Synthesis and Biological Activity of Zoapatanol Analogues

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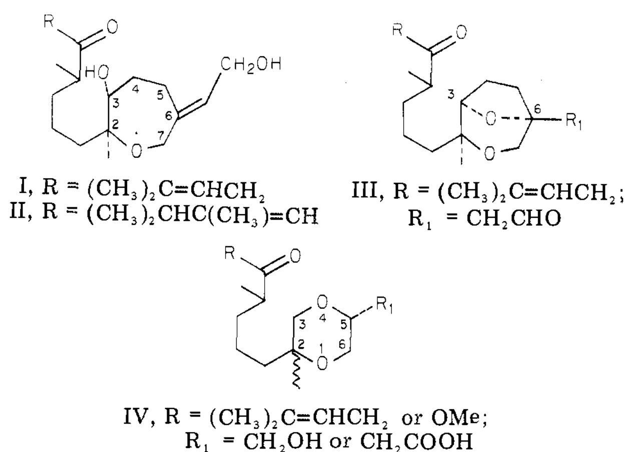
Dioxane analogues of the biologically active 3,6-oxido derivative (III) of zoapatanol (I) having substituents at the C-2 and C-5 positions, but lacking the ethano bridge, were evaluated for luteolytic and postcoital antifertility activity in the guinea pig. Whether injected sc for 3 days (days 12–14 or 22–24 postmating) or administered ip as a single dose on day 22 postmating, none of the four analogues was active at the doses tested.

Search for the biologically active components present in *Montanoa tomentosa* has led recently to the isolation of the novel oxepane diterpenoids zoapatanol (I) and

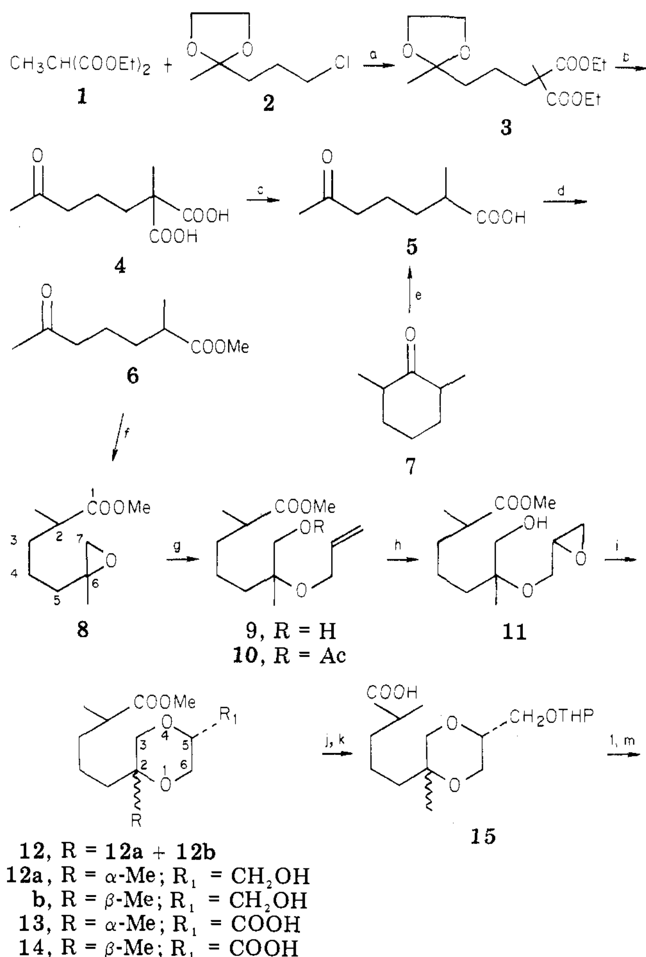


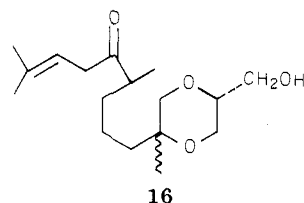
montanol (II), which appear to be responsible for the menses-inducing effects of the plant.[1,2] Recently, two different groups have reported the total synthesis of I.[3-5] Careful oxidation of the allylic primary hydroxy group in I leads to the formation of the 3,6-oxido derivative III (the numbering system used for III emphasizes its relationship to I and is different from the conventional system of numbering the bridged bicyclic compounds), which likewise possesses in full the menses-inducing properties of the parent compound.[2,6]

Atomic scale models reveal that removal of the ethano bridge from III to yield the 1,4-dioxanes IV furnishes structures in which the steric relationship of the substituents originally present at C-2 and C-6 in III is preserved. It was expected, on this basis, that the simpler structures IV should resemble the parent compounds in menses-inducing properties. Since these compounds were considered relatively easy to obtain by total synthesis, they clearly represented attractive alternatives to the components of *Montanoa tomentosa*. It was felt that the biological study of these simpler structures would help delineate the importance of the ethano bridge for menses-inducing properties. The present investigation reports the synthesis and biological evaluation of the 1,4-dioxane analogues IV.

Chemistry. The epoxy ester 8 was prepared as shown in Scheme I. It is well known that epoxides undergo acid-catalyzed ring opening to produce the most stable carbonium ion intermediates. In the case of epoxide 8, such a ring opening would be expected to give the more stable tertiary carbonium ion. If the transient carbonium ion from 8 could be captured by a 3-carbon hydroxylic reagent (such as glycerol or its precursors), it would produce an intermediate, which could eventually be converted to the desired dioxane system. While the results of the

Scheme I[a]





[a] Reagents: a = NaOEt; b = KOH/EtOH, H^+; c = Δ; d = MeOH, H^+; e = $KMnO_4$; f = NaH, $Me_3SO^+I^-$, Me_2SO; g = CH_2=CHOH, 70% $HClO_4$; h = MCPBA, i = CF_3COOH; j = dihydropyran, H^+; k = NaOH; l = $(CH_3)_2C$=$CHCH_2Li$; m = aqueous HOAc, 40 °C.

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acid-catalyzed reaction of the epoxide **8** in presence of either glycerol or dihydroxyacetone were not encouraging, allyl alcohol reacted smoothly with **8** in the presence of 70% perchloric acid. The product isolated from this reaction was identified as the allyl ether **9**. As expected, the NMR signal due to the 7-methylene group in **9** moved downfield to δ 3.4 (from δ 2.47 in the epoxide **8**) and appeared as a broad singlet. This signal became sharp on exchange with D_2O, indicating that a hydroxy group was attached to the 7-methylene group. The presence of a primary hydroxy group in **9** was further confirmed by the NMR spectrum of the monoacetate **10** in which the signal due to the 7-methylene group moved further downfield to δ 4.0.

The allyl ether **9** was transformed into the corresponding epoxy ether **11** by treatment with *m*-chloroperbenzoic acid. Treatment of a solution of the epoxy ether **11** in methylene chloride with trifluoroacetic acid gave exclusively the dioxane **12** as a 1:1 mixture of the two isomers **12a** and **12b**, which were separated on a prepacked silica gel column.

The NMR spectrum of the less polar isomer **12a** showed a group of overlapping complex multiplets from δ 3.37 to 3.73 assignable to the protons on the dioxane ring and the C-5 methylene group. The C-2 methyl resonance occurred at δ 1.266. The NMR spectrum of the more polar isomer **12b** showed the complex pattern of multiplets between δ 3.3 and 3.6. A significant difference from the spectrum of **12a** was found in the chemical shift of the C-2 methyl group, which resonated at δ 1.033.

In order to simplify the NMR spectra of **12a** and **12b** in such a way as to permit the assignment of the individual ring hydrogens, it was found necessary to oxidize the 5-hydroxymethyl group to the corresponding carboxylic acid group. This enabled us to determine the stereochemistry at C-5 by measuring the coupling constants between the 5-H and 6α-H and 6β-H.

When the dioxane **12a** was oxidized with excess Jones reagent, the acid **13** was obtained in excellent yield. Diborane reduction of **13** gave **12a**, indicating no epimerization during oxidation. The NMR spectrum (250 MHz) of **13** clearly showed all the ring hydrogens as separate multiplets. The signal at δ 4.158 (assigned to the 5-H of **12a**) appeared as a doublet of doublets with J values of 9.2 and 3.1 Hz, respectively. It has been established by Jensen and co-workers[7] that the 1,4-dioxane ring exists in a normal chair form with the coupling constants of J_{aa} = 11.7 Hz and $J_{ee} \cong 1$ Hz, respectively. It is clear that the 5-H in **13** exists in the axial position (β) and that it is coupled to 6-aH (α) with a coupling constant of 9.2 Hz (J_{aa}), as well as to the 6-eH (β) with a coupling constant of 3.1 Hz (J_{ae}). The NMR signal due to the C-2 methyl group of **13** occurred at δ 1.257.

Similarly, the acid **14** was prepared by Jones oxidation of **12b**. In this case also, the acid **14** could be converted back to the alcohol **12b** by reduction with diborane. The NMR spectrum of **14** showed the 5-H as a doublet of doublets at δ 4.14 with coupling constants of 9.2 and 3.1 Hz, respectively. This clearly showed that the 5-H in **14** is also in the axial position (β). However, the signal due to the C-2 methyl group in **14** occurred at δ 1.08.

From the above NMR data it is clear that isomeric acids **13** and **14** differ only in the configuration at C-2. A comparison of the chemical shift of the C-2 methyl group of a number of 3,6-oxidozoapatanol derivatives (e.g., III[6]) indicates that the C-2 axial methyl signal occurs between δ 1.3 and 1.33. As mentioned above, the C-2 methyl groups of **13** and **14** appear as singlets at δ 1.257 and 1.08, respectively. It is therefore reasonable to conclude that the C-2 methyl group of **13** (and hence of **12a**) is axial (α) and that of **14** (and hence of **12b**) is equatorial.

Further elaborations of the side chains at C-2 and C-5 were carried out by using the isomer **12a** with natural stereochemistry at these positions. In the total synthesis of zoapatanol,[3] the introduction of the desired ketonic side chain at C-2 was accomplished in rather poor yield (30%) by the reaction of an appropriate carboxylic acid intermediate with γ,γ-dimethylallyllithium. The allyllithium reagent was prepared by the cleavage of γ,γ-dimethylallyl phenyl ether with lithium.[8-10]

Reaction of γ,γ-dimethylallyllithium with the acid from **12a** in ether–THF gave the ketone **16** in poor yield, and a considerable amount of the unreacted acid was recovered. Varying the amount of organolithium reagent and/or reaction time did not improve the yield. In an effort to improve the solubility of the organolithium intermediate, we attempted this reaction in THF alone as a solvent. This modification did result in an increased yield of **16**. However, a considerable amount of the acid still remained unreacted. It was felt that protection of the hydroxy function in the side chain at C-5 should not only improve the solubility of the organolithium intermediate but also reduce the amount of γ,γ-dimethylallyllithium reagent. Accordingly, the hydroxy ester **12a** was converted to the corresponding tetrahydropyranyl (THP) ether and saponified to give the acid **15**. Treatment of the lithium salt of **15** with γ,γ-dimethylallyllithium in THF, followed by cleavage of the THP ether with aqueous acetic acid at 40 °C gave the ketone **16**.

Completion of the synthesis of zoapatanol analogues now required the transformation of the hydroxymethyl group at C-5 to the carboxymethyl group by a standard series of reactions. Thus, treatment of **16** with ethylene glycol in the presence of *p*-toluenesulfonic acid gave the ketal **17** in excellent yield. The protection of the ketone function was necessary to prevent the isomerization of the double bond during subsequent reactions. Reaction of **17** with *p*-toluenesulfonyl chloride in pyridine at 0 °C provided the tosylate **18** in quantitative yield. Conversion of the tosylate **18** to the corresponding nitrile **19** was accomplished by treatment with potassium cyanide in refluxing acetonitrile in the presence of 18-crown-6 ether.[11] Hydrolysis of the nitrile with aqueous methanolic potassium hydroxide, followed by ketal cleavage with aqueous acetic acid at 40 °C provided the keto acid **20**. The keto acid **20** isomerized to **21** slowly at room temperature or more rapidly under acid catalysis. Reduction of **20** with sodium borohydride

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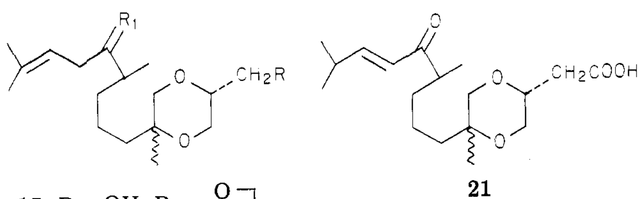

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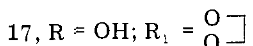

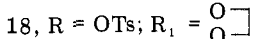

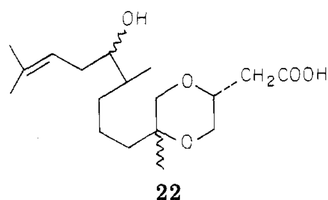

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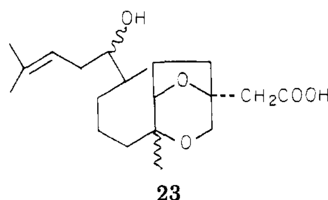

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gave the target compound **22**. The decision to synthesize **22** was based on the recently reported biological activity of the zoapatanol analogue **23**.[12] It may be noted that the analogue **22** differs from **23** only by the absence of an ethano bridge between C-3 and C-5.

Biological Results and Discussion

Daily sc administration of **12a** at 40 or 50 mg per guinea pig (five animals per dose) on days 12–14 postmating had no apparent effects on pregnancy. Similar observations were made following sc injection of **12a** at 50 or 75 mg per guinea pig (five animals per dose) on days 22–24 postmating. Compound **12b**, the C-2 β-methyl isomer of **12a**, also exerted no effects on pregnancy following sc injection of 35 mg per guinea pig per day on days 12–14 or 50 mg per guinea pig per day on days 22–24 postmating. Moreover, neigher **12a** nor **12b** caused a reduction in plasma progesterone levels at either period of pregnancy, suggesting a lack of luteolytic activity.

During the latter stages of this study, Hahn et al.[13] published data indicating that zoapatanol purified from *Montanoa tomentosa* caused resorption of implantation sites in guinea pigs when administered as a single intraperitoneal dose on day 22 of pregnancy. This led us to test our limited quantities of **21** and **22** by the intraperitoneal route on day 22 postmating. Single doses of 24 or 40 mg of **21** per guinea pig (one or two animals per dose) exerted no influence on pregnancy. At single doses of 42 or 70 mg per guinea pig, **22** caused death within a few hours of administration. Gross necropsy failed to reveal the cause of death.

Hahn et al.[13] reported that zoapatanol was partially active in the guinea pig at doses of 60 and 80 mg/kg of body weight, whereas the 100 mg/kg intraperitoneal dose was fully effective in causing resorption of implantation sites. In the present study, compounds were administered on a milligram per animal basis rather than on a milligram per kilogram basis. Since our females weighed from 500 to 700 g at the time of treatment, it was apparent that the doses employed in the present study were comparable to those at which zoapatanol was active.[13] Nontheless, the zoapatanol analogues evaluated in this study exhibited neither luteolytic nor antifertility properties.

Experimental Section

Chemical Syntheses. Mass spectra were recorded at 70 eV with a LKB-9000 mass spectrometer with GLC capability and an AEI MS-902; proton magnetic resonance spectra were obtained at 250 MHz on a Bruker 250 or at 60 MHz on a Varian EM-360 NMR instrument with tetramethyl silane as an internal standard. Chemical shifts are expressed in δ units. Gas–liquid chromatographic (GLC) analyses were performed on a Varian 1400 gas chromatograph with a 5-ft column of 3% Se-30 on Chromosorb W AWS and nitrogen carrier.

Analytical and preparative thin-layer chromatography (TLC) were carried out with EM Reagent silica gel 60 F-254 precoated silica gel plates with a surface thickness of either 0.25 or 2.0 mm. Silica gel TLC was routinely used to monitor the progress of the reactions. Analytical samples were prepared by vacuum distillation by using a Kugelrohr oven.

Reagent grade solvents were used directly, except for tetrahydrofuran (THF), which was distilled from lithium aluminum hydride immediately prior to use. Anhydrous sodium sulfate was used as a drying agent for solutions.

Methyl 2-Methyl-6-oxoheptanoate (6). Freshly cut sodium pieces (4.6 g, 0.20 g-atom) were added to 140 mL of absolute EtOH over a period of 30 min. After all the Na had dissolved, diethyl methylmalonate (**1**; 38.3 g, 0.220 mol) was added dropwise, and the mixture was heated at reflux for 5 min. The mixture was cooled and 5-chloro-2-pentanone ethylene ketal (**2**; 33 g, 0.20 mol) was added dropwise over a period of 20 min. The mixture was then refluxed for 18 h, cooled, and concentrated under reduced pressure. The residue was diluted with H_2O (200 mL) and extracted with $CHCl_3$ (3 × 100 mL). The organic layer was washed with H_2O (2 × 100 mL), dried, and concentrated under reduced pressure to afford 63 g of the crude diester **3** as a colorless oil.

A solution of 45 g of KOH in 50 mL of H_2O diluted with 500 mL of 95% EtOH was heated to a gentle reflux. The crude diester **3** was added to this solution over a period of 1 h and then refluxed for 4 h. The heterogeneous mixture was cooled, concentrated to ca. 100 mL under reduced pressure, and diluted with 500 mL of H_2O. Neutral components of the mixture were removed by shaking with Et_2O (2 × 150 mL). The cooled aqueous solution was acidified with concentrated H_2SO_4 and extracted with EtOAc (3 × 200 mL). The combined organic extracts were dried and concentrated under reduced pressure to afford 40 g of the diacid **4** as a gum, which solidified on standing.

The crude diacid 4 was decarboxylated by heating at 160 °C under a N_2 atmosphere for 1 h. After cooling, the monoacid **5** was dissolved in 200 mL of MeOH containing concentrated H_2SO_4 (2 mL), and the solution was refluxed for 4 h. Excess methanol was removed under reduced pressure. The residue was treated with H_2O (100 mL) and extracted with $CHCl_3$ (3 × 100 mL). The combined organic extracts were washed with H_2O (2 × 100 mL), dried, and concentrated under reduced pressure to afford 23.4 g (68% overall from **2**) of pure methyl 2-mthyl-6-oxoheptanoate (**6**) as an oil: bp 130 °C (25 mm); NMR ($CDCl_3$) δ 3.6 (s, 3, OMe), 2.05 (s, 3, $COCH_3$), 1.08 (d, J = 7 Hz, 3, $CHCH_3$). Anal. ($C_8H_{14}O_3$) C, H.

2-Methyl-6-oxoheptanoic Acid (5) from 2,6-Dimethylcyclohexanone (7).[14] To a stirred suspension of 2,6-dimethylcyclohexanone (**7**; 27 mL, 0.20 mol) in 300 mL of H_2O was added a solution of $KMnO_4$ (41 g, 0.26 mol) in 700 mL of H_2O over a period of 2 h. The mixture was stirred at room temperature overnight. A 5% aqueous solution of $NaHSO_3$ and concentrated HCl were added dropwise alternately until all the MnO_2 had dissolved to give a clear colorless solution. Excess concentrated HCl was then added to this solution to bring the pH to 1–2, and it was then extracted with EtOAc (6 × 500 mL). The combined

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organic extracts were concentrated to ca. 500 mL, washed with brine, and then extracted with a 10% Na_2CO_3 solution (3 × 100 mL). The aqueous extracts were cooled, neutralized with concentrated HCl, and extracted with EtOAc (5 × 100 mL). The organic extracts were washed with brine (100 mL), dried, and concentrated under reduced pressure to afford pure 2-methyl-6-oxoheptanoic acid (**5**; 21 g, 67%) as an oil, which was characterized as the ester **6** as described in the preceding experiment.

Methyl 2,6-Dimethyl-6,7-epoxyheptanoate (8). To a stirred suspension of NaH (50% dispersion in mineral oil, 5.76 g, 0.120 mol) in Me_2SO (125 mL) was added trimethyloxosulfonium iodide (28.6 g, 0.130 mol) over a period of 45 min, and stirring was continued for an additional 30 min. The keto ester **6** (17.2 g, 0.100 mol) was then added over a period of 30 min. The reaction mixture was heated at 60 °C for 30 min, poured into 200 mL of H_2O, and extracted with Et_2O (5 × 100 mL). The combined ether extracts were washed with H_2O (100 mL) and then with brine, dried, and evaporated to afford 11.46 g (61%) of pure **8** as an oil: bp 50 °C (0.2 mm); NMR ($CDCl_3$) δ 3.60 (s, 3, OMe), 2.47 (s, 2, OCH_2), 1.20 (s, 3, CCH_3), 1.07 (d, J = 7 Hz, 3, $CHCH_3$). Anal. ($C_{10}H_{18}O_3$) C, H.

Methyl 2,6-Dimethyl-6-(allyloxy)-7-hydroxyheptanoate (9). To a cooled (0 °C), stirred solution of epoxide **8** (1.86 g, 0.010 mol) in 5 mL of allyl alcohol was added 0.5 mL of 70% perchloric acid. The reaction mixture was stirred for 0.5 h, poured into 50 mL of H_2O, and extracted with Et_2O (3 × 50 mL). The combined ether extracts were washed with H_2O, dried, and evaporated under reduced pressure. Elution of the residue (2.2 g) from silica gel (100 g) with $CHCl_3$ afforded pure allyl ether **9** (1.2 g, 50%) as an oil: bp 105 °C (0.25 mm); NMR ($CDCl_3$) δ 5.5–6.2 (m, 1, $CH{=}CH_2$), 4.9–5.5 (m, 2, $CH{=}CH_2$), 3.82 (d, J = 6 Hz, 2, $OCH_2CH{=}CH_2$), 3.6 (s, 3, OMe), 3.4 (br s, 2, CH_2OH), 1.09 (s, 3, CH_3), 1.08 (d, J = 7 Hz, 3, $CHCH_3$). Anal. ($C_{13}H_{24}O_4$) C, H.

Methyl 2,6-Dimethyl-6-(allyloxy)-7-acetoxyheptanoate (10). A solution of **9** (500 mg) in pyridine (3 mL) and acetic anhydride (3 mL) was stirred at room temperature for 2 h, poured into ice–water, and extracted with Et_2O (3 × 25 mL). The organic phase was washed with H_2O and brine and dried (Na_2SO_4). The residue from the organic phase was purified by elution from silica gel (50 g) with 20% EtOAc in hexane to afford **10** (530 mg): bp 110 °C (0.05 mm); NMR ($CDCl_3$) δ 5.5–6.2 (m, 1, $CH{=}CH_2$), 4.9–5.3 (m, 2, $CH{=}CH_2$), 4.0 (s, 2, CH_2OAc), 3.82 (d, J = 6 Hz, 2, $OCH_2CH{=}CH_2$), 3.6 (s, 3, OMe), 2.0 (s, 3, CH_3CO_2), 1.16 (s, 3, CH_3), 1.06 (d, J = 7 Hz, 3, $CHCH_3$). Anal. ($C_{15}H_{26}O_5$) C, H.

Methyl 2,6-Dimethyl-6-[(2,3-epoxypropyl)oxy]-7-hydroxyheptanoate (11). To a stirred solution of the allyl ether **9** (1.60 g, 6.55 mmol) in 150 mL of CH_2Cl_2 was added *m*-chloroperbenzoic acid (80–85% pure, 1.80 g, 1.25 equiv) in portions. The reaction mixture was stirred for 20 h at room temperature and washed successively with a 10% sodium sulfite solution (100 mL), a 5% Na_2CO_3 solution (2 × 100 mL), and H_2O (2 × 100 mL). The dried CH_2Cl_2 solution was evaporated under reduced pressure to afford the epoxide 11 (1.62 g, 95% yield) as an oil: bp 130 °C (0.2 mm); NMR ($CDCl_3$) δ 3.64 (s, 3, OMe), 2.73 (d, J = 4 Hz, 2, epoxy CH_2), 1.12 (d, J = 7 Hz, 3, $CHCH_3$), 1.08 (s, 3, CH_3). Anal. ($C_{13}H_{24}O_5$) C, H.

2α-Methyl-2β-(4-carbomethoxypentyl)-5α-(hydroxymethyl)-1,4-dioxane (12a) and 2β-Methyl-2α-(4-carbomethoxypentyl)-5α-(hydroxymethyl)-1,4-dioxane (12b). To a solution of the epoxy ether 11 (0.840 g, 3.23 mmol) in 80 mL of $CHCl_3$ was added trifluoroacetic acid (0.273 mL, 1.10 equiv), and the reaction mixture was stirred at room temperature for 24 h. The $CHCl_3$ solution was then washed with H_2O (3 × 50 mL), dried, and evaporated under reduced pressure. The residual oil (0.9 g) was eluted from a prepacked column (Size C, LiChroprep Si60) with ethyl acetate–hexane (1:1). The separation was monitored by GC, and the fractions containing the less polar dioxane **12a** having a longer retention time on GC were pooled together and evaporated to afford 0.230 g of a colorless oil: bp 120 °C (0.05 mm); NMR ($CDCl_3$) δ 3.658 (s, 3, OMe), 2.66 (m, 1, $CHCH_3$), 1.266 (s, 3, CH_3), 1.145 (d, J = 7 Hz, 3, $CHCH_3$). Anal. ($C_{13}H_{24}O_5$) C, H.

The fractions containing the more polar dioxane **12b** having a shorter retention time than **12a** on GC were pooled together and evaporated to afford 0.230 g of a colorless oil: bp 120 °C (0.05 mm); NMR ($CDCl_3$) δ 3.659 (s, 3, OMe), 2.45 (m, 1, $CHCH_3$), 1.156 (d, J = 7 Hz, 3, $CHCH_3$), 1.033 (s, 3, CH_3). Anal. ($C_{13}H_{24}O_5$) C, H.

2α-Methyl-2β-[4-(carboxymethyl)pentyl]-5α-carboxy-1,4-dioxane (13). To a cooled, stirred solution of dioxane **12a** (0.015 g, 0.057 mmol) was added a stock solution of 0.7 M Jones reagent (0.20 mL, 2.3 equiv). After 30 min, the ice bath was removed, and stirring was continued for an additional 3 h. Acetone was removed under reduced pressure, and the residue was diluted with 5 mL of H_2O and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with H_2O, dried, and evaporated to give 0.0115 g of the acid **13**: bp 160 °C (0.1 mm); NMR ($CDCl_3$) δ 4.158 (d of d, J = 9.2 and 3.1 Hz, 1, H-5), 3.662 (s, 3, OMe), 2.442 (m, 1, $CHCH_3$), 1.257 (s, 3, CH_3), 1.149 (d, J = 7 Hz, 3, $CHCH_3$). Anal. ($C_{13}H_{22}O_6$) C, H.

Reduction of 13. A solution of **13** (40 mg, 0.15 mmol) in THF (2 mL) was treated with 1 M BH_3 in THF (0.2 mL). After stirring for 1.5 h at room temperature, the reaction mixture was diluted with water (5 mL) and extracted with ether (3 × 5 mL). Evaporation of the dry ether layer gave the product identical with **12a** by NMR and GC.

2β-Methyl-2α-[4-(carboxymethyl)pentyl]-5α-carboxy-1,4-dioxane (14). The oxidation of **12b** was carried out as described above to give 0.016 g of **14** from 0.020 g of **12b**: bp 160 °C (0.1 mm); NMR ($CDCl_3$) δ 4.14 (d of d, J = 9.2 and 3.1 Hz, 1, H-5), 3.661 (s, 3, OMe), 2.449 (m, 1, $CHCH_3$), 1.154 (d, J = 7 Hz, 3, CH_3), 1.08 (s, 3, CH_3). Anal. ($C_{13}H_{22}O_6$) C, H.

Reduction of 14. Treatment of **14** with BH_3 exactly as described above gave the product identical with **12b** by NMR and GC.

Phenyl γ,γ-Dimethylallyl Ether.[9] To a stirred suspension of sodium hydride (50% dispersion in mineral oil, 9.66 g, 0.20 mol) in dry DMF (300 mL) was added dropwise under cooling a solution of phenol (18.96 g, 0.20 mol) in DMF (180 mL). After stirring for 15 min at room temperature, γ,γ-dimethylallyl bromide (30.0 g, 0.20 mol) was added dropwise to the solution, and stirring was continued for 1.5 h. The mixture was then poured into 1500 mL of H_2O and extracted with petroleum ether (3 × 300 mL). The combined petroleum ether layers were washed with 10% NaOH (1 × 150 mL), H_2O (2 × 150 mL), and brine (1 × 150 mL), dried, and concentrated under reduced pressure to afford 27.6 g (85%) of the product as a pale yellow oil:[11] NMR ($CDCl_3$) δ 7.32–6.60 (m, 5, ArH), 5.40 (br t, 1, $C{=}CH$), 5.41 (d, J = 6 Hz, 2, CH_2), 1.72 (s, 6, CH_3).

2α-Methyl-2β-(4,8-dimethyl-5-oxo-7-nonenyl)-5α-(hydroxymethyl)-1,4-dioxane (16). To a solution of 5 mL of toluene and 2.4 mL of dihydropyran was added **12a** (0.25 g, 0.96 mmol) and TsOH (13.1 mg). After stirring for 1 h at room temperature, the solution was diluted with 25 mL of ether and washed with saturated $NaHCO_3$ (3 × 15 mL), H_2O (1 × 15 mL), and brine (1 × 15 mL), dried, and concentrated under reduced pressure.

The crude tetrahydropyranyl (THP) ether was combined with 5% methanolic NaOH (5 mL) and stirred at room temperature for 15 h. The solution was concentrated under reduced pressure, diluted with 25 mL of H_2O, and extracted with ether (3 × 5 mL). The aqueous phase was then cooled by an ice bath and acidified to pH 2 with concentrated HCl. The solution was immediately extracted with ethyl acetate (6 × 25 mL), dried, and concentrated under reduced pressure to afford 0.32 g of **15**, which was used without further purification in the next step.

A solution of phenyl γ,γ-dimethylallyl ether (0.95 g, 0.006 mol) in THF (5 mL) was added dropwise to a stirred suspension of Li wire (1.00 g, 0.15 g-atom) in THF (5 mL). After stirring for approximately 2 h, a deep red color developed, and stirring was continued for an additional 1 h.

To a stirred suspension of LiH (30% in oil, 0.20 g, 0.009 mol) in THF (10 mL) was added dropwise a solution of crude **15** (0.32 g, 0.001 mol) in THF (10 mL). After refluxing for 2 h, the reaction mixture was cooled (0 °C), and the above γ,γ-dimethylallyllithium solution was added via a syringe. When the addition was complete, the cooling bath was removed, and stirring was continued for 19 h at room temperature. The deep red solution was subsequently poured into 100 mL of saturated NH_4Cl solution, the two layers were separated, and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ (2 × 50 mL), 10% NaOH (1 × 50 mL), H_2O (1 × 50 mL), and brine (1 × 50 mL), dried, and concentrated under

reduced pressure to afford 0.73 g of yellow oil.

The crude oil was combined with 45 mL of a 2:1 mixture of acetic acid and water and heated at 40 °C for 2 h. The solution was then cooled and diluted with 25 mL of H_2O, and the acid neutralized with solid Na_2CO_3. The neutral solution was extracted with ether (3 × 50 mL), and the combined extracts were washed with saturated $NaHCO_3$ (2 × 50 mL), H_2O (1 × 50 mL), and brine (1 × 50 mL), dried, and concentrated under reduced pressure to afford 0.53 g of yellow oil. This oil was chromatographed on 20 g of silica gel with 30% ethyl acetate in toluene, providing 0.16 g of **16** for a total yield of 56%: bp 140 °C (0.01 mm); NMR ($CDCl_3$) δ 5.20 (br t, 2, C=C*H*), 3.08 (d, *J* = 6 Hz, 2, CH_2), 1.69 and 1.57 [s, 6, $(CH_3)_2C$], 1.22 and 1.00 (s, 6, CH_3), plus other unresolved absorptions. Anal. ($C_{17}H_{30}O_4$) C, H.

2α-Methyl-2β-[4,8-dimethyl-5-(ethylenedioxy)-7-nonenyl]-5α-(hydroxymethyl)-1,4-dioxane (17). A solution of the ketone **16** (0.79 g, 2.70 mmol) and TsOH (40 mg) in freshly distilled ethylene glycol (50 mL) was slowly distilled under reduced pressure [60 °C (0.4 mm)] for 1.5 h. The solution was then cooled and poured into 150 mL of saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 50 mL), and the extract was dried. Concentration under reduced pressure afforded 0.87 g (96%) of pale yellow oil, which was used without purification in the next step: NMR ($CDCl_3$) δ 5.08 (br t, 1, C=C*H*), 3.85 (s, 4, ketal), 1.67 and 1.59 [s, 6, $(CH_3)_2C$=], 1.22 (s, 3, CH_3), 0.88 (d, *J* = 6 Hz, 3, CH_3). MS Calcd for $C_{19}H_{35}O_5$ (M^+ + 1): 343.2484. Found: 343.2487.

2α-Methyl-2β-[4,8-dimethyl-5-(ethylenedioxy)-7-nonenyl]-5α-(cyanomethyl)-1,4-dioxane (19). A cooled (0 °C) solution of **17** (0.87 g, 2.5 mmol) and TsCl (0.97 g) in dry pyridine (13 mL) was allowed to stand in the refrigerator for 15 h. The reaction mixture was then diluted with ethyl acetate (100 mL) and 5% $NaHCO_3$ (100 mL) and stirred for 5 min. After separation of the layers, the aqueous layer was extracted with $CHCl_3$ (100 mL). The combined organic layers were dried and concentrated to afford the tosylate **18** (1.2 g, 100%).

The crude tosylate was combined with dry KCN (0.33 g), 18-crown-6 ether (0.2 g), and acetonitrile (8 mL) and refluxed for 46 h. The mixture was then cooled, diluted with 30% ethyl acetate in hexane, and filtered. The residue from the filtrate was then eluted from silica gel (10 g) with 30% ethyl acetate in hexane. Concentration of the filtrate provided the nitrile **19** (0.77 g, 86%): NMR ($CDCl_3$) δ 5.08 (br t, 1, C=C*H*), 3.86 (s, 4, ketal), 1.67 and 1.59 [s, 6, $(CH_3)_2C$=], 1.26 (s, 3, CH_3), 0.88 (d, *J* = 6 Hz, CH_3). MS Calcd for $C_{20}H_{33}NO_4$: *m/e* 351.2409. Found: *m/e* 351.2402.

2α-Methyl-2β-(4,8-dimethyl-5-oxo-7-nonenyl)-5α-(carboxymethyl)-1,4-dioxane (20). A solution of the nitrile **19** (760 mg) in MeOH (7.0 mL) and 10 N aqueous KOH (7.0 mL) was refluxed for 15 h under N_2. The reaction mixture was then diluted with H_2O (150 mL) and washed with ether (2 × 50 mL). The aqueous layer was cooled, acidified (pH 2), and extracted with EtOAc (5 × 50 mL). The organic layer was shaken with brine, dried, and evaporated to afford the crude ketal acid (0.68 g): NMR ($CDCl_3$) δ 5.06 (br t, 1, CH=C*H*), 3.86 (s, 4, ketal), 2.4 (d, *J* = 6 Hz, 2, C*H*$_2$COOH), 1.66, 1.61 [s, 6, $(CH_3)_2C$=], 1.23 (s, 3, CH_3), 0.85 (d, *J* = 6 Hz, 3, CH_3).

The crude ketal acid was dissolved in glacial HOAc (28 mL) and water (14 mL) and heated at 40 °C for 2 h. The reaction mixture was then diluted with H_2O (200 mL) and extracted with EtOAc (3 × 50 mL). The organic layer was worked up as above to give **20** (0.57 g) as an oil: bp 170 °C (0.05 mm); NMR ($CDCl_3$) δ 5.18 (br t, 1, CH=C*H*), 2.38 (d, *J* = 6 Hz, 2, C*H*$_2$COOH), 1.68, 1.58 [s, 6, $(CH_3)_2C$=], 1.22 (s, 3, CH_3), 1.03 (d, *J* = 6 Hz, 3, CH_3). Anal. ($C_{18}H_{30}O_5 \cdot H_2O$) C, H.

2α-Methyl-2β-(4,8-dimethyl-5-oxo-6-nonenyl)-5α-(carboxymethyl)-1,4-dioxane (21). A solution of **20** (5.0 mg) in MeOH (2 mL) and 2 N HCl (0.5 mL) was stirred at room temperature for 3 h. The solvents were removed under vacuum, and the residue was eluted from silica gel (1.0 g) with 40% EtOAc in hexane to afford **21** (3.0 mg): bp 170 °C (0.05 mm). The formation of **21** was also observed when **20** was allowed to stand at room temperature for several days: NMR ($CDCl_3$) δ 6.82 (d of d, *J* = 16 and 2 Hz, 1, H-7′), 6.15 (d, *J* = 16 Hz, 1, H-6′), 1.33 [apparent s, 6, $(CH_3)_2CH$], 1.17 (d, *J* = 6 Hz, 3, CHC*H*$_3$), 1.00 (s, 3, CH_3). Anal. ($C_{18}H_{30}O_5 \cdot H_2O$) C, H.

2α-Methyl-2β-(4,8-dimethyl-5-hydroxy-7-nonenyl)-5α-(carboxymethyl)-1,4-dioxane (22). To a cooled solution of the crude keto acid **20** (0.57 g) in absolute ethanol (40 mL) was added $NaBH_4$ (600 mg) in small portions. After stirring for 5 min, the ice bath was removed, and stirring was continued for an additional 1.5 h. The reaction was quenched by adding 10 mL of acetone and stirring for 30 min. Solvents were removed under vacuum, and the residue was treated with 2 N HCl (75 mL). The aqueous solution was extracted with ether (3 × 50 mL), and the ether layer was dried and evaporated to give 400 mg of crude product, which was eluted from silica gel (15 g) with 60% EtOAc in hexane to give **22** (0.162 g, 41%) as an oil: bp 190 °C (0.05 mm); NMR ($CDCl_3$) δ 5.06 (br t, 1, CH=C*H*), 2.41 (d, *J* = 6 Hz, 2, C*H*$_2$COOH), 1.66, 1.60 [s, 6, $(CH_3)_2C$=], 1.23 (s, 3, CH_3), 0.84 (d, *J* = 6 Hz, 3, CH_3). Anal. ($C_{18}H_{32}O_5$) C, H.

Biological Procedures. Young adult Duncan–Hartley guinea pigs were purchased from Dutchland Laboratories (Denver, PA). Female guinea pigs were bred with proven fertile males during cyclic or postpartum estrus. Day 1 of pregnancy was defined as the day a copulatory plus was observed. Propylene glycol (control vehicle) or test compounds were injected subcutaneously on days 12–14 or 12–24 or intraperitoneally on day 22 postmating. In order to assess luteolytic activity, blood was drawn by cardiac puncture prior to the first injection and 24 h after the final injection. Plasma was obtained by centrifugation and stored at −20 °C. Plasma progesterone levels were determined by radioimmunoassay.[15,16] Treated females were sacrificed on day 25 or 35 postmating, the gravid uterus was weighed, and fetuses and/or implantation sites were counted. The fetuses were excised, examined, and weighed individually. The treated female was considered pregnant if her uterus contained one or more live fetuses.

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