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TOTAL SYNTHESIS OF TETRACYCLIC TRITERPENES 2
AN EFFICIENT SYNTHESIS OF 1,4-DIMETHOXY-14α-METHYL-11-OXOESTRA-1,3,5(10)-TRIENE.

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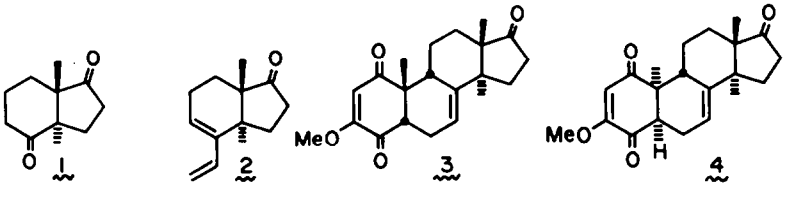
Abstract: Diels-Alder cycloaddition of 1,4-benzoquinone with diene **2** gave the α-endo adduct **6** in good yield. Acid catalyzed aromatization of **6** was controlled so as to give either the unconjugated hydroquinone derivative **7** or the conjugated $\Delta^{9(11)}$ isomer **9**. The dimethoxy derivative **12** gave acid-labile epoxides **17** and **18**, which were assigned the β and α configuration respectively on the strength of their characteristic ^{1}Hnmr spectra. Acid-catalyzed rearrangement of these epoxides yielded the stereoisomeric 11-ketones **19** and **20**. A comparison of ^{1}Hnmr data for **19** and **20** with previously-reported analogs in which either the 11-carbonyl function or the 14α-methyl group are absent led to assignment of the 9β-configuration (BC-cis) to the former and the 9α-configuration to **20**. X-ray analysis has confirmed the configurations of **19** and **20**. Significant distortion of ring C is found in both isomers, and is attributed to dipole repulsion between the 1-methoxyl substituent and the carbonyl function. The common enolate anion derived from these ketones gave only O-methylation, and on protonation gave a mixture of enol **21** and **19**.

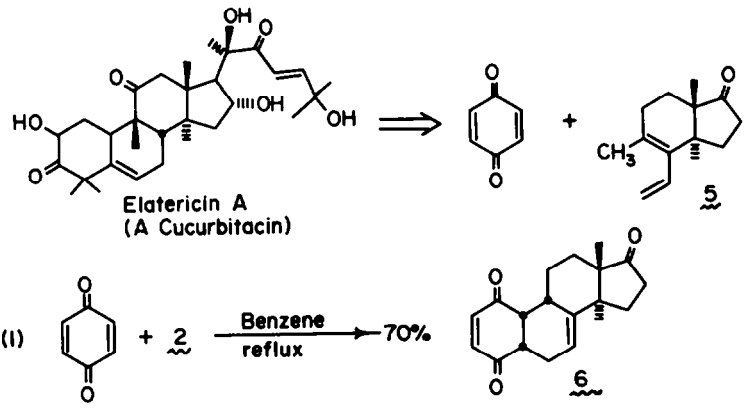
Dehydrogenation reactions of **7** and its bis-methyl ether **10** yielded naphthoquinone derivatives **13** and **14**, and the dimethoxy naphthalene **15**.

Eight years ago we noted that trans-1,6-dimethylbicyclo[4.3.0]nonane-2,7-dione (**1**) might serve as a CD-synthon for the synthesis of tetracyclic triterpenes.[1] To put this expectation into practice we elected to use an A + CD Diels-Alder strategy, employing diene **2**[2] and quinone dienophiles. In every case studied, such Diels-Alder reactions gave predominantly α-endo adducts, as for example, **3** from the BF_3-catalyzed reaction of **2** with 2-methoxy-5-methyl-1,4-benzoquinone.[3] Subsequently we found that the lanostane-like configuration of **3** could be converted to the euphane-like configuration of **4** in three high-yield steps.[4] Two of the largest families of tetracyclic triterpenes[5] are thereby potentially accessible by this approach.



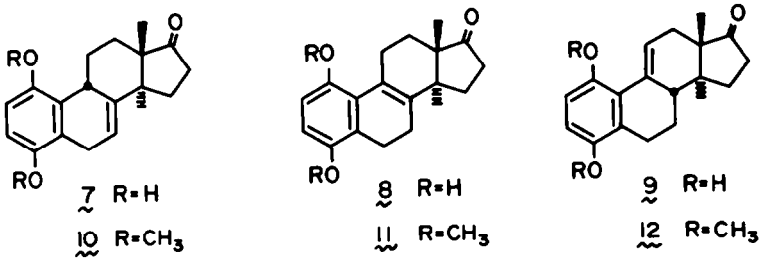
The cucurbitacins,[5,6] a third important triterpene family, require a modification of the above synthetic strategy. Since the C-19 methyl group is located at C-9 in the cucurbitacin skeleton, it must either be incorporated in the diene reactant before the tetracyclic nucleus is assembled (i.e. by using **5** rather than **2**) or introduced at a later stage of the synthesis, presumably with the assistance of an 11-ketone function. In practice, diene **5** failed to react with common dienophile reagents[7], including esters of acetylene dicarboxylic acid. Consequently,

we have focused our attention on the latter approach and have studied functional modifications of **6**, the adduct from 2 and 1,4-benzoquinone (eq. 1).



In this paper we describe acid-catalyzed isomerizations of **6**, some dehydrogenation reactions of the resulting aromatic 14α-methylestratetraene derivatives, and the introduction of an 11-ketone function via a 9,11-epoxide rearrangement. Our studies compliment recent work of Bull and Bischofberger,[8] in which 3-methoxy-14α-methyl estratetraenes were prepared from **1** by a different route.

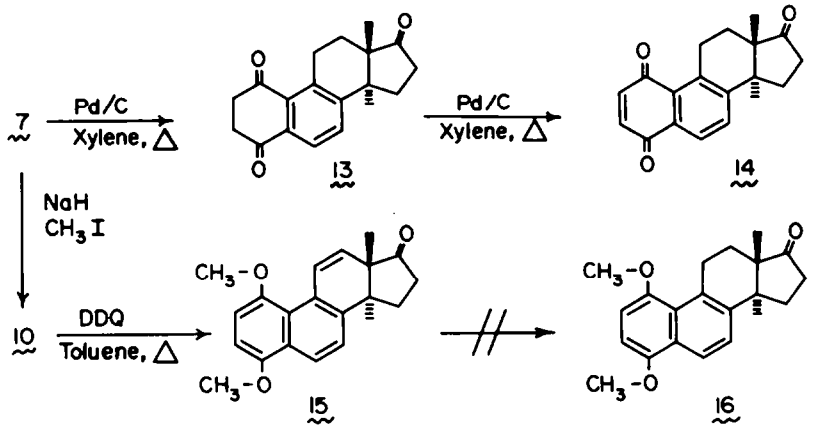
Aromatization of ring A in **6** was effected by brief treatment with hydrochloric acid in hot acetic acid solution. As reported by Ansell et. al,[9] this procedure gave the unconjugated hydroquinone derivative **7** (ca. 80% yield) together with small amounts (ca. 10%) of the conjugated isomers **8** and **9**, the former predominating. The relative insolubility of **7** hindered its purification; so it was converted in high yield to the corresponding bis methyl ether derivative (**10**) by reaction with sodium hydride in THF, followed by addition of methyl iodide. Chromatography on silica gel gave crystalline **10**, which still contained small amounts (<5%) of isomer **11**, and which stubbornly resisted further purification efforts. Both **7** and **10** displayed large homoallylic coupling between C-6 and C-9 protons ($J_{6\alpha,9}$=5.5 Hz, $J_{6\beta,9}$=8.0 Hz). This, together with other coupling constants ($J_{6\alpha,7}$=5.2 Hz, $J_{6\beta,7}$=2.0 Hz, $J_{6\alpha,6\beta}$=22.6 Hz), serves to establish the assigned structure.[10]



On more vigorous treatment with acid (p-toluenesulfonic acid in refluxing toluene or conc. hydrochloric acid in acetic acid for >10 hr.), **7** and **10** were isomerized completely to a mixture of Δ^8 and $\Delta^{9(11)}$-14α-methylestratetraenes. In the dimethoxy series, **11** and **12** were formed in a roughly 1:2 ratio in almost quantitative yield. This corresponds to the equilibrium composition of equivalent 3-methoxy-19-norsteroids.[11] We find that the ^{1}Hnmr angular methyl signals for **11** and **12** are within 0.1 ppm of those reported by Bull for his 3-methoxy analogs. However, the C-11 olefinic proton in **12** has shifted downfield by ca. 0.9 ppm due to its proximity to the 1-methoxyl group.

Since we had planned to use the $\Delta^{9(11)}$ isomer as a precursor to an 11-carbonyl function, the mediocre ratio of **12** to **11** was disappointing. Fortunately, this ratio improved markedly in the dihydroxy series. Thus **7** (or better still **6**) was transformed into a 5:1 mixture of **9** and **8** in 95% yield on prolonged acid treatment. A pure sample of **12** was then obtained by base-induced methylation. We speculate that this difference is due to hydrogen bonding of the 1-hydroxyl group to the double bond in **9**.

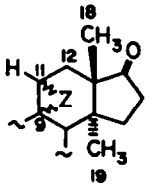
Scheme I



Dehydrogenation reactions of **7** and **10** were examined next (Scheme 1). Prolonged treatment of **7** with a palladium catalyst (10% on charcoal) in refluxing xylene gave naphthoquinone **14** in high yield. The interesting diketone **13** proved to be an intermediate in this reaction, since it was obtained in over 50% yield under milder conditions. It is surprising that the diketone tautomer is favored over the dihydroxynaphthalene isomer in this case, since simpler systems do not display such behavior.[12] In contrast to this high yield conversion, treatment of **10** under similar conditions gave mixtures of products in which the dimethoxynaphthalene **16** was a component, but could not be isolated. An alternative dehydrogenation of **10** by the action of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing benzene gave **15** in high yield. Efforts to reduce **15** to **16** using several catalytic hydrogenation systems were unsuccessful.

From the beginning we had planned to introduce a carbonyl function into the tetracyclic substrate at C-11. Since naphthoquinone **14** was easily prepared, we explored the possibility of effecting a photochemical oxidation at C-11, following the procedure of Rommel and Wirz[13] as applied to 5-methyl-1,4-naphthoquinone. In our hands, only intractable mixtures were obtained from such reactions. A second approach involving hydroboration of **12** also proved disappointing. Thus treatment of an ether solution of **12** with excess diborane reduced the 17-carbonyl function

TABLE I



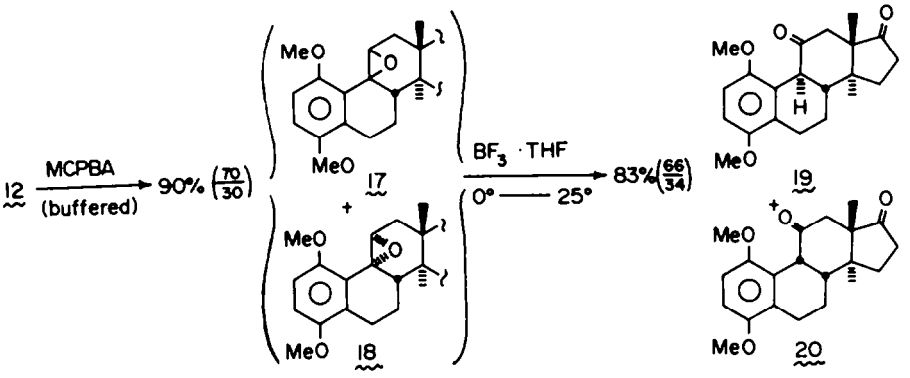
Proton NMR Data

Compound	Z	δ^{*}_{11} (Multiplicity/Japp)	δ^{*}_{18}	δ^{*}_{19}
12	9(11) C=C	7.17 (doublet/6.0 Hz)	1.06	0.86
17	β-epoxide	5.04 (triplet/2.4 Hz)	1.18	0.86
18	α-epoxide	4.88 (doublet/5.8 Hz)	1.06	0.98

* Chemical shifts in ppm from TMS are ± 0.02

to a mixture of epimeric alcohols, but left the 9(11)-double bond unchanged! Oxidation of the alcohol mixture with pyridinium chlorochromate returned **12** in good yield.

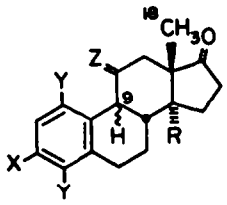
Finally, an epoxidation/rearrangement sequence provided an effective route to **19** and **20** from **12**. Since epoxides **17** and **18** proved to be very sensitive to acids, it was necessary to use the buffered-peracid reaction conditions described by Anderson and Veysoglu[14] for their preparation. Trace amounts of pyridine were also added during workup and spectroscopic characterization as a precaution against acid-catalyzed rearrangement.[15] In this fashion a 70:30 mixture of the β- and α-epoxides **17** and **18** was obtained as a broad-melting solid in over 90% yield from **12**. Our assignment of configuration to these isomeric epoxides was based on previously-established vicinal coupling constants for steroid epoxides,[15,16] and the substantial deshielding effect of an epoxide oxygen atom on protons forced close to it.[17] Table I presents this data, which suggests that the latter deshielding factor is ca. 0.12 ppm.[18] Molecular models (Dreiding) of **17** and **18** show torsional differences in the 11-12 bond that correspond to the different coupling patterns observed for the 11-proton. In all cases the 1-methoxyl group deshields the 11-proton by 0.8 to 1.0 ppm.



The sensitivity of epoxides **17** and **18** to acids required careful optimization of the conditions used to effect their rearrangement to **19** and **20**. For example, boron trifluoride etherate in methylene chloride at 0° gave poor yields of a diene mixture; and lithium perchlorate in refluxing benzene[19] converted the epoxides to a mixture of the desired 11-ketones together with substantial amounts of dienes in less than 50% combined yield. By conducting the rearrangement in tetrahydrofuran solution, the reactivity of boron trifluoride was moderated sufficiently to permit isolation of a 2:1 mixture of 11-keto epimers (**19** and **20**) in 83% yield. These isomers were easily separated by chromatography or fractional crystallization.

Although several 11-ketoestra-1,3,5(10)-triene derivatives have been studied and their BC-cis and trans isomers characterized[15,20], the corresponding assignment of cis and trans configurations to **19** and **20** proved unexpectedly perplexing. In the steroid system (no 14α-methyl group) equilibrium favored the BC-cis isomer; and in most cases rapid quenching of the enolate anion (kinetic protonation) gave predominantly the trans isomer. Clearly, these relationships may be changed significantly if a 14α-methyl substituent is present. Such 14α-methylestra-1,3,5(10)-triene derivatives having both the 9α and 9β configurations have been prepared by others.[8,21] However, these compounds (e.g. **25** and **26** in Table II) differ from **19** and **20** in two important ways. First, they lack an 11-carbonyl function; consequently, equilibrium studies were not reported. Second, the 1-methoxyl substituent in **19** and **20** is not present in the reference compounds (Table II), and resulting interactions with groups at C-11 are necessarily absent. We noted earlier one such interaction that led to an improved synthesis of the $\Delta^{9(11)}$-tetraene **9**.

TABLE II



Proton NMR Data

Compound	R	X	Y	Z	C-9	δ H-9 (m, J)	δ H-18	δ H-19	Ref.
23	H	OCH_3	H	O	α	3.48 (d, 9.5 Hz)	0.86*	--	15,20
24	H	OCH_3	H	O	β	3.64 (d, 5.5 Hz)	0.90*	--	15,20
25	CH_3	OCH_3	H	H_2	α	----	1.03	0.90	8,21
26	CH_3	OCH_3	H	H_2	β	----	1.13	0.32	8
20	CH_3	H	OCH_3	O	α	3.98 (d, 12.8 Hz)	1.00	1.25	this work
19	CH_3	H	OCH_3	O	β	4.22 (d, 8.8 Hz)	1.50	0.80	this work

* These chemical shifts were obtained from the corresponding 17-ethylenedioxy ketal.[15] The C-18 deshielding increment for this ketal is within ± 0.01 ppm of the 17-ketone increment.

Before considering interconversion studies of **19** and **20**, we wanted to make a structural assignment based on their physical properties alone. Of course, the well-established stereoselectivity of Lewis acid-induced steroid epoxide rearrangments to ketones[22] suggested that **19** was the trans isomer (from **17**) and **20** the cis isomer (from **18**). However, the lability of these compounds makes this a tenuous assignment at best. We therefore compared ^{1}Hnmr chemical shifts of the angular methyl groups (C-18 and C-19) and the C-9 proton in **19** and **20** with corresponding values reported for some reference compounds (Table II).

To begin with, we needed to evaluate the shielding effect of the methoxyl substituents at C-1 and C-4 on the angular methyl groups. Since the C-18 and C-19 resonance signals for olefin **12** (Table I) are shifted 0.07 ppm downfield from the equivalent signals reported by Bull[8] for the analogous-3-methoxy derivative (C-18: δ 0.98; C-19: δ 0.79); we applied this increment in our calculations for the equally rigid trans-fused isomer. Taking **25** as our reference (Table II), we apply appropriate carbonyl shielding increments (Δ = 0.033 for C-18; Δ = 0.275 for C-19)[23] together with the 0.07 increment and arrive at calculated methyl resonances of δ 1.07 and δ 1.25 ppm for the 9α isomer. These values fit well with the observed signals for isomer **20**. Furthermore, the signal from the 9α-proton is consistent with its anti-periplanar orientation to the 8β-proton ($J_{8,9}$ = 12.8 Hz).

If the remaining isomer is assigned the 9β (BC-cis) configuration **19**, its ^{1}Hnmr spectrum presents three puzzling features. First, the 14α-methyl group signal at δ 0.80 ppm is further downfield than expected from reference compound **26** (δ calculated = 0.30 + 0.275 + 0.07 = 0.67 ppm). Second, the 13β-methyl group signal at δ 1.50 ppm is also further downfield than expected (δ calculated = 1.13- 0.03 + 0.07 = 1.17 ppm). Finally, the 9β-proton is shifted downfield and displays a larger $J_{8,9}$ than expected from reference compound **24**. We believe that these peculiarities in the ^{1}HNMR spectrum of **19** are explained by a conformational change induced by dipole repulsion of the carbon:oxygen bonds at C-1 and C-11. Thus, if ring C assumes a boat-like conformation by a folding down of the 11-carbonyl function, the protons at C-8 and C-9 become eclipsed and $J_{8,9}$ increases. In this conformation the aromatic A-ring no longer shields the 14α-methyl group; however, some shielding by the 11-carbonyl function is expected. Consequently, the chemical shift of the C-19 protons should be less than δ 0.90 ppm (compound **25** as reference).

The effect of this conformational change on the 13β-methyl group is most dramatic. The C-18 protons now lie behind the 11-carbonyl function in a strongly deshielding region. We estimate this deshielding increment to be at least 0.275 ppm (the increment for a 7-carbonyl function acting on the C-10 methyl group). Using compound **26** as our reference, we calculate the 13β-methyl chemical shift to be about δ 1.48 ppm (1.13 + 0.275 + 0.07). We recognize that calculations of this kind have limited significance, but the trends certainly support the assignments we have made.

To confirm the structures assigned here to **19** and **20** we first considered a nOe experiment to demonstrate the proximity of the 9α-proton to the 14α-methyl group in **20**. However, the boat-like conformation our arguments attribute to ring C in **19** forces the 13β-methyl group very close to the 9β-proton in this cis-fused isomer. Consequently, we concluded such a study would be ambiguous. Since **19** is nicely crystalline, the most direct way to establish its configuration proved to be an X-ray analysis. This proceeded smoothly, and an ORTEP drawing resulting from this experiment is shown in Figure 1a.[24] All of the structural features proposed above for **19** are confirmed by this analysis, which also shows disorder in ring B (carbons 6 and 7).

A study of the base-catalyzed interconversion of isomers **19** and **20** gave ambiguous results, which proved so puzzling that we decided to confirm enolate formation by isotope exchange. Treatment of the cis isomer **19** with a 0.05 M solution of sodium methoxide in methanol-O-d gave rapid deuterium exchange at C-9 (30 min. at reflux), but no equivalent exchange for the trans isomer **20** was observed after 8 hr at reflux. Naturally, this caused us to reevaluate the structure of the latter isomer-a bridged ketone substructure, incorporating rings B and C, might have been formed in the epoxide rearrangement step. Surprisingly, an x-ray structure analysis of **20** confirmed our initial assignment (Figure 1b)[24]. Furthermore, an explanation for the very slow enolization of **20** was evident from this structural analysis. Thus a severe dipole repulsion between the carbon:oxygen bonds at C-1 and C-11 has forced the carbonyl group to bend upward. Because of this, the axial C-9:hydrogen bond intersects the plane of the carbonyl function at a 139° angle! The nearly 50° twisting of this bond from alignment with the π-orbital of the carbonyl group is expected to raise the energy of the deprotonation transition state by 10 to 15 kcal/mole, as demonstrated by earlier workers.[25] The sluggish enolization of **20** is remarkable because it is caused by severe distortion imposed upon a normally well-behaved steriod-like structure.

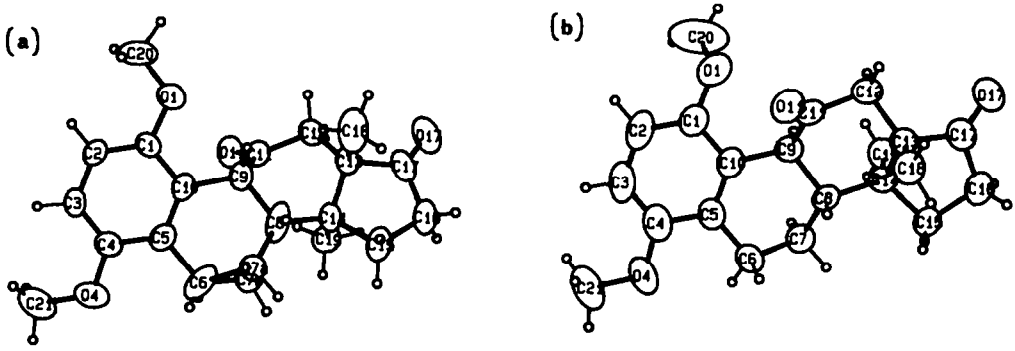
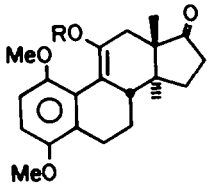


Figure 1. ORTEP diagrams of (a) **19** and (b) **20**. Carbon and oxygen atoms are represented by thermal ellipsoids at the 50% level.

Enolate anion formation from **20** could be forced by using more than one molar equivalent of base, but our efforts to establish an equilibrium between **19** and **20** were rendered ambiguous by formation of enol **21**. Thus treatment of **19** (or **20**) with refluxing 5% methanolic potassium hydroxide for 8 hr., followed by an aqueous quench and methylene chloride extraction, gave a 60:40 mixture of **21** and **19**. This enol isomer was never isolated in a pure state, and its structure was assigned on the strength of its ^{1}Hnmr spectrum. The corresponding O-methyl derivative **22** was the only product obtained from reaction of the enolate anion (prepared in THF

solution by treatment of **19** or **20** with potassium t-butoxide) with methyl iodide. The angular methyl chemical shifts for **21**, **22** and olefin **12** are reasonably consistent: δ_{18} = 1.08, 1.18 and 1.06 ppm; δ_{19} = 0.91, 0.92 and 0.86 ppm respectively. Other alkylating agents, such as allyl bromide and ethyl bromoacetate, also gave exclusive O-alkylation. Consequently, another method for introducing a 9β-methyl group must be developed.



21 R=H
22 R=CH_3

EXPERIMENTAL

Except where otherwise indicated, all reactions were conducted under a dry argon or nitrogen atmosphere using solvents distilled from appropriate drying agents. Small scale chromatographic separations were accomplished with the use of 2 mm silica gel plates (Merck F-254, 20 x 20 cm). Larger scale separations were effected by flash chromatography (40-63 millimicron silica gel, Merck 9385). Melting points in degrees Centigrade were determined on either a Thomas-Hoover capillary melting point apparatus or a Reichert hot-stage microscope and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 237B grating spectrophotomer. Mass spectra (MS) were obtained with a Finnigan 4000 GC/MS spectrometer. Proton magnetic resonance spectra (^{1}Hnmr) were taken in deuterochloroform solution, using either a Varian T-60 or a Bruker WM 250 spectrometer, and are calibrated in parts per million (δ) from tetramethylsilane (TMS) as an internal standard. Carbon magnetic resonance spectra (^{13}Cnmr) were recorded on a Bruker WM 250 spectrometer at 69.8 MHz using deuterochloroform as solvent and are calibrated in parts per million (δ) from TMS as internal standard.

Microanalyses were performed by Spang Microanalytical Labs, Eagle Harbor, Michigan.

Preparation of 6 by Diels-Alder Cycloaddition

To a refluxing solution of 6.5 g of p-benzoquinone in 200 mL of benzene was added 4.0 g of diene **2** in 150 mL of benzene, under argon, over a period of one hour. The reaction mixture was refluxed overnight, cooled and washed with 100 mL of 10% sodium bisulfite solution. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Removal of solvents yielded an oil which on trituration with ether gave 4.66 g of a light yellow crystalline solid. The solid was found to be a mixture of two products. The major isomer (ca. 85%) displayed the following properties: m.p. 170-173°; IR 1740, 1690, 1600 cm^{-1}; ^{1}Hnmr 1.05 (s, 3H), 1.20 (s, 3H), 1.4-2.8 (m, 11H), 3.2 (broad s, 2H), 5.20 (q, 1H, J=2.9 Hz), 6.53 (dd, 1H, J=1.2 and 10.3 Hz), 6.62 (d, 1H, J=10.3 Hz); ^{13}C nmr 219.2, 201.0, 198.9, 144.8, 141.0, 137.0, 115.6 ppm and eleven higher-field signals; MS m/e (re. abund.) 298 (14), 189 (27), 145 (25), 131 (27), 123 (100), 91 (65).

Analysis: Calculated for $C_{19}H_{22}O_3$ C, 76.49; H, 7.43
Found C, 76.58; H, 7.44

The α-endo configuration of **6** is assigned because of its similarity (^{1}Hnmr) to other quinone adducts of known configuration.[3] Lewis acid catalysis (BF_3 or $SnCl_4$) gives the same adduct, **6**, but in somewhat poorer yield.

The minor component appears to be a stereoisomer of **6**, as yet not identified.

Acid-Catalyzed Isomerization of 6

To **7**: A solution of **6** (500 mg) in hot glacial acetic acid (ca. 2 mL) was mixed with two drops of conc. hydrochloric acid and slowly cooled to room temperature. Filtration and washing with water gave a colorless crystalline solid (447 mg, 90%), which proved to be 85:15 mixture of **7** and **8** along with a little **9**. This relatively insoluble material exhibited the following properties: m.p. 220-240°; IR 3200-2400, 1725, 1600 cm^{-1}; MS m/e (rel. abund.) 298 (100), 283 (37), 265 (26); ^{1}Hnmr (CD_3COCD_3), major isomer, 1.12 (s, 3H), 1.22 (s, 3H), 1.5-2.7 (m, 8H), 3.03 (ddd, 1H, J=2.5, 7.8, 22.3 Hz), 3.3 (m, 1H), 3.43 (dt, 1H, J=5.2, 22.3 Hz), 3.85 (2H, OH), 5.85 (dt, 1H, J=5.2, 2.5 Hz), 6.5 (s, 2H).

To **9**: a solution of **6** (1.0 g) in hot glacial acetic acid (5 mL) was mixed with five drops of conc. hydrochloric acid and stirred overnight at room temperature. The colorless crystalline solid that precipitated was filtered and washed with water to give 950 mg (95%) of a 85:15 mixture of **9** and **8**, m.p. 220-225° (d). The major isomer exhibited the following properties: MS m/e (rel. abund.) 298 (100), 283 (26), 265 (24); ^{1}Hnmr (CD_3COCD_3) 0.76 (s, 3H), 0.94 (s, 3H), 1.4-3.0 (m, 11H), 3.1 (2H, OH), 6.50 (d, 1H, J=8.5 Hz), 6.55 (d, 1H, J=8.5 Hz), 7.18 (dt, 1H, J=5.0, 2.6 Hz).

Preparation of Methyl Ethers 10 and 12

10: To 100 mg of **7** in cold (0°) THF solution was added 75 mg of 60% sodium hydride (washed with pentane). After this mixture was stirred for 30 min. a 0.3 mL portion of methyl iodide was added and this solution was stirred overnight at room temperature. An equal volume of cold water was added, and the resulting mixture was extracted with ether. The dried ether extracts yielded 96 mg (91%) of a colorless solid which proved to be **10** (> 80%) together with its $\Delta^{8(9)}$-isomer **11**. Even after extensive chromatographic purification, compound **10** was contaminated with **11**.

Characteristic properties of **10** are: m.p. 124-128°; IR 1730, 1600, 1475, 1250, 1075 cm^{-1}; ^{1}Hnmr 1.05 (s, 3H), 1.26 (s, 3H), 1.4-3.0 (m, 8H), 3.13 (m, 2H), 3.5 (dt, 1H, J=5.5 and 22.6 Hz), 3.78 (brs, 6H), 5.78 (dt, 1H, J=5.5 and 2.5 Hz), 6.7 (brs, 2H) ppm; MS m/e (rel. abund.) 326 (100), 311 (31), 293 (11).

12: A 500 mg sample of 60% sodium hydride (in mineral oil) was washed with pentane and then mixed with a solution of **9** (1.27 g) in 10 mL of THF. After stirring for 30 min. at room temperature this mixture was cooled to 0° and treated with 0.5 mL of methyl iodide. Following an overnight reaction period at room temperature, this mixture was quenched with water and extracted with ether. Evaporation of the dried extracts gave 1.28 g of crude product which was chiefly **12**. Crystallization from ether gave 1.1 g of **12** (85%) m.p. 160-162°. Characteristic properties of **12** are: ^{1}Hnmr 0.86 (s, 3H), 1.06 (s, 3H), 1.5-3.1 (m, 11H), 3.85 (brs, 6H), 6.72 (d, 1H, J=9Hz), 6.80 (d, 1H, J-9 Hz), 7.17 (br d, 1H, 6 Hz) ppm; MS m/e (rel. abund.) 326 (100), 311 (22), 293 (7), 269 (10).

Analysis: Calculated for $C_{21}H_{26}O_3$ C, 77.27; H, 8.03
Found C, 77.41; H, 7.95

Palladium-Catalyzed Dehyrogenation Reactions of **7**

A solution of hydroquinone **7** (900 mg), containing 15 to 20% of conjugated isomer **8**, in 50 ml xylene was mixed with 200 mg of 10% palladium on charcoal and brought to reflux. After 10 hr. this mixture was cooled, filtered and crystallized from ethanol to give 450 mg (50%) of **13**, m.p. 138-141°. The mother liquor contains a mixture of **13** and **14**. Characteristic properties of **13** are: IR ($CHCl_3$) 1735, 1685 cm^{-1}; ^{1}Hnmr 80.8 (s, 3H), 1.1 (s, 3H), 1.8-2.8 (m, 6H), 3.0 (br.s, 4H), 3.4 (m, 2H), 7.52 (d, 1H, J=8.0 Hz), 8.02 (d, 1H, J-8.0 Hz) ppm; MS m/e (rel. abund.) 296 (100), 281 (47), 239 (65).

Analysis: Calculated for $C_{19}H_{20}O_3$ C, 77.00; H, 6.80
Found C, 77.05; H, 6.69

If the dehydrogenation described above was conducted with a larger amount of catalyst (weight ratio of substrate to catalyst ca. 1.5) and longer reflux (24 hr) the conversion to naphthoquinone **14** was quantitative. Crystallization from ethanol gave pure **14** as an orange solid, m.p. 202-205°. Characteristic properties of **14** are: IR ($CHCl_3$) 1740, 1660 cm^{-1}; ^{1}Hnmr δ 0.80 (s, 3H), 1.10 (s, 3H), 1.8-2.8 (m, 6H), 3.5 (m, 2H), 6.9 (s, 2H), 7.55 (d, 1H, J= 8.0 Hz), 8.10 (d, 1H, J=8.0 Hz) ppm; MS m/e (rel. abund.) 294 (100), 279 (21), 252 (74).

Analysis: Calculated for $C_{19}H_{18}O_3$ C, 77.52; H, 6.16
Found C, 77.51; H, 6.06

Dehydrogenation of **10** to **15**

To a solution of **10** (652 mg) in 10 mL of benzene was added 2.2 g of DDQ, and the resulting mixture was reluxed for 20 hr. The cooled reaction solution was then poured through a short column of neutral alumina, and the product was eluted with methylene chloride. Evaporation followed by crystallization of the crude product from ether gave 570 mg (87%) of **15** as a light yellow solid, m.p. 155-157°. Characteristic properties of **15** are: IR 1740, 1600 cm^{-1}; ^{1}Hnmr δ 1.00 (s, 3H), 1.18 (s, 3H), 2.1-2.8 (m, 4H), 3.90 (s, 3H), 4.00 (s, 3H), 6.36 (d, 1H, J=10.0 Hz), 6.66 (d, 1H, J= 8.5 Hz), 6.78 (d, 1H, J= 8.5 Hz), 7.31 (d, 1H, J= 8.5 Hz), 8.02 (d, 1H, 10.0 Hz), 8.26 (d, 1H, J= 8.5 Hz) ppm; ^{13}Cnmr δ 214.4, 151.6, 149.9, 142.0 128.7, 128.6, 128.3, 126.9, 123.5, 122.6, 122.4, 106.7, 102.6, 56.0, 55.7, 53.1, 46.1, 35.2, 26.8, 24.4, 18.4 ppm; MS m/e (rel. abund.) 322 (100), 307 (25), 265 (63).

Analysis: Calculated for $C_{21}H_{22}O_3$ C, 78.23; H, 6.88
Found C, 78.14; H, 6.75

Epoxidation of **12** to **17** and **18**

A solution of **12** (75 mg) in 5 mL of methylene chloride was mixed with 2.5 mL of 10% aqueous sodium bicarbonate, and to this stirred two-phase system was added 110 mg of 3-chloroperbenzoic acid (85%). After stirring for 4 hr, the reaction mixture was quenched by addition of 10 mL of 2% aqueous sodium sulfite and stirred an additional 15 min. The mixture was diluted with ether containing a few drops of pyridine, and then washed with dilute sodium bicarbonate solution followed by water. The organic layer was dried over anhydrous potassium carbonate, and the residue left after evaporation of the solvent gave 74 mg of a colorless solid on trituration with a little ether. The ^{1}Hnmr spectrum of this solid demonstrated it to be a 70:30 mixture of epoxides **17** and **18**. In addition to the nmr data given in Table I, this mixture exhibited the following properties: IR 1740, 1475, 1250 cm^{-1}; MS m/e (rel. abund.) 342 (3.86), 326 (2.08), 311 (1.68), 217 (1.57), 173 (4.19), 149 (4.59), 40 (100).

Preparation of Isomeric 11-Ketones **19** and **20**.

To a 70:30 mixture of epoxides **17** and **18** (194 mg) dissolved in 10 mL tetrahydrofuran and cooled to 0° was added 100 mL of freshly-distilled boron trifluoride etherate. This mixture was stirred overnight at room temperature; poured into water and extracted with ether. The ether extracts were then washed with dilute bicarbonate solution followed by brine. These extracts yielded 208 mg of a crude product, which on chromatography (silica gel) gave 163 mg of a mixture of **19** and **20**. These isomers were separated by crystallization from ether/hexane, and displayed the following properties.

19: m.p. 229-231°; IR 1710, 1735, 1275, 900 cm^{-1}; ^{1}Hnmr δ 0.81 (s, 3H), 1.51 (s, 3H), 1.6-2.9 (11H, m), 3.68 (s, 3H), 3.78 (s, 3H), 4.22 (d, 1H, J=8.85 Hz), 6.72 (d, 1H, J=8.5 Hz), 6.78 (d, 1H, J=8.5 Hz) ppm; ^{13}Cnmr δ 217.5, 209.3, 151.7, 150.5, 128.7, 123.1, 108.9, 108.0, 56.0 (2 peaks), 54.1, 45.2, 45.1, 44.5, 39.4, 34.5, 31.9, 22.6, 21.6, 20.7, 20.0 ppm; MS m/e (rel. abund.) 342 (41), 217 (47), 190 (75), 175 (41), 159 (25), 115 (41), 110 (21), 67 (57), 41 (100).

Analysis: Calculated for $C_{21}H_{26}O_4$ C, 73.66; H, 7.66
Found C, 73.65; H, 7.52

20: m.p. 175-176°; IR 1715, 1740, 1250, 880 cm^{-1}; ^{1}Hnmr δ 1.0 (s, 3h), 1.26 (s, 3H), 1.4-3.0 (11 H, m), 3.68 (s, 3H), 3.76 (s, 3H), 3.98 (d, 1H, J=12.8 Hz), 6.7 (s, 2H) ppm; ^{13}Cnmr δ 214.9,

206.5, 152.2, 151.5, 128.0, 122.9, 108.7, 108.5, 57.7, 55.7 (2 peaks), 49.2, 45.4, 43.7, 43.0, 34.6, 29.3, 24.5, 22.3, 18.2, 17.4 ppm; MS m/e (rel. abund.) 342 (51), 243 (7), 217 (64), 190 (100), 175 (49), 159 (36), 115 (50).

Analysis: Calculated for $C_{21}H_{26}O_4$ C, 73.66; H, 7.66
Found C, 73.57; H, 7.52

Formation of Enol 21

A solution of **19** (50 mg) in 5 mL of 5% methanolic potassium hydroxide was heated under reflux for 8 hr. The excess methanol was evaporated, water was added and this mixture was extracted with methylene chloride. These washed and dried extracts yielded 50 mg of a yellow solid, which appeared to be a 60:40 mixture of **21** and **19**. Enol **21** displayed the following ^{1}Hnmr signals: δ0.91 (s, 3H), 1.08 (s, 3H), 3.76 (s, 3H), 3.85 (s, 3H), 6.78 (ABq, 2H), 6.92 (s, 1H). The latter signal disappeared on D_2O exchange.

Preparation of O-Methyl Derivative 22

A solution of **20** (30 mg) in 2 mL of THF was mixed with 1 mL of t-butanol containing 25 mg of potassium t-butoxide. Following 10 min. of stirring, this solution was cooled by an ice bath and mixed with 100 μL of methyl iodide. After 2 hr. at room temperature, this reaction was quenched with water and extracted with ether. The washed and dried ether extracts yielded 32 mg of an oil, which was crystallized from ether/pentane to give 20 mg of pure **22**, m.p. 227-230°. Characteristic properties of **22** are: IR 1735, 1475, 1230, 1075 cm^{-1}; ^{1}Hnmr δ 0.92 (s, 3H), 1.18 (s, 3H), 1.5 to 3.2 (m, 11 H), 3.48 (s, 3H), 3.78 (s, 3H), 3.80 (s, 3H), 6.71 (s, 2H); MS m/e (rel. abund.) 356 (100), 341 (7), 309 (4), 283 (5), 267 (11), 215 (34).

Analysis: Calculated for $C_{22}H_{28}O_4$ C, 74.13; H, 7.92
Found C, 73.88; H, 7.96

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