structure analysis of **17**, an oxidation product of **11**. Accordingly, simple octahydronaphthal-8(9)-en-3-ones undergo clean enolization toward C-2 and generate twist-boat enolate anions that capture electrophiles at this site overwhelmingly from the axial direction.

The octahydronaphthal-8(9)-en-3-one ring system (**1**) has served as a useful building block in the synthesis of various natural products including telekin,[3] alantolactone,[3] artemisin,[4] valencene,[5] and nootkatone.[5] Moreover, several methods for the preparation of variously substituted derivatives are available. Of these, the cationic cyclization of 2-(3-butenyl)-2-cyclohexen-1-ols has seen the greatest service.[3,6] Short nonannulative schemes[7-9] are available to complement those involving stepwise six-membered ring construction.



1 **2** **3**

In conjunction with a program aimed at the total synthesis of dolastane diterpenes,[10] we had need to effect the conversion of **2** into octahydroanthracenone **3**. Not only were we dismayed to uncover that the Robinson annulation reaction has been applied only sparsely to the elaboration of linearly fused tricyclic molecules,[11-13] but that information concerning the stereochemistry of alkylation of **1**, **2**, and related molecules was not available. Enamine **4** has been alkylated with ethyl bromoacetate;[3,4] however, the subsequent hydrolysis to give **5** may well have been accompanied with equilibration. The question of stereoselectivity was viewed as somewhat cloudy in this instance because of the fact that 1,4-cyclohexanediones and related molecules favor a twist-boat ground-state conformation[14] and that the A ring of **2** may partake of these structural characteristics. On the other hand, the regioselectivity anticipated for the enolization process was somewhat more apparent,[15] though hardly conclusive.

4 **5**

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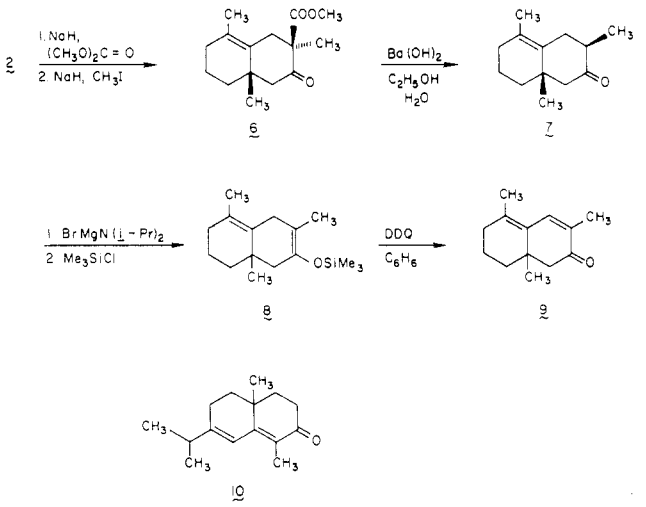
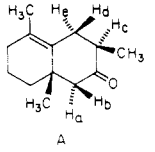
In order to clarify these questions in a relevant prototypical example, ketone **2** was transformed via **6** into the trimethyl derivative **7**. The yields at each stage were excellent. In addition, both intermediates were shown by ^{13}C NMR spectroscopy to be diastereomerically pure within the standard limits of detection. The stereochemical assignments illustrated in the formulas follow from considerations to be discussed.



That the enolization of **2** has indeed occurred toward C-2 was confirmed by conversion of **7** into its more highly substituted trimethylsilyle enol ether **8** by reaction with bromomagnesium diisopropylamide and trimethylsilyl chloride.[16] Oxidation of **8** with 2,3-dichloro-5,6-dicyanobenzoquinone[17] produced in 50% overall yield dienone **9**, whose spectroscopic properties were fully consistent with the presence of an extended conjugated system such as is found, for example, in β-cyperone (**10**).[18]

The ^1H NMR spectra of **2** and **7** both display an appreciably deshielded multiplet of unit area at approximately δ 2.9 ($CDCl_3$ solution). Double irradiation studies carried out on **7** revealed that neither H_a nor H_b is responsible for this signal (see A). Rather, the implicated



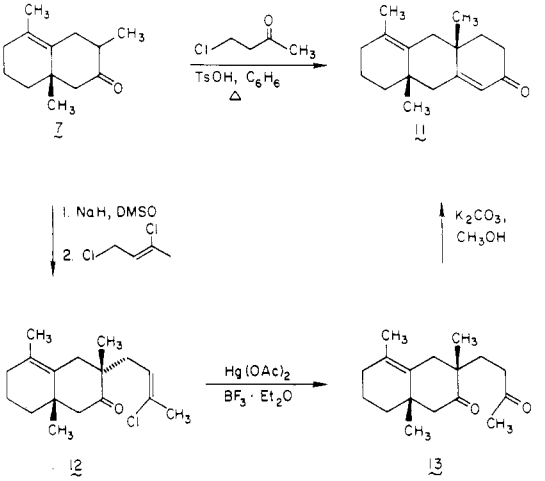
A

proton is H_e, which finds itself geminally coupled to H_d (J = 13.8 Hz) and spin interactive in an axial–equatorial sense with H_c (J = 6.3 Hz). H_e resonates 1 ppm downfield from H_d as a direct result of its position in the xy plane of the carbon–carbon double bond (plane of the page), where maximum deshielding is exerted by π-bond anisotropy.[19] Its neighbor H_d resides well above this plane. The unmistakable shielding differential for this pair of protons has been noted in many structurally related compounds.

With regioselective introduction of the methyl group accomplished, attention was next turned to proper grafting of a cyclohexenone ring as in **3**. Although cyclohexanones already carrying an α-substituent are recognized to exhibit a greater proclivity than normal for axial attack,[20] steric effects of more remote groups can cause equatorial entry to predominate heavily.[21] Example of conjugate enolate addition to methyl vinyl ketone (MVK) from the more hindered face have been reported.[22] In the present instance, application of several of the more well-established Robinson annulation procedures[23] to **7** were uniformly unsuccessful. Usually, the starting material was recovered unchanged. In one instance when recourse was made to potassium methoxide in tetrahydrofuran as catalyst for the Michael reaction and to potassium carbonate for the aldol cyclization, **11** was obtained in 12% yield.

In order to lessen the rate of polymerization of MVK, conditions were sought in which the basicity of the enolate was reduced. To this end, the enoxy borate of **7** was generated[24] [KH;[25] $(C_2H_5)_3B$·THF] and allowed to condense with MVK. Following workup with alkaline hydrogen peroxide, **11** was again found to be isomerically homogeneous. However, the extent of conversion was still unsatisfactory.

The method giving the highest efficiency was that introduced by Zoretic[26] and developed further by Heathcock.[27] This acid-catalyzed process involved heating benzene solutions of **7** with 4-chloro-2-butanone in the presence of *p*-toluenesulfonic acid. Simple chromatography delivered **11** straightfowardly in 80% yield.



A Wichterle sequence was also investigated. Deprotonation of **7** with dimsyl sodium in dimethyl sulfoxide[28] and alkylation with 1,3-dichloro-2-butene[29] afforded **12** (41%). Hydrolysis of the vinyl chloride with mercuric acetate and boron trifluoride etherate in acetic acid[30] gave

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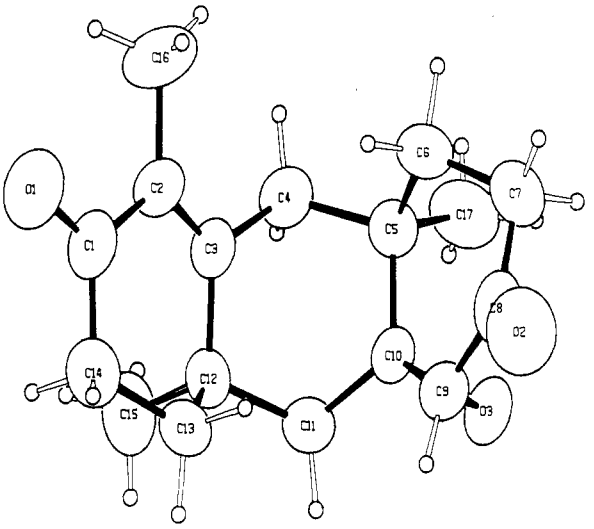


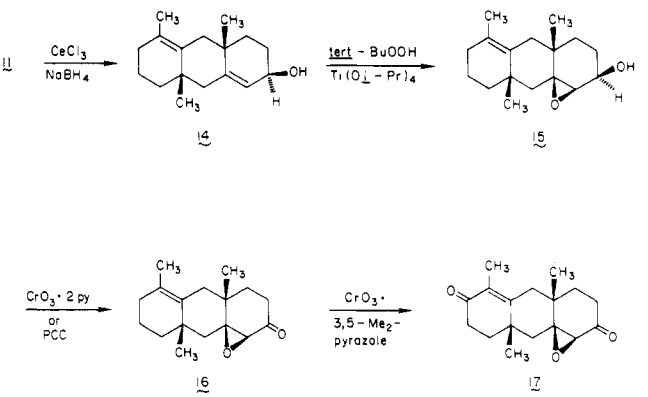
Figure 1. ORTEP diagram of **17** showing the number scheme employed in the X-ray analysis.

rise efficiently (91%) to diketone **13**. Ultimate cyclization of this intermediate provided **11** in an unattractive 23% overall yield.

Relevantly, however, all of the predescribed experiments furnished the identical stereoisomer **11**. When the application of various NMR techniques proved inadequate for determining the relative stereochemistry of the methyl groups, conversion to a highly crystalline substance suitable for X-ray analysis was considered expedient.

Attempts to oxidize **11** with alkaline 30% hydrogen peroxide in methanol[31] or with sodium hypochlorite in pyridine[32] or dioxane[33] resulted in less than 5% epoxidation after many days of exposure to these reagents. A satisfactory alternative to this direct procedure involved initial reduction with cerium trichloride doped sodium borohydride in methanol[34] and chemoselective conversion to epoxy alcohol **15** with *tert*-butyl hydroperoxide and titanium isopropoxide in methylene chloride[35] (80% overall yield). Substitution of *tert*-butyl hydroperoxide in benzene with vanadyl acetonylacetate[36] as catalyst gave rise to a complex mixture of products.[37] Oxidation of **15** with Collins reagent or pyridinium chloroformate on Celite[38] delivered epoxy ketone **16** in 60–70% yield.

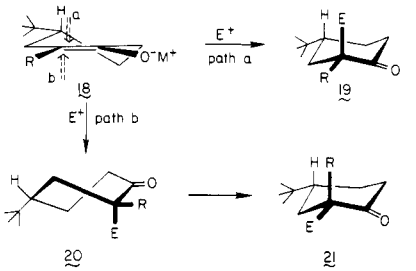
It was recognized by means of ^1H and ^{13}C NMR spectroscopy that compounds **14–16** were stereochemically homogeneous. However, none of the three proved suitably crystalline for X-ray purposes. This objective was reached upon more extensive oxidation of **16** with the chromium trioxide–3,5-dimethylpyrazole complex.[39] Allylic oxidation to produce **17** (80%) was accompanied by its isolation as a magnificently crystalline substance. The ORTEP diagram for this diketone is given in Figure 1. These data reveal that the molecule, which has no symmetry higher than C_1,



is highly concave. The dihedral angle between plane O(1)–C(1)–C(2)–C(14) in the first ring and plane O(2)–C(7)–C(8)–C(9) in the third ring is 70.2°. Most relevantly, both angular methyl groups lie on the convex side of the molecule.

Discussion

In the absence of substantial steric hindrance, conformationally anchored cyclohexanone enolates such as **18** (R = H, CH_3, $COOCH_3$, CN) exhibit modest selectivity for axial entry of the electrophile.[40] When consideration is given to the appropriate half-chair conformation illustrated, the implication is that perpendicular attack of the electrophile from above to deliver **19** is preferred, though not in kinetically overwhelming fashion. In actuality,



perpendicular approach of the coreactant from below must lead initially to a twist-boat shaped molecule, viz., **20**, which subsequently experiences conformational flexing to deliver **21**. The percentage reaction through path a is recognized to be significantly enhanced in the corresponding Schiff's base derivatives, including imines, oximes, and hydrazones.[41] Presumably, formation of the new C–C bond is further advanced in the transition states of the latter alkylation reactions.

Enolates derived from the octahydronaphthal-8(9)-en-3-one ring system are conformationally constrained somewhat differently than **18** because of the presence of a third trigonal carbon atom in the charge-bearing ring (see **22** and **23**). The present findings indicate that a very strong preference exists for introduction of the electrophilic species in that manner which produces **24** cleanly. Consequently, reactive intermediate **22** is capable of exceptionally high stereoselectivity in such processes. Should

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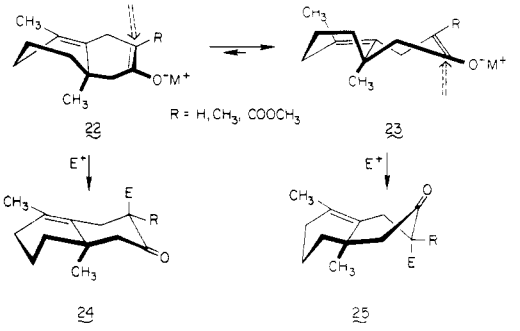

the transition states for alkylation of these enolates partake of a geometry close to the reactants, the decreased level of steric strain within **22** could well become a principal factor controlling the overall alkylation stereochemistry. This analytical interpretation has been championed by House,[42] and it is now generally accepted that the structural features associated with the metal enolate can exert an overwhelming influence on alkylation stereochemistry.[43]

Where α-substituted enolates such as **18**, **22**, and **23** are involved, it has been suggested that distortion about the double bond occurs in order to relieve interaction between the R group and the O^-M^+ substituent and to avoid $A^{(1,2)}$ strain elsewhere.[44] This type of distortion in **23** would be expected to cause partial rehybridization at C_α in the direction of generating an sp^3 orbital on the molecular bottom side. Favorable orbital overlap with a group entering from below would subsequently be experienced.

Limited data prevent us from invoking other diastereofacial control elements that may well bias matters in favor of **25**. It is notable, however, that the same stereochemical course is followed under conditions of acid catalysis where enols rather than enolates are involved. On this basis, it would seem that the alkylation of enamine **4** also proceeds with a high predilection for C-alkylation from the α face. The stereochemistry reflected in **5** arises as a consequence of configurational equilibration during the hydrolytic workup.

In principle, therefore, the stereochemical configuration at C-2 in **2** and related compounds of general formula **1** is capable of strict control. Proper adaptation of this technology to the total synthesis of several dolastane diterpenes will be reported in due course.

Experimental Section

Methyl 1,2,3,4,4a,5,6,7-Octahydro-4a,8-dimethyl-3-oxo-2-naphthoate. Sodium hydride (50% oil dispersion, 2.45 g, 51.0 mmol) was washed with dry toluene and placed under 50 mL of toluene and 11.7 mL of dimethyl carbonate (12.5 g, 140 mmol). To this stirred suspension was added 8.25 g (46.4 mmol) of **2**[3] in 30 mL of toluene at 25 °C, and the resulting mixture was heated at reflux for 8 h. The mixture was poured onto 10% aqueous hydrochloric acid (50 mL), the aqueous phase was extracted with ether (3 × 40 mL), and the combined organic layers were washed with brine (50 mL), dried, and concentrated. Distillation gave 9.38 g (86%) of β-keto ester as a pale yellow oil: bp 130 °C (0.6 torr); IR ($CDCl_3$) 2940 (s), 2875 (s), 1745 (s), 1715 (s), 1660 (s), 1460 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 11.53 (s, 0.43 H, enol), 3.80 (s, 3 H), 3.74 (m, 1 H), 3.20 (m, 1 H), 2.29 (m, 1 H), 2.03 (m, 2 H), 1.66 (s, 3 H), 1.75–1.51 (m, 6 H), 1.07 (s, 1.5 H); MS, m/z calcd (M^+) 236.1412, obsd 236.1457.

Methyl 1,2,3,4,4a,5,6,7-Octahydro-2,4a,8-trimethyl-3-oxo-2-naphthoate (6). The preceding β-keto ester (0.62 g, 2.63 mmol) in 5 mL of toluene was added to a stirred suspension of sodium hydride (0.14 g, 4.0 mmol) in 15 mL of the same solvent at 25 °C. After the mixture was stirred for 0.5 h, methyl iodide (0.96 g, 6.8 mmol) was added, and the solution was heated at 80 °C for 8 h. The mixture was poured onto 10% aqueous hydrochloric acid and extracted with ether (3 × 20 mL). The combined organic phases were washed with brine (30 mL) and dried, and the solvent was evaporated to leave 0.66 g (99%) of **6** as an oil. Purification of a small sample by MPLC on silica gel (elution with 4% ethyl acetate in petroleum ether) returned a colorless solid: mp 61–62 °C; IR ($CDCl_3$) 2920 (s), 1730 (s), 1701 (s), 1440 (w), 1250 (m) cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 3.74 (s, 3 H), 2.94 (d, J = 14.3 Hz, 1 H), 2.67 (d, J = 14.0 Hz, 1 H), 2.15 (d, J = 14.0 Hz, 1 H), 2.00 (m, 2 H), 1.66 (s, 3 H), 1.50 (m, 4 H), 1.32 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR (80 MHz, $CDCl_3$) 209.63, 173.09, 130.25, 128.62, 52.03, 51.12, 38.89, 38.57, 34.67, 32.59, 26.35, 20.95, 19.91, 19.52, 19.06 ppm; MS, m/z calcd (M^+) 250.1569, obsd 250.1574.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.86; H, 8.84.

Methyl 1,2,3,4,4a,5,6,7-Octahydro-2,4a,8-trimethyl-3-naphthalenone (7). To a stirred suspension of barium hydroxide (1.57 g, 9.2 mmol) in 5 mL of ethanol and 10 mL of water was added 0.66 g (2.63 mmol) of **6** in 2 mL of ethanol, and the suspension was heated at reflux for 20 h. The product was poured onto 10% aqueous hydrochloric acid and extracted with ether (3 × 50 mL). The organic layers were combined, washed with brine (50 mL), dried, and evaporated under reduced pressure. Chromatography on silica gel (MPLC, 8% ethyl acetate in petroleum ether) gave 0.38 g (75%) of **7** as a colorless solid: mp 58–59 °C; IR ($CDCl_3$) 2930 (s), 1700 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.90 (dd, J = 13.8, 6.3 Hz, 1 H), 2.38–1.96 (m, 6 H), 1.71 (s, 3 H), 1.64–1.51 (m, 4 H, 1.05 (d, J = 6.5 Hz, 3 H), 0.99 (s, 3 H); ^{13}C NMR (80 MHz, $CDCl_3$) 212.78, 131.98, 127.06, 55.96, 45.63, 39.54, 34.81, 32.90, 26.19, 19.68, 19.42, 14.44 ppm; MS, m/z calcd (M^+) 192.1514, obsd 192.1489.

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.28. Found: C, 81.16; H, 10.41.

Trimethylsilyl Enol Ether 8. Diisopropylamine (66 mg, 0.65 mmol) was added to a stirred solution of allylmagnesium bromide (0.92 mL, 0.6 mmol) in 4 mL of ether at 25 °C, and the resulting white suspension was stirred for 20 h. Ketone **7** (0.10 g, 0.52 mmol) was added at 25 °C, stirring was continued for 0.5 h, and then chlorotrimethylsilane (0.16 g, 1.56 mmol), triethylamine (0.18 g, 1.82 mmol), and hexamethylphosphoramide (45 mg, 0.25 mmol) were added sequentially. After 8 h of being stirred at 25 °C, the suspension was diluted with ether (25 mL), washed with saturated aqueous sodium bicarbonate solution (20 mL) and brine (20 mL), and dried. Removal of the solvent under reduced pressure gave 0.13 g (95%) of **8** as an isomerically pure pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 2.81 (d, J = 19.9 Hz, 1 H), 2.55 (d, J = 19.8 Hz, 1 H), 2.20–1.80 (m, 4 H), 1.75–1.35 (m, 4 H), 1.59 (s, 3 H), 1.57 (s, 3 H), 1.04 (s, 3 H); MS, m/z calcd (M^+) 264.1909, obsd 264.1941.

Oxidation of 8. To a stirred solution of **8** (0.14 g, 0.53 mmol) in 10 mL of dry benzene at 25 °C was added dropwise 0.12 g (0.53 mmol) of 2,3-dichloro-5,6-dicyanobenzoquinone dissolved in 2 mL of benzene. After being stirred under nitrogen for 6 h, the suspension was diluted with ether (100 mL), washed with saturated sodium bicarbonate solution (50 mL), 10% aqueous hydrochloric acid (50 mL), and brine (50 mL). Drying, removal of solvent under reduced pressure, and chromatography on silica gel (MPLC, 9% ethyl acetate in petroleum ether) gave 50 mg (50%) of **9** as a clear, colorless oil: IR ($CDCl_3$) 2940 (s), 1660 (s), 1625 (s) cm^{-1}; UV (C_2H_5OH) λ_{max} 312 nm; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (m, 1 H), 2.32 (d, J = 15.8 Hz, 1 H), 2.30 (d, J = 15.8 Hz, 1 H), 2.15 (m, 2 H), 1.85 (s, 3 H), 1.82 (s, 3 H), 1.70 (m, 2 H), 1.56 (m, 2 H), 1.07 (s, 3 H); ^{13}C NMR (80 MHz, $CDCl_3$) 199.75, 138.94, 137.41, 133.13, 131.66, 52.96, 37.75, 33.22, 25.04, 19.23, 18.08, 17.50, 15.59 ppm; MS, m/z calcd (M^+) 190.1358, obsd 190.1360.

4,4a,6,7,8,8a,9,10-Octahydro-4a,5,8a-trimethyl-2(3*H*)-anthracenone (11). A. Catalysis by Potassium Methoxide. To a stirred solution of 0.100 g (0.52 mmol) of **7** in 10 mL of tetrahydrofuran at 25 °C was added potassium methoxide (8.8

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mg, 0.13 mmol), and the suspension was stirred for 0.5 h, whereupon methyl vinyl ketone (44.0 g, 0.64 mmol) in 10 mL of the same solvent was added over 1 h. After being stirred for 24 h at 25 °C, the solution was diluted with ether (30 mL), neutralized with 10% aqueous hydrochloric acid, washed with brine (20 mL), dried, and freed of solvent under reduced pressure. Chromatography on silica gel (MPLC, 20% ethyl acetate in petroleum ether) gave 15 mg (12%) of **11** as a clear colorless oil: IR ($CDCl_3$) 2918 (s), 2870 (s), 1660 (s), 1622 (m), 1450 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.63 (m, 1 H), 2.49 (m, 2 H), 2.27 (m, 2 H), 2.14 (m, 1 H), 1.89 (m, 3 H), 1.63 (m, 2 H), 1.58 (s, 3 H), 1.42 (m, 2 H), 1.30 (m, 2 H), 1.24 (s, 3 H), 1.15 (s, 3 H); ^{13}C NMR (80 MHz, $CDCl_3$) 199.37, 171.90, 132.30, 127.31, 125.20, 46.57, 40.37, 38.97, 38.52, 35.26, 34.75, 34.43, 30.98, 29.96, 24.08, 19.36, 19.04 ppm; MS, m/z calcd (M^+) 244.1827, obsd 244.1866.

B. Enoxy Borate Method. To a stirred suspension of 22 mg (0.55 mmol) of potassium hydride in 4 mL of dry tetrahydrofuran at 25 °C was added 0.100 g (0.52 mmol) of **7** in 2 mL of the same solvent via syringe. After the mixture was stirred for 0.5 h, triethylborane–tetrahydrofuran complex (0.6 mL, 0.65 mmol) was added, and stirring was continued for 0.5 h, whereupon methyl vinyl ketone (36 mg, 0.52 mmol) was introduced dropwise over 10 min. The mixture was stirred at 25 °C for 24 h, chilled to 0 °C, treated with 3 N sodium hydroxide (1 mL) and 30% hydrogen peroxide (1 mL), and stirred for 4 h at 25 °C. This mixture was diluted with ether (50 mL), the organic layer was separated, and the etheral phase was washed with 10% aqueous sodium bisulfite solution (20 mL) and brine (20 mL) prior to drying. Removal of solvent under reduced pressure and chromatography on silica gel (MPLC, 8% ethyl acetate in petroleum ether) provided 30 mg (34% based on recovered **7**) of **11** as a clear colorless oil spectroscopically identical with the substance isolated in part A.

C. Acid-Catalyzed Annulation. A solution of **7** (3.0 g, 15.6 mmol), 4-chloro-2-butanone (2.5 g, 23.4 mmol), and *p*-toluenesulfonic acid (0.3 g, 1.6 mmol) in 100 mL of benzene was heated at the reflux temperature for 48 h. After removal of the bulk solvent, the residue was dissolved in ether (200 mL), washed with saturated aqueous sodium bicarbonate solution (100 mL) and brine (100 mL), and dried. The solvent was evaporated, and the oil was purified by chromatography on silica gel (HPLC, elution with 9% ethyl acetate in petroleum ether) to provide 3.0 g (80%) of **11** as a colorless oil. Its spectroscopic properties were identical with those reported above.

Wichterle Reaction. Dimethyl sulfoxide (10 mL) was added to 20 mg (1.2 mmol) of sodium hydride in a 25-mL flask at 25 °C, and the suspension was stirred and heated to 70 °C for 1 h. After cooling, **7** (0.20 g, 1.04 mmol) was added dropwise in 2 mL of dimethyl sulfoxide, and the reaction mixture was stirred for 1 h. (*E*)-1,3-Dichloro-2-butene (0.14 g, 1.10 mmol) was added in 2 mL of dimethyl sulfoxide, and the solution was stirred for 15 h at 25 °C. The product was partitioned between saturated aqueous ammonium chloride solution (50 mL) and ether (25 mL), the aqueous phase was extracted with ether (2 × 25 mL), and the combined ethereal layers were washed with brine (25 mL), dried, and evaporated. Chromatography on silica gel (MPLC, 11% ethyl acetate in petroleum ether) gave 0.12 g (41%) of **12** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.35 (t, J = 6.0 Hz) and 5.16 (t, J = 7.1 Hz) (total 1 H), 2.15–1.90 (m, 5 H), 2.01 (s) and 2.00 (s) (total 3 H), 1.68 (s, 3 H), 1.65–1.40 (m, 4 H), 1.01 (s, 3 H); MS, m/z calcd (M^+) 280.1594, obsd 280.1597.

To a stirred solution of **12** (0.12 g, 0.43 mmol) in 5 mL of glacial acetic acid at 25 °C was added mercuric acetate (0.21 g, 0.65 mmol) in small portions over 2 min. After the mixture was stirred for 10 min, boron trifluoride etherate (92 mg, 0.65 mmol) was added dropwise, and stirring was continued for 5 h. The bulk acetic acid was removed under reduced pressure, saturated aqueous sodium bicarbonate solution was cautiously added to the residue, and the aqueous phase was extracted with ether (3 × 50 mL). The combined ethereal layers were washed with brine (50 mL) and dried, the solvent was removed under reduced pressure, and the oil was chromatographed on silica gel (20% ethyl acetate in petroleum ether) to give 0.10 g (91%) of **13** as a colorless oil, which was taken on in crude form: ^1H NMR (60 MHz, $CDCl_3$) δ 2.80–2.00 (m, 8 H), 2.20 (s, 3 H), 1.80 (s, 3 H), 1.50 (m, 6 H), 1.00 (s, 6 H).

A solution of **13** (0.10 g, 0.38 mmol) and potassium carbonate (0.28 g, 2.0 mmol) in methanol (10 mL) was heated at reflux for 5 h, at which time the bulk solvent was evaporated. The residue was dissolved in ether (50 mL) and washed with 10% aqueous hydrochloric acid (30 mL) and brine (30 mL) prior to drying. Purification by chromatography on silica gel (MPLC, elution with 8% ethyl acetate in petroleum ether) provided 57 mg (61%) of **11**, which was spectroscopically identical with the material obtained previously.

2,3,4,4a,6,7,8,8a,9,10-Decahydro-4a,5,8a-trimethyl-2-anthrol (14). Anhydrous cerium trichloride (0.20 g, 0.81 mmol) was added to a solution of **11** (0.18 g, 0.74 mmol) in 10 mL of dry methanol, and the suspension was stirred at 25 °C for 0.5 h. After the reaction mixture was chilled to 0 °C, sodium borohydride (56 mg, 1.5 mmol) was added in very small portions over 1 h, and stirring was continued for 3 h. The mixture was poured onto 10% aqueous sodium hydroxide (30 mL) and extracted with ether (3 × 30 mL). The combined organic phases were washed with brine (50 mL) and dried. Evaporation of the solvent left 0.17 g (92%) of **14** as a colorless oil: IR ($CDCl_3$) 3430 (s), 2920 (s), 1450 (s), 1375 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.16 (m, 1 H), 4.10 (m, 1 H), 2.20 (m, 2 H), 2.02–1.92 (m, 3 H), 1.89–1.40 (m, 4 H), 1.53 (s, 3 H), 1.20 (m, 6 H), 1.13 (s, 3 H); ^{13}C NMR (80 MHz, $CDCl_3$) 146.52, 133.62, 125.96, 124.49, 68.28, 45.71, 29.42, 38.82, 38.11, 35.32, 34.99, 31.27, 29.96, 29.71, 26.68, 26.13, 19.24 ppm; MS, m/z calcd (M^+) 246.1984, obsd 246.1991.

1,9a-Epoxy-1,2,3,4,4a,6,7,8,8a,9,9a,10-dodecahydro-4a,5,8a-trimethyl-2-anthrol (15). Titanium tetraisopropoxide (57 mg, 0.06 mL, 0.20 mmol) was added via syringe to 5 mL of cold (–20 °C) methylene chloride, to be followed by **14** (50 mg, 0.2 mmol) in 2 mL of methylene chloride. Dry *tert*-butyl hydroperoxide (0.15 g, 1.6 mmol) was added dropwise via syringe, and the solution was stirred at –20 °C for 5 h. The product was diluted with ether (50 mL) and washed with saturated aqueous sodium bicarbonate solution (30 mL) and brine (30 mL) prior to drying. Removal of solvent and chromatography on silica gel (MPLC, elution with 26% ethyl acetate in petroleum ether) afforded 45 mg (87%) of **15** as a very pale yellow oil: IR ($CDCl_3$) 3460 (s), 2940 (s), 2860 (m), 1450 (m), 1210 (m), 1030 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.80 (m, 1 H), 3.07 (s, 3 H), 2.18 (m, 2 H), 2.04 (m, 2 H), 1.90–1.60 (m, 4 H), 1.58 (s, 3 H), 1.50–1.10 (m, 6 H), 1.06 (s, 6 H), 0.81 (d, J = 13.5 Hz, 1 H); ^{13}C NMR (80 MHz, $CDCl_3$) 132.91, 126.51, 69.82, 66.92, 64.13, 45.10, 38.11, 36.08, 35.65, 33.84, 31.11, 27.31, 25.64, 22.09, 19.57, 19.08 (one carbon not observed) ppm; MS, m/e calcd (M^+) 262.1933, obsd 262.1937.

1,9a-Epoxy-1,4,4a,6,7,8,8a,9,9a,10-decahydro-4a,5,8a-trimethyl-2(3*H*)-anthracenone (16). Pyridinium chlorochromate (45 mg, 0.21 mmol) was added to a stirred suspension of Celite (0.51 g) in 10 mL of methylene chloride at 25 °C. Epoxy alcohol **15** (40 mg, 0.15 mmol) was introduced in the same solvent, and stirring was continued for 4 h. The mixture was diluted with ether (50 mL) and filtered through Celite. The filtrate was washed with 10% aqueous sodium hydroxide solution (2 × 20 mL) and brine (20 mL) before drying. Removal of solvent and purification by MPLC (silica gel, elution with 8% ethyl acetate in petroleum ether) furnished 30 mg (75%) of **16** as a colorless solid: mp 67–69 °C; IR ($CDCl_3$) 2935 (s), 1718 (s), 1200 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.98 (s, 1 H), 2.67 (m, 1 H), 2.23 (m, 2 H), 2.10–1.60 (m, 9 H), 1.57 (s, 3 H), 1.40 (m, 4 H), 1.23 (s, 3 H), 1.08 (s, 3 H), 0.81 (d, J = 13.8 Hz, 1 H); ^{13}C NMR (80 MHz, $CDCl_3$) 208.63, 131.91, 127.63, 72.06, 62.16, 44.72, 38.01, 37.69, 37.11, 35.71, 33.47, 30.85, 27.47, 21.97, 19.48, 18.90 (one carbon not observed) ppm; m/z calcd (M^+) 260.1776, obsd 260.1773.

Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.25; H, 9.28.

1,9a-Epoxy-1,4,4a,6,7,8,8a,9,9a,10-decahydro-4a,5,8a-trimethyl-6-oxo-2(3*H*)-anthracenone (17). Chromium trioxide (21 mg, 0.2 mmol) was suspended in 10 mL of methylene chloride, and 3,5-dimethylpyrazole (20 mg, 0.2 mmole was added quickly as possible at –20 °C. After 30 min, **16** (0.61, 2.3 mmol) was added, and stirring was continued for 2 h. Sodium hydroxide (10% in water, 10 mL) was added, and the mixture was allowed to warm to 25 °C. The organic layer was separated and washed with 10% aqueous hydrochloric acid (20 mL) and brine (20 mL) prior to drying. Removal of the solvent and purification by chromatography on silica gel (elution with 30% ethyl acetate in petroleum ether) furnished 41 mg (80%) of **17** as a colorless crystalline solid: mp 125–126 °C; IR ($CDCl_3$) 2935 (m), 2860 (w), 1715 (s), 1660

Table I. Experimental Data for X-ray Diffraction Study of 17

(A) Crystal Parameters at Room Temperature	
space group	$P2_1/n$
a, Å	13.191 (2)
b, Å	9.107 (1)
c, Å	13.438 (2)
β, deg	108.63 (1)
V, Å^3	1529.65
Z	4
M_r	274.36
ρ_{calcd}, g cm^3	1.191
$\mu_{M0\,K\alpha}$, cm^{-1}	0.748
(B) Measurement of Data	
diffractometer	Enraf-Nonius CAD4
radiation	M0 Kα (λ = 0.71073)
reflections measured	$+h$, $+k$, $\pm l$
2θ range, deg	4–45
scan type	ω–2θ
scan angle (ω)	(0.75 ± 0.35) tan θ
scan speed, deg/min	0.65–5[a]
total reflections collected	2019, symmetry independent, with $1175I > 2.5\sigma(I)$
standard reflections	6 reflections were measured after 3 exposure h[b]
final R_f[c]	0.029
R_{wf}[c]	0.034

[a] In ω. [b] No decay indicated during the period of data collection. [c] With 270 variable parameters.

(s), 1625 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.97 (s, 1 H), 2.62 (m, 1 H), 2.39 (m, 3 H), 2.08 (m, 2 H), 1.70 (s, 2 H), 1.53 (m, 5 H), 1.31 (s, 3 H), 1.21 (s, 3 H), 0.91 (d, J = 14.0 Hz, 1 H); ^{13}C NMR (80 MHz, $CDCl_3$) 206.98, 197.52, 159.77, 131.09, 70.60, 61.72, 44.08, 39.68, 37.63, 37.19, 36.80, 34.25, 34.06, 33.03, 25.62, 22.11, 11.38 ppm; MS, m/z calcd (M^+) 274.1569, obsd 274.1563.

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.42; H, 8.08. Found: C, 74.03; H, 8.10.

X-ray Analysis of 17. A prismatic colorless crystal of approximate dimensions 0.15 × 0.20 × 0.25 mm was mounted on the tip of a thin glass fiber. Both X-ray examination of the crystal and data collection were carried out at room temperature with the aid of an Enraf-Nonius CAD4 diffractometer with graphite-monochromated Mo K radiation. The cell parameters and standard deviations were determined by least-squares fitting from 24 reflections, well distributed in reciprocal space and lying in the 2θ range between 25° and 30°. Intensity data were collected by ω–2θ scan mode with the 2θ range lying between 4° and 45°. A total of 2019 reflections were measured with 1174 unique data having $I > 2.5\sigma(I)$. Details of the data collection are given in Table I. The data were corrected for Lorentz and polarization effects.

The analytical form of the scattering factors for neutral atoms was used throughout the analysis and both $\Delta f'$ and $i\Delta f''$ terms were included for all atoms. All crystallographic computations were carried out on a PDP11/44 computer using the SDP (Structure Determination Package).

The systematic absences showed that the space group would be $P2_1/n$. From the calculated density, there are four molecules per unit cell, one per asymmetric unit. The structure was solved via MULTAN 82. All the non-hydrogen atoms were located in the E map. After several cycles of full-matrix least-squares refinements of the positional and isotropic thermal parameters for these atoms, all the hydrogen atoms appeared in the difference electron density maps.

The function minimized during the least-squares refinement process was $\sum w(|F_o| - |F_c|)^2$, where the assigned weights are given as $w = 4F_o^2/[\sigma^2(I)+(pI)^2]$, and $p = 0.03$ was chosen to make $\sum w\Delta F$ uniformly distributed in $|F_o|$, sin θ/λ, and parity class of the crystallographic indices. The final full-matrix least-squares refinement cycle with anisotropic thermal parameters for all non-hydrogens, fixed isotropic for hydrogen atoms, gave $R_f = 0.029$, and $R_{wf} = 0.034$, for 1175 reflections with 270 variable parameters, where $R_f = \sum||F_o| - |F_c||/\sum|F_o|$, and $R_{wf} = \sum w^{1/2}||F_o| - |F_c||/\sum w^{1/2}|F_o|$. The final difference Fourier map showed no significant features.

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Supplementary Material Available: Tables of bond distances, bond angles, weighted least-squares planes, and final positional and thermal parameters **17**, as well as a stereodrawing of the unit cell (8 pages). Ordering information is given on any current masthead page.