Approaches to the Synthesis of Ring C Transposed Progesterone Analogues.[1] *rac*-7β,15α-Ethano-11,12-seco-11,19-bisnor-17α-pregn-4-ene-3,20-dione and *rac*-4,4-Dimethyl-7,7-(ethylenedioxy)-(4aα,4bβ,8aα,10aβ)-perhydro-3-phenanthrenone

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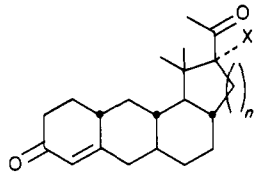
In an approach to the synthesis of ring C transposed progesterone derivatives *rac*-4,4-dimethyl-7,7-(ethylenedioxy)-(4aα,4bβ,8aα,10aβ)-perhydro-3-phenanthrenone (30) and *rac*-7β,15α-ethano-11,12-seco-11,19-bisnor-17α-pregn-4-ene-3,20-dione (28) have been synthesized from 6-methoxytetralone. The structure of 28 has been established by X-ray crystallographic analysis.

For some time we have been concerned with the structure–activity relationships of progesterone and its analogues.[4-6] Currently, we are attempting to determine the manner by which the C ring contributes to the biological activity of these compounds. To achieve this goal, we required a supply of compounds 1 and 2 which we regard as ring C transposed analogues of 19-norprogesterone or of 17α-acetoxy-19-norprogesterone: We report below the results of our initial attempts to synthesize 1 and 2.



1, *n* = 1, X = H or OAc
2, *n* = 2, X = H or OAc

Previous studies support the view that the β-face of gestogens interacts with their receptor, that particularly important contributions to binding come from interactions of the receptor with the A ring enone and a C(17β) alcohol or C(20) ketone and that the fit between the receptor and the gestogen is tight near C(10β) but is less restrictive near C(13β).[5,6] More recently, Kontula et al. reported[7] that gestogen–receptor interaction involves a free energy change of approximately 12 kcal/mol and about half of this is caused by polar interactions involving the A ring enone and the C(20) or C(17β) oxygen functions. The remaining binding energy was attributed to hydrophobic interactions and is far less than the maximum amount of hydrophobic binding energy which might be generated by molecules of this sort.[7]

In view of the above, we inferred that the contributions of the B and C rings to the binding of gestogens to their receptor should consist of the following factors: (1) These rings serve to maintain the correct geometrical relationship between the polar substituents in the A and D rings. (2) They may contribute a substantial portion of the hydrophobic binding energy discussed above.

In structures 1 and 2, the transposed C ring serves to maintain a geometrical relationship between the AB ring system and the D ring similar to that of the natural steroids. Models indicate that the principal difference caused by cleaving the C ring of a steroid while introducing a C(7β),C(15α) ethano bridge is to rotate the C(17)–C(20) bond slightly clockwise (viewed from above). In the expectation that 1 would show this deformation, we have chosen also to synthesize 2 in which the corresponding bond is rotated slightly counterclockwise. While neither 1 nor 2 should have its C(17)–C(20) bond in the exact orientation of that of progesterone, it is our hope that the receptor will be able to accommodate at least one of these structures.

In structures 1 and 2 only C(11) of progesterone has been deleted. The high affinity for the progesterone receptor reported[8] for gestogens substituted at the 11β-position by bulky substituents indicates that the receptor probably is not in close contact with the gestogen at C(11β) and therefore that C(11) probably contributes little hydrophobic binding energy. Moreover, any loss in binding affinity which results from deletion of C(11) may be compensated for by new interactions involving the C(7β),C(15α) ethano bridge.

Our assumption that the receptor can tolerate the bulk of the 7β,15α-ethano bridge is based solely on a report that 7β-methylprogesterone is as active as progesterone.[9] Initially, we had planned to rigorously test the point by synthesizing and bioassaying 7β,15α-ethanoprogesterone, but we found that compound to be a more elusive target than 1 or 2.[10]

Wani et al. have reported[11] the synthesis and bioassay of what may be regarded as a ring B transposed progesterone analogue. The low affinity which this substance

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(4) Solo, A. J.; Kumar, V.; Alks, V.; Duax, W. L. *J. Med. Chem.* **1979**, *22*, 129.
(5) Solo, A. J.; Singh, B. *J. Med. Chem.* **1967**, *10*, 1048.
(6) Solo, A. J.; Kapoor, J. N. *J. Med. Chem.* **1973**, *16*, 270.
(7) Kontula, K.; Janne, O.; Vihko, R.; Jager, E.; Visser, J.; Zeelen, F. *Acta Endocrinol. (Copenhagen)* **1975**, *78*, 574.
(8) (a) Belanger, A.; Philibert, D.; Teutsch, G. *Steroids* **1981**, *37*, 361. (b) Teutsch, G.; Belanger, A.; Philibert, D.; Tournemine, C. *Steroids* **1982**, *39*, 607.
(9) (a) Salhanick, H. A.; Swanson, J. In *Progesterone*; Barnes, A. C., Ed.; Brook Lodge Symposium; Brooke Lodge: Augusta, MI, 1961; pp 119–132. (b) Myake, T.; Rooks, W. H., II In *Methods in Hormone Research Vc*; Dorfman, R. I., Ed.; Academic: New York, 1966; p 133.
(10) Unpublished work.
(11) Wani, M.; Rector, D. H.; White, D. H.; Pitt, C. G.; Kimmel, G. L. *J. Med. Chem.* **1977**, *20*, 547.

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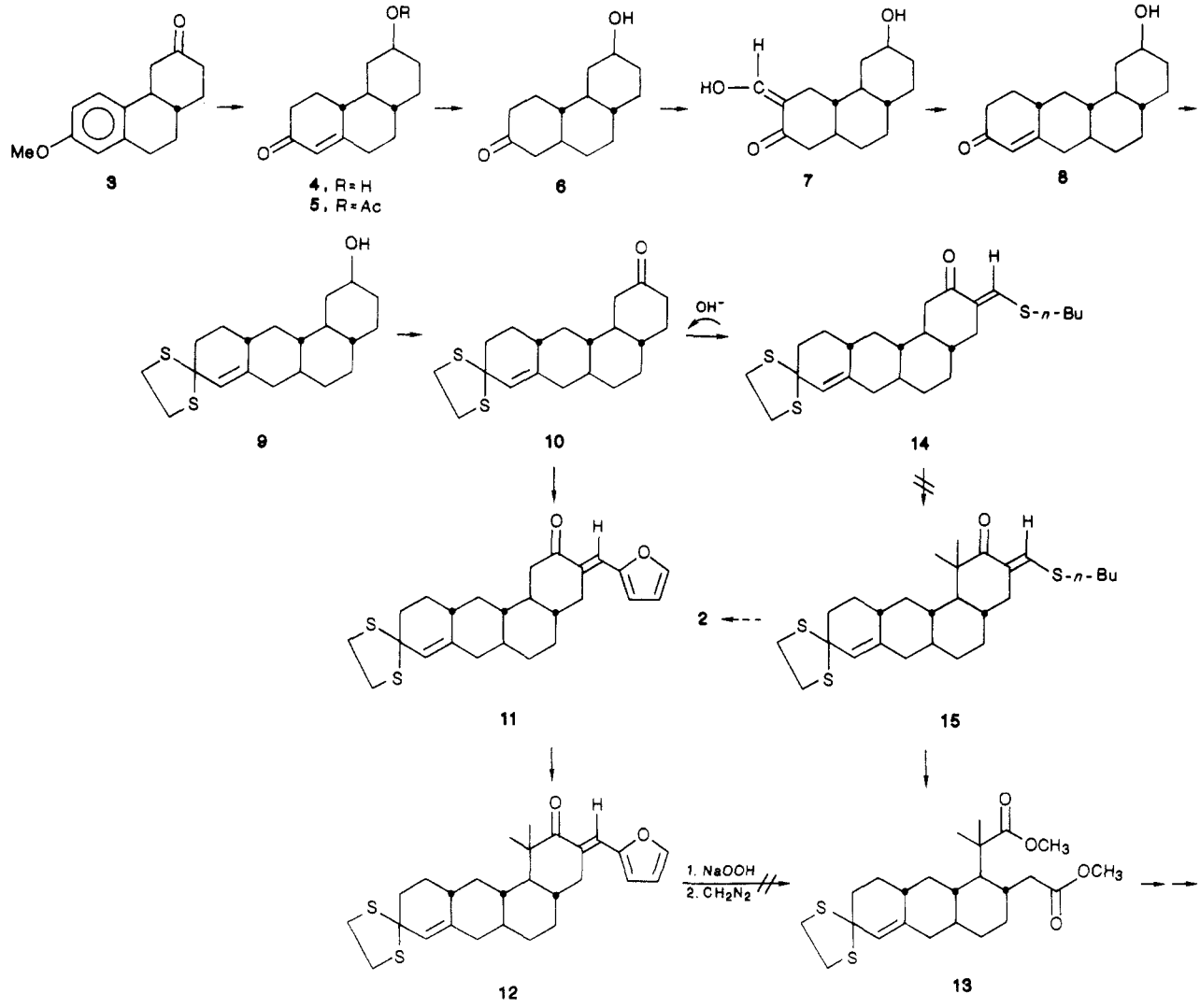
Scheme I



had for a progesterone receptor does not argue for or against the probability of **1** and/or **2** having such an affinity.

Our choice of a synthetic route to **1** and **2** was guided by a desire, in so far as possible, to use a common path to these two compounds, by a wish to minimize stereochemical ambiguities, and by a need to minimize the time required to get small testable quantities of **1** and **2**. With the exception of ambiguity with respect to the stereochemistry of the acetyl side chain of **1**, Scheme I appeared to meet these criteria and therefore was chosen.

The tricyclic ketone **3** was prepared by the literature procedures.[12,13] Lithium–ammonia reduction of **3** was followed by acid hydrolysis to form enone alcohol **4**, which was acetylated to form **5** in a yield of 66%. Reduction of enone **5** with lithium, under the conditions of Dryden,[14] reproducibly afforded **6** in yields of 75% on a scale of 10–15 g, but the yield declined if the scale was increased. Robinson annelation converted **6** via the hydroxymethylene derivative **7** to tetracyclic enone alcohol **8** in a yield of 60%.

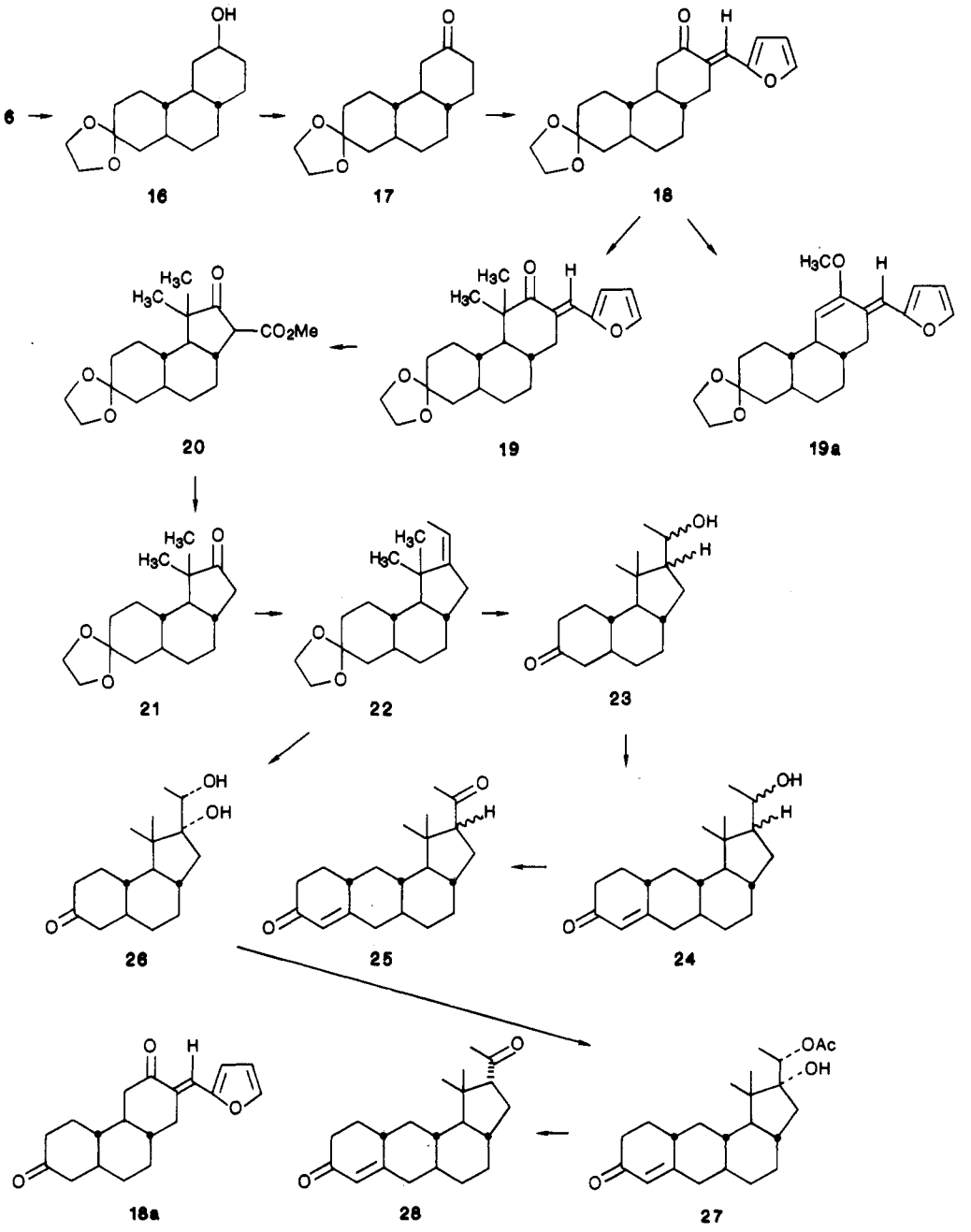
To convert **8** to **1** or **2**, it was necessary to protect the enone moiety. This most readily could be done by converting the ketone to a ketal or thioketal. The latter was chosen because thioketals are generally considered to be more stable than ketals and because use of a thioketal avoids problems arising from probable migration of the 7α,8-double bond. Thioketal **9** formed from **8** in 96% yield. The hydroxyl group of **9** was oxidized by pyridium chlorochromate to afford ketone **10** in a yield of 78%.

In an attempt to synthesize **1** from **10**, we chose to follow a sequence developed by Johnson for his synthesis of testosterone.[15] Furfurylidine ketone **11** formed readily, but dimethylation of **11** at C(1) proved to be very difficult. The alkylation could be carried out in a yield of 55% by running the reaction in benzene for 8 days at room temperature in the presence of large excesses of potassium hydride and methyl iodide. Attempts to accelerate the reaction by raising the temperature or by increasing the polarity of the solvent resulted in formation of polar byproducts and decreased the yield of **12**. Reaction of **12** with alkaline hydrogen peroxide resulted in a multicomponent mixture. Analysis of NMR spectra indicated that substantial attack on the unsaturated thioketal has occurred. None of the desired product, **13**, could be isolated.

We then attempted to convert **10** to D-homo analogue **2**. To accomplish this, we needed to reversibly block the 3-position of ketone **10** toward alkylation. To that end the

(12) Fahrenholtz, K. E.; Capomaggi, A.; Lurie, M.; Goldberg, M. W.; Kierstead, R. W. *J. Med. Chem.* **1966**, *9*, 304.
(13) Johns, W. F.; Salamon, K. W. *J. Org. Chem.* **1979**, *44*, 958.
(14) Dryden, H. L. In *Organic Reactions in Steroid Chemistry*; Fried, J., Edwards, J., Eds.; Van Nostrand Reinhold: New York, 1972; Vol. I, pp 37–43.
(15) Johnson, W. S.; Bannister, B.; Pappo, R.; Pike, J. E. *J. Am. Chem. Soc.* **1956**, *78*, 6354.

Scheme II



(*n*-butylthio)methylene[16] derivative **14** was prepared. However, repeated attempts to alkylate **14** resulted in no more than a trace of **15** being formed.

Because of the problems described above, we decided to modify the synthesis to use a ketal in place of the thioketal, but we chose to introduce it as a protecting group for the saturated tricyclic ketone **6** in order to avoid the problem of double bond migration. As shown in Scheme II, **6** was converted, in high yield, via hydroxy ketal **16** and ketone ketal **17** to the furfurylidine blocked ketone **18**. Reaction of **18** in benzene with methyl iodide and potassium hydride, under conditions used to form **12** resulted in recovery of starting material contaminated by various byproducts. Reaction in tetrahydrofuran or glyme gave the desired product plus substantial amounts of O-alkylation product. However, reaction of **18** in dioxane for 44 h at room temperature with 15 equiv each of potassium hydride and methyl iodide gave the *gem*-dimethyl compound **19** in 60% yield. Ozonolysis of **19** gave a dicarboxylic acid, which was esterified with diazomethane. The diester cyclized to afford keto ester **20** in 58% yield. The keto ester decarboxylated in 92% yield to form **21** when it was heated with lithium chloride in dimethyl sulfoxide.[18,19] A Wittig reaction converted **21** to the ethylidene derivative **22** in 87% yield. The latter compound could be hydroborated with oxidative workup and then hydrolyzed to form keto alcohol **23**. An A ring was added to **23** by a Robinson annelation sequence using conditions similar to those employed to convert **6** to **8**. Oxidation of the alcohol moiety of **24** with pyridinium chlorochromate converted it to the ketone of **25**.

(16) Ireland, R.; Marshall, J. *J. Org. Chem.* **1962**, *27*, 1615, 1620.
(17) Johnson, W. S.; et al. *J. Am. Chem. Soc.* **1956**, *78*, 6331, 6339, 6347.
(18) Krapcho, A.; Weimaster, J.; Eldridge, E.; Jahngen, A.; Lorey, A.; Stephens, N. *J. Org. Chem.* **1978**, *43*, 138.
(19) In our hands, decarboxylation catalyzed by DBN gave far inferior yields to that obtained from the Krapcho procedures.

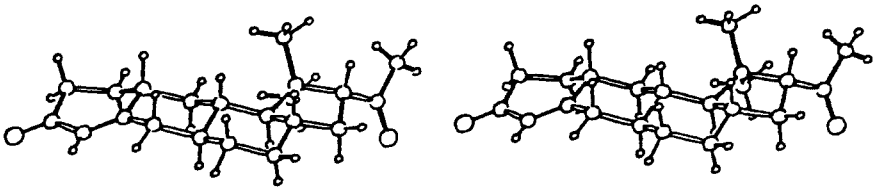
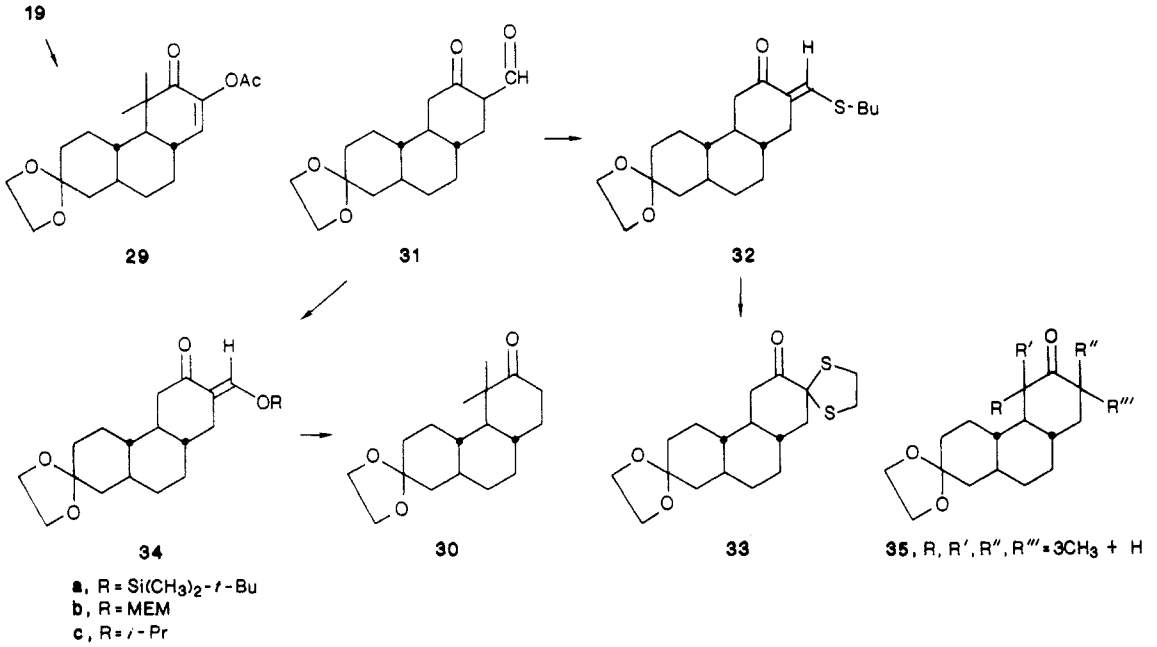


Figure 1. Stereo view of 7,15-ethano-9,12-seco-11,19-dinor-17α-pregn-4-ene-3,20-dione.

Scheme III



CPK molecular models of **22** indicated that the β-face of the ethylidene side chain was almost as accessible to attack as the α-face. However, **23** and **24** seemed by TLC and NMR (60 MHz) to be essentially single isomers. Later reexamination of **23** at 90 MHz showed a doubling of the *gem*-dimethyl peaks. In contrast, at 60 MHz, **25** showed a doubling of the peaks attributed to the *gem*-dimethyl groups with evidence described below permitting the assignment of peaks at δ 1.01 and 1.20 to the isomer with the α-acetyl group and by default allowing assignment of peaks at 0.85 and 1.39 to the β-acetyl compound.

Because osmium tetraoxide is a more bulky reagent than diborane, we hoped that it might be more stereoselective than diborane in attacking the ethylidene moiety of **22**. Hydrolysis of the ketal of **22** could be followed by osmylation to form **26**, but osmylation of **22** followed by cleavage of the osmate ester and then by hydrolysis of the ketal proved to be a more efficient route to **26**. Essentially, the same procedure as had been used to convert **23** to **24** was used to add the A ring onto **26**. The crude product was a foam but acetic anhydride–pyridine acetylated the secondary alcohol to afford crystalline **27**. Serini reaction of **27** gave **28**. NMR spectra showed that the crude **28** was slightly contaminated (~10%) by its side chain epimer, but this contaminant was removed by a recrystallization from ethyl acetate. The structure of **28** (Figure 1) was established by the X-ray crystallographic analysis reported below. Because the Serini reaction[36] inverts the stereochemistry of the side chain, this evidence establishes that the α-face of the ethylidene portion of **22** is slightly more accessible than the β-face.

In an approach to the D-homo compound **2**, as shown in Scheme III, the furfurylidine ketone **19** was ozonized. The resulting ozonide was reduced in situ with triphenylphosphine. The crude diosphenol which resulted was acetylated to form **29**. Attempts to convert **29** to **30** either by metal–ammonia reduction or by catalytic hydrogenation followed by metal–ammonia reduction were unsuccessful.

The formyl derivative **31** of **17** was prepared and used in a number of approaches to **30**. Initially, we tried to synthesize the (*n*-butylthio)methylene derivative **32** in order to alkylate it and to hydrolyze the dialkylation product to **30**. Because of the ease with which we had prepared **14**, we were surprised to find that **32** was too unstable to purify. An attempt to alkylate a crude preparation of **32** failed. The thioketal **33** was readily prepared from **31**, but, as expected,[20] it could not be C-alkylated.

Conditions were found for preparing the *tert*-butyldimethylsilyl enol ether **34a**. Attempts to obtain an analytical sample of **34a** resulted in a loss of the silyl group, but NMR and TLC indicated that **34a** was pure enough to use in the alkylation step. The alkylation was run in tetrahydrofuran in the presence of a large excess of both potassium hydride and methyl iodide. The crude product was immediately hydrolyzed by reaction with tetrabutylammonium fluoride. Rapid flow linear gradient chromatography resulted in isolation of the desired compound **30** in 15–20% yield based on starting ketone **17**. A trimethyl analogue **35** was isolated in 25% yield; 5% of starting ketone **17** and 11% of unidentified more polar substances also were isolated. The quantity of trimethyl compound **35** isolated seems too great to have resulted from alkylation of **17** or **31** possibly present as impurities in the starting material. It probably resulted from loss of the blocking group during the course of the alkylation reaction. Trimethylsilyl ethers are known[21] to be suscep-

(20) References 16 and 18.

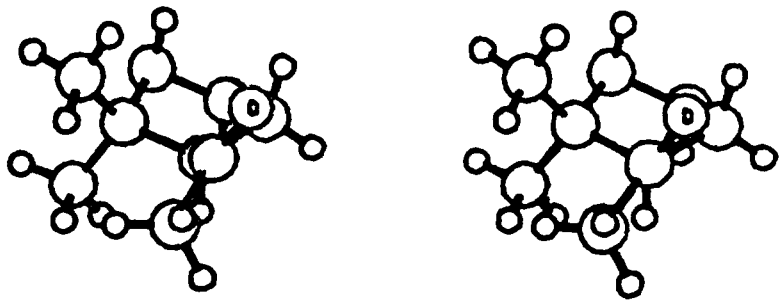


Figure 2. Newman projection in stereo illustrating the staggered conformation of substituents on C(17) and C(20) and the preferred orientation of the carbonyl oxygen toward the α face of the steroid.

tible to attack by hydride and while *tert*-butyldimethylsilyl ethers are reported[21,22] to be less reactive toward base than trimethylsilyl ether, they are not inert. Moreover, the fact that **34a** is both an enol ether and an enone may contribute to its lack of stability.

In an attempt to increase the yield of **30**, we studied variants on structure **34** in the hope of finding a blocking group that would be stable to our alkylation procedure. Reaction of **31** with (methoxyethoxy)methyl chloride in the presence of triethylamine[23] resulted in recovery of starting material, but the sodium salt of **31** reacted with (methoxyethoxy)methyl chloride in tetrahydrofuran to give a mixture of C- and O-alkylated material in a ratio of 7 to 3. Because of the poor ratio of O- to C-alkylation, we shifted to a study of the isopropyl enol ether **34c**. Reaction of **31**, in acetone, with potassium carbonate and isopropyl iodide gave C- and O-alkylated material in a ratio of 1 to 3 (NMR estimate). The enol ether **34c** was isolated in a yield of 58%. Several attempts to alkylate **34c** failed to result in isolation of any clean product.

Currently, we are building up additional stocks of intermediates with the intention of completing the synthesis of compounds **1** and **2**.

The crystallographically observed conformation of 7,15-ethano-9,12-seco-11,19-dinor-17α-pregn-4-ene-3,20-dione (**28**) is illustrated in Figure 1. The bond lengths and angles are unexceptional. The A ring has a conformational midway between a 1α-sofa and a 1α,2β-half chair.[24] The B ring and the C(7)–C(15) containing ring have normal chair conformations. The D ring has a 15β-envelope conformation, which is rarely observed in normal steroid structures. The orientation of the 17α-side chain simultaneously minimizes eclipsing of bonds to the C(17) and C(20) atoms and nonbonding interactions between the substituents on the C(13) and C(20) atoms (Figure 2). The side chain takes up a conformation in which the carbonyl oxygen is oriented toward the β-face [C(16)–C(17)–C(20)–O(20) = 25°]. The only other crystallographic determinations of steroids having 17α-acetyl substituents provide three examples of a similar orientation [C(16)–C(17)–C(20)–O(20) = 33°, 33°, and 42°][25,26] indicating a strong preference for this orientation. The overall conformation of **28** is compared with that of 19-nonprogesterone[27] in Figure 3. The similarity in the overall conformations of the A and B rings is evident in **3a**. The displacement of the D ring and the 17-substituent is clearly illustrated in **3b**.

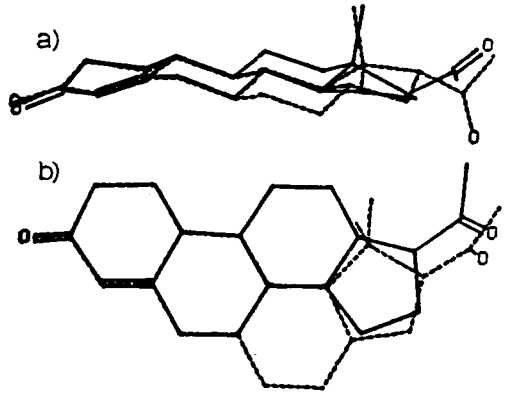


Figure 3. Comparison of the overall conformation of **28** and 19-nonprogesterone. The fit was achieved by least-squares minimization of displacement of atom C(1) to C(10) and C(14) in the two structures.

Experimental Section

NMR spectra were obtained on a Varian A-60 or T-60A and are reported in parts per million downfield from Me_4Si. Infrared spectra were recorded on a Perkin-Elmer 297 or a Berkman IR-8 spectrometer or on a Nicolet Model 4000 Fourier transform infrared spectrophotometer. Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA.

Rapid linear gradient chromatography consisted of chromatography over Woelm silica gel, mesh 70–230, using a linear gradient and a flow rate of approximately 10 mL/min for a column having a diameter of 1 cm. The more polar solvent mixture used to establish the gradient is one in which the desired compound has an R_f of approximately 0.3 on TLC on silica gel plates.[28]

3-Acetoxy-1,2,3,4,4aα,4bβ,5,9,10,10aβ-decahydro-7-phenanthrenone (5). Into a 5-L three-necked round-bottom flask, fitted with a dry ice container was distilled 1.5 L of ammonia. To this was added 42 g of **3**[12,13] (0.184 mol), dissolved in 320 mL of dry tetrahydrofuran and 200 mL of isopropyl alcohol, over 20 min. Then, very carefully, 40 g of sodium (1.73 mol) was added as fast as the reaction would allow. This mixture was stirred until the blue color faded (1 h). Then 60 mL of methanol was added. After evaporation of the ammonia, the residue remaining was partitioned between water and benzene. The organic layer was collected and concentrated to yield a yellow-white solid. The solid was dissolved in 600 mL of methanol, 40 mL of water, and 40 mL of hydrochloric acid and stirred for 2.5 h at room temperature. The red solution was concentrated to one-half its original volume, diluted with water, and extracted with methylene chloride. The organic layer was dried and concentrated to yield a yellow solid,

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(22) Corey, E. J.; Venkateswarlu, *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(23) Corey, E. J.; Gras, J.; Ubrich, P. *Tetrahedron Lett.* **1976**, 809.
(24) Duax, W. L.; Weeks, C. M.; Rohrer, D. C. In *Topics in Stereochemistry*; *Allinger*, N. L., Elied, E. L., Eds.; Wiley: New York, 1976; Vol. 9, pp 271–381.
(25) Huber, C. P.; Ahmed, F. R. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1984**, *C40*, 703.
(26) Galdecki, Z.; Grochulski, P.; Wawrzak, Z.; Duax, W. L.; Strong, P.; Segaloff, A. *Steroids*, in press.
(27) Duax, W. L.; Rohrer, D. C.; Strong, P. D. *Acta Crystallogr., Sect. B* **1979**, *B35*, 2741.

(28) The method is a variation on a procedure given us by James Matson of Bristol Laboratories, Syracuse, NY.

which proved difficult to crystallize. The solid was dissolved in 50 mL of pyridine, and 50 mL of acetic anhydride was added. After being stirred overnight, the reaction mixture was diluted with water, extracted with methylene chloride, and washed with 10% hydrochloric acid and finally with water. The solution was dried ($MgSO_4$) and concentrated to give a yellow solid. Recrystallization from acetone–hexanes gave **5** in a yield of 32.6 g (66%); mp 125–127 °C. Recrystallization gave an analytical sample, mp 127–129 °C: NMR ($CDCl_3$) δ 2.03 (s, 3 H), 4.70 (m, 1 H), 5.83 (s, 1 H); IR ($CHCl_3$) ν_{max} 1725, 1665 cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.17; H, 8.47.

3-Hydroxy-(4aα,4bβ,8aα,10aβ)-perhydro-7-phenanthrenone (6). Into a 2-L three-necked round-bottom flask, equipped with a dry ice condensor, was distilled 1 L of ammonia, under argon. To this was added 2.14 g of lithium (0.30 mol) followed by 13.4 g of **5** (0.05 mol) dissolved in 350 mL of dry tetrahydrofuran and 5.86 mL of *tert*-butyl alcohol (0.05 mol). The blue solution was stirred, under argon, for 50 min, quenched with ethylene dibromide, and then a solution of 53 mL of methanol and 13 mL of acetic acid was added. The flask was warmed with a heating mantle to evaporate the ammonia, and the residue was diluted with water and extracted with methylene chloride. The organic layer was dried and concentrated to yield an oil, which was dissolved in 130 mL of methanol, 130 mL of water, and 0.65 g of potassium hydroxide and stirred for 18 h at room temperature. This was then concentrated, diluted with water, and extracted with methylene chloride. The organic layer was dried ($MgSO_4$) and concentrated to give 11.8 g of an oil. This was crystallized as white plates from acetone–hexanes to afford **6** in a yield of 7.21 g (64%). The mother liquors were chromatographed over silica gel to provide another 1.24 g of **6** identical in all respects with the first batch: mp 115–116 °C; NMR ($CDCl_3$) δ 3.51 (m, 1 H); IR ($CHCl_3$) ν_{max} 3200–3600 (broad peak), 1705 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_2$, C, 75.61; H, 9.97. Found: C, 75.46; H, 9.99.

2-Hydroxy-1,2,3,4,4aβ,5,6,6aα,7,11,11aβ,12,12aβ,12bα-tetradecahydro-9(10*H*)benz[*a*]anthracenone (8). To 1 g of sodium hydride (0.043 mol) in 25 mL of benzene was added 1.26 mL of dry methanol (0.043 mol). The mixture was refluxed, under argon, for 0.5 h. The suspension was allowed to cool, and 4 g of **6** (0.018 mol) in 25 mL of benzene was added followed by 3.2 mL of ethyl formate (0.04 mol). This was stirred for 20 h at room temperature. Then 20 mL of water was added carefully to decompose any excess base. The solution was partitioned between ether and water (100 mL each) and the aqueous layer collected. This was acidified with acetic acid and extracted with methylene chloride. The organic layer was then dried and concentrated to a foam: UV λ_{max} 283 nm.

The foam was dissolved in 25 mL of dry methanol and cooled to 0 °C, and 2 mL of methyl vinyl ketone (0.025 mol) was added. To this suspension was added dropwise 2.25 mL of triethylamine (0.016 mol). The mixture became homogeneous after 30 min and was stirred overnight at room temperature. The dark brown solution was then diluted with 10% sodium bicarbonate and extracted with ether. The ether layer was dried and concentrated. The residue was dissolved in 125 mL of methanol, and 1.7 g of sodium methoxide (0.03 mol) was added. The mixture was stirred at room temperature for 2 h, then refluxed for 1 h, concentrated, diluted with water, and extracted with ether. The organic layer was dried ($MgSO_4$) and concentrated to afford an oil, which crystallized from acetone to afford **8** in a yield of 1.15 g (23% from **6**): mp 162–164 °C; NMR ($CDCl_3$) δ 3.55 (m, 1 H), 5.8 (s, 1 H); IR ($CHCl_3$) ν_{max} 3300–3500 (broad peak), 1660 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.83; H, 9.48. Found: C, 79.10; H, 9.50.

2-Hydroxy-9,9-(ethylenedithio)-1,2,3,4,4aβ,5,6,6aα,7,9,10,11,11aβ,12,12aβ,12bα-hexadecahydrobenz[*a*]anthracene (9). The enone alcohol **8** (4 g, 15 mmol) was dissolved in 28 mL of glacial acetic acid, and the resulting solution was treated with ethanedithiol (1.86 mL, 15 mmol) and boron trifluoride etherate (1.86 mL, 15 mmol). The mixture was swirled and allowed to stand for 5 min. The resulting yellow-orange solution then was poured into water (300 mL), and the product was extracted with three portions of methylene chloride (400 mL total). The organic layers were combined and washed twice with 5% sodium hydroxide solution, dried over magnesium sulfate, and concentrated to dryness to give 4.9 g (96%) of the thioketal **9** as a white foam. Recrystallization from methylene chloride–hexane gave the analytical sample: mp 142–144 °C; NMR ($CDCl_3$) δ 3.31 (s, dithiolane), 5.54 (s, vinyl proton); IR ($CHCl_3$) ν_{max} 3450, 1450 cm^{-1}. Anal. Calcd for $C_{20}H_{30}O_1S_2$: C, 68.52; H, 8.63; S, 18.29. Found: C, 68.58; H, 8.63; S, 18.19.

9,9-(Ethylenedithio)-1,3,4,4aβ,5,6,6aα,7,10,11,11aβ,12,12aβ,12bα-tetradecahydrobenz[*a*]anthracen-2(9*H*)-one (10). To a suspension of pyridinium chlorochromate (5.5 g, 25 mmol) in 20 mL of dry methylene chloride was added 4.5 g (13 mmol) of **9** dissolved in 30 mL of methylene chloride. After being stirred at room temperature for 2 h, the reaction was diluted with 200 mL of ether and the brown mixture poured into a beaker. A black gum remained in the reaction flask, and this material was repeatedly treated with more ether until all that remained was a black granular residue. The ether fractions were combined and filtered through Florisil (110–200 mesh). The filtrate was concentrated in vacuo to give a white solid, which was recrystallized from acetone–hexane to give 3.5 g (78%) of the ketone **10**: mp 153–155 °C; NMR ($CDCl_3$) δ 3.33 (s), 5.56 (s); IR ν_{max} ($CHCl_3$) 1708 cm^{-1}. Anal. Calcd for $C_{20}H_{28}OS_2$: C, 68.92; H, 8.10; S, 18.40. Found: C, 68.93; H, 8.13; S, 18.38.

2′-Oxo-3′-(phenylmethylidene)-1′,2′,3′,4′,4a′β,5′,6′,6a′α,7′,11′,11a′β,12′,12a′β,12b′α-tetradecahydrospiro[1,3-dithiolane-2,9′(10′*H*)-benz[*a*]anthracene]. The ketone **10** (0.5 g, 1.4 mmol) was dissolved in 50 mL of methanol. Sodium methylate (1 g) was added as a solid followed by addition of 0.7 mL of benzaldehyde. The reaction mixture was refluxed under nitrogen for 4 h. The cooled mixture was diluted with water, and the resulting precipitate was collected by filtration. The crude precipitate contained the desired product plus some starting ketone and was subjected to preparative thin-layer chromatography (benzene/silica gel). The pure benzylidene derivative was obtained by recrystallizing one of the chromatographic fractions from ether–hexane to give 102 mg of crystals: mp 144–146 °C; NMR ($CDCl_3$) δ 3.29 (s, dithiolane), 5.54 (s, vinyl proton), 7.31 (s, phenyl); IR ν_{max} 1675, 1595 cm^{-1}. Anal. Calcd for $C_{27}H_{32}OS_2$: C, 74.26; H, 7.39; S, 14.69. Found: C, 74.09; H, 7.32; S, 14.63.

2′-Oxo-3′-(2-furanylmethylidene)-1′,2′,3′,4′,4a′β,5′,6′,6a′α,7′,11,11a′β,12′,12a′β,12b′α-tetradecahydrospiro[1,3-dithiolane-2,9′(10′*H*)-benz[*a*]anthracene] (11). A mixture of the ketone **10** (1.25 g, 3.6 mmol) and furfuraldehyde (1.67 g, 17 mmol) in 130 mL of methanol was treated with 1.3 mL of 10% aqueous potassium hydroxide. After standing at room temperature for 18 h, the reaction mixture was poured onto crushed ice. The resulting precipitate was collected by filtration and washed with cold water to give 1.2 g (80%) of the furfurylidene **11** as a pale yellow solid. This material proved difficult to crystallize but was finally obtained as an amorphous solid from methylene chloride: mp 212–215 °C; NMR ($CDCl_3$) δ 3.32 (s, dithiolane), 5.56 (s, vinyl proton), 6.50 (m, 2 protons, furanyl), 7.24 (s, 1 proton, furanyl), 7.50 (s, vinyl methylidene); IR ν_{max} ($CHCl_3$) 1722, 1595 cm^{-1}. Anal. Calcd for $C_{25}H_{28}O_2S_5$: C, 70.72; H, 6.65; S, 15.10. Found: C, 70.41; H, 7.13; S, 15.05.

2′-Oxo-1′,1′-dimethyl-3′-(2-furanylmethylidene)-1′,2′,3′,4′,4a′β,5′,6′,6a′α,7′,11′,11a′β,12′,12a′β,12b′α-tetradecaspiro[1,3-dithiolane-2,9′(10′*H*)-benz[*a*]anthracene] (12). A suspension of potassium hydride (25%, 8.5 g, 53 mmol) was placed in a 500-mL three-neck flask and washed 3 times with hexane under a nitrogen atmosphere and then covered with 150 mL of benzene freshly distilled from sodium metal. The suspension was cooled to 0 °C, and a solution of the furfurylidene ketone **11** (1.5 g, 3.5 mmol) in 150 mL of benzene containing one drop of *tert*-butyl alcohol was added. After 3 min methyl iodide (7.6 g, 53 mmol) was added in one portion by syringe, and the reaction mixture was stirred at room temperature for 8 days. Water was added dropwise to the reaction mixture to decompose the excess base present, and then 200 mL of water was added. The benzene layer was separated and diluted with ether. The organic layer was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution, and dried over magnesium sulfate. Evaporation of the solvents under reduced pressure gave 1.53 g of a yellow oil. The crude oil was chromatographed on 200 g of silica gel (60–200 mesh) and eluted with chloroform containing 2% acetone to give 0.87 g (55%) of the crystalline *gem*-dimethylated ketone **12**: mp 181–183 °C; NMR ($CDCl_3$) δ 1.25 (s, *gem*-dimethyl), 3.34 (s, dithiolane), 5.56 (s, vinyl), 6.51 (m, 2 protons, furanyl), 7.17 (s, 1 proton, furanyl), 7.50 (s, vinyl); IR

ν_{max} ($CHCl_3$) 1720, 1590 cm^{-1}. Anal. Calcd for $C_{27}H_{34}O_2S_2$: C, 71.32; H, 7.54; S, 14.10. Found: C, 71.35; H, 7.58; S, 14.07.

Attempted Synthesis of 1′-[1-Methyl-1-(methoxycarbonyl)ethyl]-2′-[(methoxycarbonyl)methyl]-1′,2′,3′,4′,4a′α,8′,8a′β,9′,9a′β,10′-decahydrospiro[1,3-dithiolane-2,6′(7′H)-anthracene] (13). A solution of sodium methylate (14 g) in 200 mL of methanol and a solution of the ketone **12** (0.2 g, 0.4 mmol) in 200 mL of methanol were combined with external cooling. The resulting mixture was transferred to a Waring blender with the aid of 50 mL of methanol. Hydrogen peroxide (30%, 50 mL) was added, resulting in the formation of a white precipitate. High-speed stirring was commenced, and aliquots of the mixture were checked periodically for ultraviolet absorption at 323 nm. After 6 h the mixture showed no absorption at that wavelength, and the stirring was stopped. The reaction mixture was transferred to a round-bottom flask, and the volume was reduced to approximately 100 mL by rotary evaporation. Water (800 mL) was added, and the mixture was washed once with methylene chloride. The aqueous phase was acidified to pH 3 with cold 5% sulfuric acid and quickly extracted with methylene chloride. This extract was washed with water and dried over magnesium sulfate and concentrated to dryness to give 160 mg of a multicomponent oil (TLC analysis). The ^1H NMR spectra of the crude material indicated that the dithiolane group, the A ring vinyl proton, and the furfurylidene were lost, suggesting overoxidation was occurring. This oil was treated with etheral diazomethane and worked up in the usual way to give another oil that showed the presence of methyl esters in the IR and ^1H NMR spectra but was not identified as the desired product. Due to the complexity of the oil it was not purified further.

3-[(*n*-Butylthio)methylidene]-9,9-(ethylenedithio)-1,4,4aβ,5,6,6aα,7,9,10,11,11aβ,12,12aβ,12bα-tetradecahydrobenz[*a*]anthracen-2(3*H*)-one (14). A mixture of sodium hydride (0.43 g, 18 mmol) and 0.57 mL of methanol in 15 mL of benzene was brought quickly to reflux under an atmosphere of nitrogen. The cooled suspension was added to the ketone **10** (1.8 g, 5 mmol) in 10 mL of benzene. To this mixture was added ethyl formate (1.45 mL, 18 mmol), which had been freshly distilled from phosphorus pentoxide. The reaction mixture was stirred for 20 h at room temperature. The excess base was then destroyed with 8 mL of water, and the resulting opaque suspension was diluted with 100 mL of water and 100 mL of ether. The aqueous layer was separated, and the ether–benzene layer was washed one time with water. The aqueous layers were combined and washed once with ether. The yellow aqueous layer was acidified to pH 6 with glacial acetic acid, and the product was extracted with methylene chloride. The methylene chloride extract was dried over magnesium sulfate and concentrated to dryness to yield 1.8 g of amorphous yellow solid hydroxymethylene ketone. This material exhibited UV absorption at 283 nm, indicating the presence of the desired β-dicarbonyl compound. The crude substance was not purified but immediately was dissolved in 250 mL of benzene. This solution was treated with 0.55 mL of *n*-butanethiol and a few crystals of *p*-toluenesulfonic acid and refluxed under nitrogen. The water of dehydration was separated by use of a Dean–Stark head. After 4.5 h the yellow transparent benzene solution was cooled, washed with water, twice with 5% sodium hydroxide solution, and finally with saturated sodium chloride solution. The benzene layer was dried over magnesium sulfate and concentrated under reduced pressure to give 2.2 g of a yellow solid. The crude material was taken up in chloroform and filtered through a short pad of Florisil to give, after recrystallization from acetone, the (*n*-butylthio)methylene ketone **14** (2 g, 87%): mp 136–137 °C; NMR ($CDCl_3$) δ 3.32 (s, dithiolane), 5.56 (vinyl proton), 7.51 (thioenol ether). Anal. Calcd for $C_{25}H_{36}OS_3$: C, 66.91; H, 8.09; S, 21.44. Found: C, 66.91; H, 8.09; S, 21.39.

Attempted Alkylation of 14. To a flame-dried flask was added potassium hydride (1 g, 6.3 mmol, 25%) which was washed three times with 1-mL portions of hexane under nitrogen. Benzene (200 mL) was added followed by a solution of **14** (2 g, 0.4 mmol) in 30 mL of benzene. After standing for 3 min at room temperature, the reaction flask was cooled in an ice bath (0–5 °C), and methyl iodide (0.9 g, 6.3 mmol) was added by syringe. This was stirred for 5 days at room temperature. Water (200 mL) was then added, and the benzene layer was separated and diluted with ether. The aqueous layer was washed one time with ether, and the organic layers were combined, washed with water and saturated sodium chloride solution, dried over magnesium sulfate, and concentrated to dryness in vacuo to give a crude yellow oil weighing 0.21 g. The crude material was purified by chromatography (repetitive thin layer) to give 30 mg of a clear oil. The ^1H NMR spectra indicated the presence of the desired *gem*-dimethylated ketone along with some of the monoalkylated product. Further attempts to purify this mixture were unsuccessful [NMR ($CDCl_3$) δ 1.25 (s, *gem*-dimethyl), 3.34 (s, dithiolane), 5.55 (s, vinyl proton) 7.37 (thienol ether proton)]; 0.342 g of an oil was afforded. Crystallization from acetone gave **14** in a yield of 0.255 g (60%): mp 135–136 °C; NMR ($CDCl_3$) δ 3.31 (s, 4 H), 5.55 (s, 1 H), 7.35 (s, 1 H); IR ($CHCl_3$) ν_{max} 1680–1665 (broad peak) cm^{-1}.

3-Hydroxy-7,7-(ethylenedioxy)-(4aα,4bβ,8aα,10aβ)-perhydrophenanthracene (16). To a 1-L round-bottom flask were added 480 mL of benzene and 13.5 mL of ethylene glycol (0.24 mol). This was azeotroped for 1 h to remove traces of water. The solution was cooled and 0.324 g of *p*-toluenesulfonic acid monohydrate (0.0017 mol) followed by 4.27 g of **6** (0.0192 mol) in 20 mL of benzene was added. This was refluxed, under argon, for 18 h using a Dean–Stark head to azeotropically remove water. At the end of this time 10 mL of 5% sodium hydroxide was added to 500 mL of 5% sodium hydroxide, and the layers were separated. The organic layer was dried ($MgSO_4$) and concentrated to give **16** in a yield of 5.0 g (98%) as an oil, which later solidified. Recrystallization from acetone–hexanes provided the analytical sample: mp 94–96 °C; NMR ($CDCl_3$) δ 3.93 (s, 4 H); IR ($CHCl_3$) ν_{max} 3200–3600, 1450 cm^{-1}. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.83. Found: C, 71.95; H, 9.79.

7,7-(Ethylenedioxy)-(4aα,4bβ,8aα,10aβ)-perhydro-3-phenanthranone (17). To a suspension of 2.2 g of pyridinium chlorochromate (10.2 mmol) in 200 mL of methylene chloride was added 1.09 g of **16** (4.12 mmol) in 20 mL of methylene chloride. This was stirred for 7 h at room temperature, diluted with 1 L of ether, and filtered through Florisil. The combined organic layers were concentrated to give 1.1 g of **17** as an oil. Recrystallization from methanol gave the analytical sample: mp 58–59 °C; NMR ($CDCl_3$) δ 3.93 (s, 4 H); IR ($CHCl_3$) ν_{max} 1720, 1450 cm^{-1}. Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.65; H, 9.17.

7,7-(Ethylenedioxy)-2-furfurylidene-(4aα,4bβ,8aα,10aβ)-perhydro-3-phenanthranone (18). A mixture of 14.5 g of **17** (0.054 mol) in 1500 mL of methanol was cooled to 0 °C, and 455 mL of 33% sodium hydroxide was added followed by 11.7 mL of freshly distilled furaldehyde (0.14 mol). This yellow solution was stirred for 3 h, under argon, and then 200 mL of water was added and stirring continued for an additional hour. Then 1 L of water was added, and the resulting solid was collected by vacuum filtration, washed with water, and dried to give 17.1 g of a yellow solid. Recrystallization from ethyl acetate gave **18** in a yield of 14.76 g (79%): mp 177–178 °C; NMR ($CDCl_3$) δ 3.93 (s, 4 H), 6.60 (m, 2 H), 6.80 (m, 2 H); IR ($CHCl_3$) ν_{max} 1666, 1587 cm^{-1}. Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.68; H, 7.60. Found: C, 73.68; H, 7.68.

4,4-Dimethyl-7,7-(ethylenedioxy)-2-furfurylidene-(4aα,4bβ,8aα,10aβ)-perhydro-3-phenanthrenone (19). To a 5-L three-necked flask which had been flame-dried and flushed with argon was added 66.5 mL of potassium hydride oil dispersion (23.8%, 15.83 g of KH, 0.4 mol). This was washed three times with dry hexanes, under argon, and then dried under vacuum. The flask was again filled with argon and 50 mL of dry dioxane was added with a syringe. Then 9 g of **18** (0.026 mol) in 600 mL of dioxane was added. The mixture was stirred for 5 min and then an additional 2000 mL of dioxane was added. This deep red solution was stirred for 15 min, and then 24.5 mL of methyl iodide (0.40 mol) was added with a syringe. The mixture was stirred, under argon, for 44 h. During the course of the reaction the deep red color disappeared, and the resulting mixture became a light orange to beige.

The mixture was worked up by first carefully decomposing the excess base with water and concentrating the resulting yellow solution to about three-fourths its original volume. The residue was diluted with water and extracted with methylene chloride. The organic layer was dried and concentrated to yield 12.12 g of a dark oil. Chromatography over 115 g of silica gel (rapid linear gradient chromatography, benzene–10% ethyl acetate/benzene) gave **19** in a yield of 5.87 g (60%): mp 130–131 °C; NMR ($CDCl_3$)

δ 1.26 (2 s, 6 H), 3.96 (s, 4 H), 6.6 (m, 2 H), 6,8 (m, 2 H); IR ($CHCl_3$) ν_{max} 1597, 1600 cm^{-1}. Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.59; H, 8.16. Found: C, 74.57; H, 8.19.

During one of the attempts some monoalkylated material was obtained as crystals from ethyl acetate: mp 148–149 °C; NMR ($CDCl_3$) δ 1.23 (d, 3 H, J = 7 Hz), 3.98 (s, 4 H), 6.6 (m, 2 H), 7.23 (br s, 1 H), 7.61 (s, 1 H); IR ($CHCl_3$) ν_{max} 1664, 1588 cm^{-1}. Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.91. Found: C, 74.17; H, 7.96.

Also isolated from one of the alkylation attempts was some O-alkylated material, **19a**. This was obtained by thick-layer chromatography as an oil: NMR ($CDCl_3$) δ 3.65 (s, 3 H, OCH_3), 3.96 (s, 4 H), 5.1 (s, 1 H), 6.36 (m, 2 H), 6.7 (s, 1 H), 7.06 (m, 1 H). This material was treated with dilute acid to give diketone **18a** identical in all respects (TLC, NMR, IR, mp) with **18a** prepared by hydrolysis of **18** (see below).

2-Furfurylidene-(4aα,4bβ,8aα,10aβ)-perhydrophenanthrene-3,7-dione (18a). A solution of 0.05 g of **18** in 3 mL of methanol and 1 mL of water was heated to reflux on a steam bath. Then 2 drops of concentrated sulfuric acid was added and the mixture allowed to cool. The solid which precipitated was collected by filtration, washed with water, and dried to afford **18a** in a yield of 0.04 g (93%). An analytical sample was prepared by recrystallization from methanol/water: mp 206–208 °C; NMR ($CDCl_3$) δ 6.57 (m, 2 H), 7.33 (m, 1 H), 7.55 (m, 1 H); IR ($CHCl_3$) ν_{max} 1712, 1675 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 75.78; H, 7.45.

1,1-Dimethyl-3-carbomethoxy-7,7-(ethylenedioxy)-(3aβ,5aα,9aβ,9bα)-perhydro-2-cyclopenta[*a*]naphthalenone (20). A solution of 1.16 g of **19** (3.13 mmol) in 300 mL of ethyl acetate was cooled to −78 °C in a dry ice/acetone bath and ozone was bubbled in until the solution became blue. The solution was allowed to warm to room temperature, and was concentrated in vacuo at room temperature. To the residue was immediately added 42 mL of 5% potassium hydroxide and 63 mL of 30% hydrogen peroxide. The mixture was stirred until homogeneous (3–4 h). A solution of 200 mL of ether and 150 mL of 5% sulfuric acid was cooled to 0 °C, in a separatory funnel, with ice. The reaction mixture was added to the separatory funnel, the layers were quickly separately, and the ether layer was washed with a saturated solution of ferrous sulfate and then with water. The organic layer was added to a solution of diazomethane (prepared from 3 g of Diazald) in ether at 0 °C. The reaction mixture was allowed to warm to room temperature. It then was concentrated first on a steam bath to three-fourths of the original volume and then on a rotary evaporator to give 6,6-(ethylenedioxy)-1β-(1-carbomethoxy-1-methylethyl)-2α-(carbomethoxymethyl)-(4aα,8aβ)-perhydronaphthalene in a yield of 0.97 g (84%) as an oil: NMR ($CDCl_3$) δ 3.66 (s, 6 H), 3.93 (s, 4 H). This compound was not characterized further but used directly in the next step.

A solution of 1.89 g of diester (5.16 mmol)e and 2.89 g of potassium *tert*-butoxide (25.80 mmol) in 475 mL of benzene was refluxed until an aliquot showed only one spot on TLC. The reaction mixture was cooled and poured into a separatory funnel containing 20 mL of 5% sulfuric acid, 500 mL of water, and 100 mL of ether (all at 0 °C). The layers were separated quickly, and the ether layer was washed with water dried ($MgSO_4$) and concentrated to afford **20** in a yield of 1.22 g (71%). Recrystallization from ethanol gave the analytical sample: mp 137.5–139 °C; NMR ($CDCl_3$) δ 1.00 (s, 3 H), 1.16 (s, 3 H), 3.73 (s, 3 H), 3.93 (s, 4 H); IR (CCl_4) ν_{max} 1752, 1722 cm^{-1}.

When the conversion of **19** to **20** was run without isolation of intermediates and with addition of diazomethane until a faint yellow color persisted, yields of 65–70% were common, and yields of 80% were occassionally achieved. Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.79; H, 8.41.

1,1-Dimethyl-7,7-(ethylenedioxy)-(3aβ,5aα,9aβ,9bα)-perhydro-2-cyclopenta[*a*]naphthalenone (21). A solution of 0.86 g of **20** (2.56 mmol), 0.21 g of lithium chloride (5.00 mmol), 0.04 mL of water, and 4.4 mL of dimethyl sulfoxide was heated to 170 °C for 1.25 h. After 20 min of heating, gas evolution was evident. The solution was allowed to cool. It was poured into ice-water and extracted with ether. The organic layer was washed with a saturated sodium chloride solution, dried ($MgSO_4$), and concentrated to afford **21** in a yield of 0.66 g (92%). Recrystallization from ethanol gave the analytical sample: mp 93–95 °C; NMR ($CDCl_3$) δ 0.95 (s, 3 H), 1.11 (s, 3 H), 3.96 (s, 4 H); IR (CCl_4) ν_{max} 1741 cm^{-1}. Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.32; H, 9.42.

In an alternative procedure, **20** was heated under reflux with diazobicycloundecene in xylene. After the usual workup, **21** could be isolated in a yield of 50%.

1,1-Dimethyl-2-ethylidene-7,7-(ethylenedioxy)-(3aβ,5aα,9aβ,9bα)-perhydrocyclopenta[*a*]naphthalene (22). To a flame-dried flask was added 0.29 g of 57% sodium hydride oil dispersion (6.88 mmol). The hydride was washed three times with hexanes and dried under reduced pressure. Then 6.6 mL of dry dimethyl sulfoxide was added and the mixture heated for 40 min, under argon, at 65 °C. To this solution of dimsyl sodium was added 2.86 g of ethyltriphenylphosphonium iodide (6.85 mmol) in 7.1 mL of dimethyl sulfoxide to form the ylide.

To the ylide was added 0.44 g of **21** (1.58 mmol) dissolved in 8.8 mL of benzene. The mixture was stirred, under argon, at 80 °C for 24 h, cooled, and poured into a saturated sodium chloride solution. This was extracted with ether, dried ($MgSO_4$), and concentrated to afford 2.1 g of an oil. The residue was chromatographed over 100 g of alumina (hexanes/benzene) to give **22** as an oil, in a yield of 0.40 g (87%); bp 65–70 °C (1 mm); NMR ($CDCl_3$) δ 1.1 (s, 3 H), 1.31 (s, 3 H), 3.93 (s, 4 H), 5.25 (q, 1 H). Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.62; H, 10.34. Found: C, 78.54; H, 10.43.

1,1-Dimethyl-2-(1-hydroxyethyl)-7-keto-(3aβ,5aα,9aβ,9-bα)-perhydrocyclopenta[*a*]naphthalene (23). To a solution of 0.297 g of **22** (1.02 mmol) in 15 mL of tetrahydrofuran was added 1.86 mL of 1 M diborane in tetrahydrofuran (1.86 mmol). The solution was stirred at room temperature for 1.25 h. Then 7.4 mL of 10% sodium hydroxide was added, the mixture cooled to 0 °C, and 5 mL of 30% hydrogen peroxide was added. The reaction mixture was stirred for another hour. At the end of this time the solution was partitioned between ether and water, and the ether layer was dried and concentrated to a solid. This was dissolved in 15 mL of methanol and heated to reflux on a steam bath. Then 3 mL of 3 N hydrochloric acid was added. Upon cooling a precipitate formed and was collected by filtration. It was washed with water and dried to afford **23** in a yield of 0.246 g (91%). The analytical sample was prepared by recrystallization from ether–hexanes: mp 123–126 °C; NMR ($CDCl_3$) δ 0.97 (s, 3 H), 1.26 (s, 3 H), 4.00 (m, 1 H): IR (CCl_4) ν_{max} 1717 cm^{-1}. Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.17; H, 10.70.

7β,15α-Ethano-11,12-seco-11,19-bisnor-20-hydroxy-17-pregn-4-en-3-one (24). Into a flame-dried flask flushed with argon was added 0.06 g of 57% sodium hydride oil dispersion. This was washed with hexanes two times and dried under reduced pressure. Then 10 mL of dry benzene and 0.145 mL of ethanol (2.50 mmol) were added, under argon. This was stirred for 0.5 h, and then 0.24 g of **23** (0.91 mmol) in 20 mL of benzene and 0.195 mL of ethyl formate (2.41 mmol) was added. This was stirred for 18 h and diluted with 100 mL of water and 50 mL of ether. The aqueous layer was collected, acidified to pH 4 with acetic acid, and extracted with methylene chloride. The organic phase was dried ($MgSO_4$) and concentrated to afford 0.213 g of a yellow oil. This was not characterized but was used directly.

To a solution of the oil (0.213 g) in 2 mL of methanol was added 0.08 mL of methyl vinyl ketone (0.98 mmol). This was cooled to 0 °C, and a solution of 0.12 mL of triethylamine (0.86 mmol) in 4 mL of methanol was added dropwise. The ice bath was removed, and the mixture was stirred at room temperature for 20 h. The dark solution was diluted with ether and washed with sodium bicarbonate (10%). The ether layer was dried and concentrated to afford 0.23 g of an oil.

This oil was dissolved in 10 mL of methanol and 0.07 g of sodium methoxide (1.76 mmol) was added. The solution was refluxed for 1 h. The mixture was cooled, concentrated and partitioned between ether and water. The ether layer was dried and concentrated to afford 0.179 g of **24** (62%). A small sample was recrystallized twice from methanol to give the analytical sample. The remainder was carried through to the next step; mp 180–181 °C; NMR ($CDCl_3$) δ 0.95 (s, 3 H), 1.13 (br s, 3 H), 1.3 (s, 3 H), 3.9 (m, 1 H), 5.80 (s, 1 H); IR (KBr) ν_{max} 3415, 1653 cm^{-1}. Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. $C_{21}H_{32}O_2 \cdot {}^1/_4H_2O$: C, 78.57; H, 10.21. Found: C, 78.76; H, 10.24.

7β,15α-Ethano-11,12-seco-11,19-bisnor-17-pregn-4-ene-3,20-dione (25). To a solution of 0.18 g of pyridinium chlorochromate (0.83 mmol) in 5 mL of methylene chloride was added 0.132 g of **24** (0.41 mmol) in 5 mL of methylene chloride. This was stirred at room temperature until the reaction was complete as determined by TLC (3–4 h). The reaction mixture was diluted with 50 mL of ether, filtered through Florisil, and concentrated to afford a crude oil in a yield of 0.122 g (91%). This was chromatographed (thick layer) to provide **25** in a yield of 0.075 g (57%). The compound was recrystallized from ether to give an analytical sample: mp 127–130 °C; NMR ($CDCl_3$) δ 0.85 (s), 1.01 (s), 1.20 (s), 1.39 (s), 2.16 (s), 5.81 (s); IR (CCl_4) ν_{max} 1708, 1667 cm^{-1}. Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.15; H, 9.68.

1,1-Dimethyl-2α-hydroxy-2β-(1-hydroxyethyl)-7-keto-(3aβ,5aα,9aβ,9bα)-perhydrocyclopenta[*a*]naphthalene (26). (A) To a solution of 1.8 g of **22** in 100 mL of acetone was added 5 mL of 10% aqueous hydrochloric acid. The mixture was stirred at room temperature until TLC indicated that the reaction was complete. The resulting 1,1-dimethyl-2-ethylidene-7-keto-(3aβ,5aα,9aβ,9bα)-perhydrocyclopenta[*a*]naphthalene, was isolated in a yield of 97%: NMR ($CDCl_3$) δ 1.16 (s), 1.33 (s), 5.22 (8).

To 5 mL of a 0.107 M solution of osmium tetraoxide in pyridine was added 0.200 g of **22a**. The mixture was stirred overnight at room temperature in the dark. Then a solution of 0.465 g of sodium bisulfate in 7.47 mL of water and 3.66 mL of pyridine was added. Stirring was continued for 30 min, then 50 mg of sodium bisulfate was added, and stirring was maintained for 10 min. The mixture was partitioned between chloroform and water. The organic phase was washed successively with aqueous hydrochloric acid, aqueous bicarbonate, and with water and then was dried and concentrated to 80 mg of a residue. The latter was allowed to react with a solution of aqueous sodium hydrosulfide for 18 h and then was again worked up as above to yield 50 mg of a pale yellow gum, which crystallized from acetone–chloroform, mp 116–117 °C. Recrystallization from ether afforded an analytical sample of **26**; mp 139–139.5 °C. Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.07. Found: C, 72.57; H, 10.09.

(B) To a solution of 2.51 g of osmium tetraoxide in 50 mL of pyridine was added 2.20 g of **22**. The mixture was stirred at room temperature in the dark for 20 h. Then 2.85 g of sodium bisulfate in 43 mL of water was added, and stirring was continued for 1 h. The mixture was partitioned between water and chloroform. The organic phase was washed with dilute acid and then water, dried, and concentrated to 3.4 g of a dark residue. The latter was dissolved in 70 mL of methanol, and 15 mL of a 10% solution of hydrochloric acid was added. The mixture was briefly heated to reflux and then was stirred at room temperature until the reaction appeared complete by TLC. Standard workup gave 2.6 g of an oil, which was fractionated by rapid linear gradient chromatography using a gradient of chloroform and a 10% solution of acetone in chloroform. A total of 1.34 g (63%) of **26**, was recovered.

DL-3-Oxo-7β,15α-ethano-11,12-seco-11,19-bisnorpregn-4-ene-17α,20α-diol 20-Acetate (27). Into a flame-dried flask flushed with argon was added 0.145 g of 57% sodium hydride oil dispersion. This was washed twice with hexanes and dried under reduced pressure. Then 10 mL of dry benzene and 0.201 mL of ethanol was added under argon. This was stirred for 30 min, and then 0.307 g of **26** and 0.346 mL of ethyl formate in 25 mL of benzene were added. This was stirred for 18 h and then diluted with 100 mL of water and 50 mL of ether. The aqueous layer was acidified to pH 4 with acetic acid and extracted with methylene chloride. The organic phase was dried and concentrated to give 0.30 g of a solid.

To a solution of the solid in 4.4 mL of methanol and 0.15 mL of methyl vinyl ketone at 0 °C slowly was added 0.182 mL of triethylamine in 4.4 mL of methanol. The mixture was stirred at 0 °C until it became homogeneous and then was stirred at room temperature overnight. A white foam, 0.32 g, was isolated after workup. To a solution of the diketone in 25 mL of methanol, at 0 °C under argon, was added 0.106 g of sodium methoxide in 10 mL of methanol. The mixture was stirred in the cold for 10 min, allowed to warm to room temperature, and then heated under reflux for 1 h. Standard workup gave 300 mg of a foam.

The foam was dissolved in 0.5 mL of pyridine and 0.5 mL of acetic anhydride and stirred overnight at room temperature. The solution was diluted with water and extracted with methylene chloride. The organic phase was dried and concentrated to leave 340 mg of a yellow solid. Trituration with ether afforded **27** in a yield of 160 mg (39%) as colorless crystals. Recrystallization from ethyl acetate afforded an analytical sample: mp 203–205 °C; NMR ($CDCl_3$) δ 0.91 (s), 1.15 (s), 1.28 (d, J = 6.2 Hz), 2.05 (s), 4.99 (q, J = 6.2 Hz), 5.79 (s). Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.56; H, 9.11.

***rac*-7β,15α-Ethano-11,12-seco-11,19-bisnor-17α-pregn-21-ene-3,20-dione (28).** To 0.79 g of **27** in 79 mL of distilled xylene was added 15.8 g of activated zinc. The mixture was refluxed under argon for approximately 24 h and then was filtered through Celite. The residue was washed with benzene. The organic phase was washed with water, dried, and concentrated to leave a residue, which crystallized from ethyl acetate to give 0.67 g of **28** which seemed pure by NMR and TLC. Recrystallization from ethyl acetate gave an analytical sample of **28** in a yield of 0.45 g: mp 157–159 °C; NMR ($CDCl_3$) δ 1.01 (s), 1.20 (s), 2.16 (s). Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.10; H, 9.69.

2-Acetoxy-4,4-dimethyl-7,7-(ethylenedioxy)-4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-decahydro-3(4*H*)-phenanthrenone (29). A solution of 200 mg of **19** in 12.6 mL of methanol and 18 mL of methylene chloride was saturated with ozone (persistent blue color) at −78 °C. A stream of argon was bubbled through the solution to remove the excess ozone and then 0.45 g of triphenylphosphine was added. The mixture was stirred, under argon at −78 °C for 1 h and then was allowed to warm to room temperature. It was concentrated and then partitioned between water and methylene chloride. The organic phase was dried and concentrated to dryness. The residue was dissolved in 0.5 mL of acetic anhydride and 0.5 mL of pyridine, left overnight, and then again partitioned between water and methylene chloride. The organic phase was concentrated and then subjected to rapid linear gradient chromatography over 20 g of silica gel using a gradient varying from toluene to 12% ethyl acetate in toluene to obtain 130 mg of **29** (70%) as a white solid. Recrystallization from ether gave **29** (100 mg) as white crystals: mp 155.5–156 °C; NMR ($CDCl_3$) δ 1.13 (s), 1.40 (s), 2.19 (s), 3.92 (s), 6.18 (d, J = 2 Hz); IR (KBr) ν_{max} 1755, 1680 cm^{-1}. Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.86; H, 8.11.

7,7-(Ethylenedioxy)-2-(hydroxymethylene)-(4aα,4bβ,8aα,10aβ)-perhydro-3-phenanthrone (31). To 120 mL of dry benzene were added 0.855 g of sodium hydride (36.8 mmol) and 2.06 mL of ethanol (37.0 mmol). This was stirred for 45 min, and then 1.95 g of **17** (7.38 mmol) and 6.8 mL of ethyl formate (84.26 mmol) were added. This mixture was stirred overnight at room temperature, under argon. The thick viscous reaction mixture was poured into a separatory funnel, diluted with ether, and cooled to 0 °C with pieces of ice. A solution of 5% sulfuric acid (200 mL) was cooled to 0 °C and quickly poured into the separatory funnel. The layers were separated immediately, and the organic layer was washed with water. The ether phase was dried ($MgSO_4$) and concentrated to afford **31** as a yellow solid, in a yield of 2.05 g (95%): mp 118–124 °C; NMR ($CDCl_3$) δ 3.91 (s, 4 H), 8.63 (br s, 1 H); IR ($CHCl_3$) ν_{max} 3200–3300 (broad peak), 1697 cm^{-1}; UV λ_{max} 283 nm. This compound was too unstable for further purification so it was used immediately after its preparation.

2-[(Butylthio)methylidene]-7,7-(ethylenedioxy)-(4aα,4bβ,8aα,10aβ)-perhydro-3-phenanthrenone (32). To 25 mL of benzene and a crystal of *p*-toluenesulfonic acid monohydrate was added 0.145 g of **31** (0.49 mmol) and 0.07 mL of *n*-butanethiol (0.49 mmol). This was refluxed for 7 h under a Dean–Stark head to azeotropically remove water. The yellow mixture was partitioned between water and benzene, the benzene layer was washed with 5% potassium hydroxide, dried ($MgSO_4$), and concentrated to afford **32** in a yield of 0.155 g (86%) as an oil.

2,2-(Ethylenedithio)-7,7-(ethylenedioxy)-(4aα,4bβ,8aα,-10aβ)-perhydro-3-phenanthrenone (33). To a solution of 0.89 g of **31** (3.00 mmol) in 20 mL of ethanol was added 1.22 g of ethylene dithiotosylate[29] (3.00 mmol) and 0.9 g of potassium

(29) Woodward, R. B.; Patcher, I.; Scheinbaum, M. *J. Org. Chem.* **1971**, *36*, 1137.

acetate (9.1 mmol). This was refluxed for 24 h, concentrated, and partitioned between ether and water. The ether layer was dried ($MgSO_4$) and concentrated. The crude product was crystallized from ethyl acetate to afford **33** in a yield of 0.34 g (31%): mp 212–214 °C; NMR ($CDCl_3$) δ 3.30 (m, 4 H), 3.93 (s, 4 H); IR ($CHCl_3$) ν_{max} 1709 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O_3S_2$: C, 60.98; H, 7.39; S, 18.08. Found: C, 60.85; H, 7.38; S, 18.04.

Attempted Alkylation of 2,2-(Ethylenedithio)-7,7-(ethylenedioxy)-(4aα,4bβ,8aα,10aβ)-perhydro-3-phenanthrenone (33). Into a flame-dried three-necked flask was added 0.16 mL of potassium hydride oil dispersion (22.2%, 0.35 g, 0.875 mmol). This was washed with hexanes and dried under reduced pressure. To this was added 0.1 g of **33** (0.28 mmol) in 10 mL of glyme. This was stirred, under argon, for 5 min, then 0.07 mL of methyl iodide (1.1 mmol) was added, and stirring was continued for 18 h. The mixture was diluted with water and extracted with ether. The ether layer was dried ($MgSO_4$) and concentrated to afford 0.106 g of a mixture. Separation was achieved by thick-layer chromatography to provide 0.021 g of recovered **33** (TLC and NMR) and 0.058 g of a more polar material which contained at least four products (TLC).

7,7-(Ethylenedioxy)-2-[(dimethyl-*tert*-butylsiloxy)methylene]-(4aα,4bβ,8aα,10aβ)-perhydro-3-phenanthrenone (34a). Into an argon flushed three-necked flask was placed 0.042 g of 57% sodium hydride oil dispersion (1.00 mmol). The sodium hydride was washed three times with hexanes and dried under reduced pressure. Then 0.26 g of **31** (0.89 mmol) in 39 mL of dry benzene was added and stirred, under argon. After 15 min 0.148 g of dimethyl-*tert*-butylsilyl chloride was added, and stirring was continued for 20 h. Water was added, and the mixture was extracted with ether. The ether layer was dried and concentrated to afford **34a** as a yellow solid in a yield of 0.305 g (84%). This compound was too unstable to purify further, but by TLC (2.5% acetone/chloroform) and NMR, it appeared to be clean enough to use: NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.93 (s, 9 H, *t*-butyl), 4.20 (s, 4 H), 8.93 (s, 1 H).

Alkylation of 34a: Synthesis of 4,4-Dimethyl-7,7-(ethylenedioxy)-(4aα,4bβ,8aα,10aβ)-perhydro-3-phenanthrenone (30) and 7,7-(Ethylenedioxy)-2,2,4-trimethyl-(4aα,4bβ,8aα,10aβ)-perhydro-3-phenanthrenone (35). To a flame-dried flask was added 4.13 mL of potassium hydride oil dispersion (22.2%, 0.916 g, 22.92 mmol). The hydride was washed with hexanes and dried under reduced pressure. The flask was filled with argon, and 0.59 g of **34a** (1.45 mmol) in 20 mL of tetrahydrofuran was added with a syringe. This was stirred for 5 min, and 1.4 mL of methyl iodide (22.92 mmol) was added. The mixture was stirred, under argon, for 18 h. Water was added carefully, and the mixture was extracted with ether. The organic layer was dried and concentrated to an oil (0.789 g), which was immediately dissolved in 20 mL of tetrahydrofuran and treated with 4.0 mL of 1 M tetrabutylammonium fluoride. This was stirred at room temperature for 2.5 h and then was partitioned between ether and water. The ether layer was dried and concentrated to afford 0.480 g of an oil, which was chromatographed over 20 g of silica gel (rapid linear gradient chromatography, benzene/5% ethyl acetate in benzene) to give four products. The first which proved to be **35** was isolated in a yield of 0.12 g (27%). It was recrystallized from methanol: mp 115–116 °C; NMR ($CDCl_3$) δ 1.08 (s, 3 H), 1.10 (d, 2 H, J = 3 Hz), 1.30 (s, 3 H), 3.96 (s, 4 H); IR (KBr) ν_{max} 1692 cm^{-1}. Anal. Calcd for $C_{19}H_{30}O_3$, C, 74.46; H, 9.86. Found: C, 74.17; H, 10.01.

The second which proved to be **30** was isolated in a yield of 0.10 g (24%). It was recrystallized from methanol: 134–136 °C; NMR ($CDCl_3$) δ 1.03 (s, 3 H), 1.15 (s, 3 H), 3.93 (s, 4 H), IR (KBr) ν_{max} 1694 cm^{-1}. Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.87; H, 9.70.

The third proved to be **17**. It was isolated in a yield of 0.023 g (5%) and its identity was established by NMR and TLC. A more polar material of unknown structure was also isolated (0.05 g).

7,7-(Ethylenedioxy)-2-[((2-methoxyethoxy)methoxy)methylene]-(4aα,4bα,8aα,10aβ)-perhydro-3-phenanthrenone (34b). To a flame-dried flask flushed with argon was added 0.035 g of sodium hydride oil dispersion (57%, 0.83 mmol). It was washed with hexane and dried under reduced pressure. Then 0.22 g of **31** (0.75 mmol) in 10 mL of tetrahydrofuran was added and stirred for 15 min. (2-Methoxyethoxy)methyl chloride, 0.11 mL (0.99 mmol), was added, and stirring was continued for 5 h. At the end of this time, water was added, and the mixture was extracted with ether. The ether layer was dried ($MgSO_4$) and concentrated to yield 0.287 g of a mixture. This was separated by the use of thick-layer chromatography (8% acetone/chloroform). The C- and O-alkylated products were isolated in yields of 0.16 and 0.048 g, respectively. These were identified by NMR and not characterized further. C-Alkylated **34b**: NMR ($CDCl_3$) δ 3.36 (s, 3 H), 3.53–3.93 (m's, 4 H), 3.93 (s, 4 H), 5.20 (s, 2 H), 10.2 (s, 1 H), IR ($CHCl_3$) ν_{max} 1710–1725 cm^{-1}. O-Alkylated **34b**: NMR ($CDCl_3$) δ 3.38 (s, 3 H), 3.66 (m, 4 H), 3.95 (s, 4 H), 5.10 (s, 2 H), 7.43 (s, 1 H), IR ($CHCl_3$) ν_{max} 1700–1710 cm^{-1}.

7,7-(Ethylenedioxy)-2-[(isopropoxy)methylene]-(4aα,4bβ,8aα,10aβ)-perhydro-3-phenanthrenone (34c). To a solution of 1.02 g of **31** (3.49 mmol) in 110 mL of acetone was added 3.41 g of potassium carbonate (24.7 mmol) and 3.41 mL of isopropyl iodide (34.1 mmol). This was refluxed for 24 h, under argon, concentrated, diluted with water, and extracted with ether. The ether layer was dried and concentrated to afford 1.18 g of a mixture of the O-alkylated **34c** and the C-alkylated product in a ratio of about 3:1 (NMR integration vinyl proton vs. the aldehyde proton). Crystallization from hexanes afforded **34c** in a yield of 0.68 g (58%). Recrystallization from acetone–hexanes gave the analytical sample: mp 132–133 °C; NMR ($CDCl_3$) δ 1.28 (d, 6 H, J = 6 Hz), 3.90 (s, 4 H), 7.36 (br s, 1 H), IR ($CHCl_3$) ν_{max} 1672 cm^{-1}. Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82, H, 9.04. Found: C, 71.76; H, 9.06.

X-ray Crystal and Molecular Structure Determination of 7,5-Ethano-9,12-seco-11,19-bisnor-17α-pregn-4-ene-3,20-dione (28). A single hydrated crystal of **28** of dimensions 0.16 × 0.24 × 0.40 mm was used for the experimental X-ray measurements, which were performed on Nonius CAD4 diffractometer. The systematic absences in the diffraction pattern were consistent with the orthorhombic space group $P2_12_12_1$ and the cell constants were determined by a least-squares analysis of the 20 values for 25 reflections [at 20 °C; λ(Mo Kα) = 0.71069 Å]. The crystal data: $C_{21}H_{30}O_2$; MW 314.47; a = 119752 (1) Å, b = 14.523 (2) Å, c = 10.632 (1) Å; V = 1814.7 $Å^3$; Z = 4; D_X = 1.15 gm/cm.

Integrated intensities were measured for 1875 independent reflections having $0 < 68°$ by using Cu Kα radiation. Lorentz and polarization corrections [$1 + \cos^2 2\theta$] were applied, and normalized structure factor amplitudes were computed. The structure was then solved by a straight forward application of the MULTAN program.[30] The positional and anisotropic thermal

Table I. Fractional Positional Parameters (×10⁴) and Equivalent Isotropic Atomic Displacement Parameters (U_{eq} × 10 $Å^2$) for the Non-Hydrogen Atoms

atom	X/A (σ)	Y/B (σ)	Z/C (σ)	U_{eq} (σ)
C(1)	1286 (2)	8202 (2)	7319 (3)	44 (1)
C(2)	199 (2)	8637 (2)	7846 (3)	47 (1)
C(3)	−648 (2)	7919 (2)	8221 (3)	47 (1)
C(4)	−199 (2)	7055 (2)	8716 (2)	42 (1)
C(5)	925 (2)	9875 (1)	8780 (2)	34 (1)
C(6)	1366 (2)	6037 (2)	9450 (2)	39 (1)
C(7)	2304 (2)	5526 (1)	8732 (2)	35 (1)
C(8)	3268 (2)	6195 (1)	8369 (2)	29 (1)
C(9)	2760 (2)	6970 (1)	7572 (2)	33 (1)
C(10)	1805 (2)	7509 (1)	8232 (2)	34 (1)
C(12)	5245 (2)	6548 (2)	5983 (2)	42 (1)
C(13)	5344 (2)	6158 (1)	7321 (2)	31 (1)
C(14)	4222 (2)	5663 (1)	7716 (2)	29 (1)
C(15)	4625 (2)	4846 (1)	8511 (2)	34 (1)
C(16)	5620 (2)	4488 (1)	7735 (3)	41 (1)
C(17)	6275 (2)	5362 (1)	7421 (2)	36 (1)
C(18)	5668 (2)	6929 (1)	8227 (2)	39 (1)
C(20)	7038 (2)	5286 (2)	6281 (3)	47 (1)
C(21)	8053 (3)	5910 (3)	6239 (5)	70 (1)
C(22)	2725 (2)	4701 (2)	9494 (3)	45 (1)
C(23)	3673 (2)	4181 (1)	8830 (3)	45 (1)
O(3)	−1671 (1)	8072 (2)	8181 (3)	72 (1)
O(20)	6871 (2)	4743 (2)	5450 (2)	75 (1)

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Table II. Hydrogen Atom Positional Parameters ($X10^3$) and Isotropic Displacement Parameters (U_{iso} X 10)

atom	X/A (σ)	Y/B (σ)	Z/C (σ)	U_{iso}
H(1A)	114 (2)	784 (2)	647 (3)	45
H(1B)	179 (2)	861 (2)	712 (3)	45
H(2A)	-18 (2)	899 (2)	706 (3)	47
H(2B)	35 (3)	905 (2)	858 (3)	47
H(4)	-71 (2)	665 (2)	903 (2)	42
H(6A)	64 (2)	568 (1)	959 (2)	38
H(6B)	172 (2)	624 (1)	1038 (3)	38
H(7A)	197 (2)	529 (2)	797 (2)	36
H(8B)	355 (2)	639 (1)	915 (2)	30
H(9A)	245 (2)	674 (2)	680 (2)	32
H(9B)	331 (2)	742 (2)	728 (2)	32
H(10B)	219 (2)	785 (1)	907 (2)	34
H(12A)	464 (2)	703 (2)	588 (3)	42
H(12B)	611 (2)	683 (2)	574 (2)	42
H(12C)	509 (2)	611 (2)	532 (3)	42
H(14A)	396 (2)	539 (1)	689 (2)	31
H(15B)	493 (2)	505 (2)	929 (2)	35
H(16A)	528 (2)	417 (2)	700 (3)	42
H(16B)	610 (2)	403 (2)	816 (3)	42
H(17B)	675 (2)	554 (2)	816 (2)	38
H(18A)	576 (2)	669 (2)	915 (2)	41
H(18B)	650 (2)	714 (2)	789 (3)	41
H(18C)	511 (2)	748 (2)	812 (3)	41
H(21A)	856 (3)	574 (2)	707 (4)	65
H(21B)	845 (3)	583 (2)	548 (3)	65
H(21C)	785 (3)	656 (2)	618 (3)	65
H(22A)	202 (2)	423 (2)	946 (3)	42
H(22B)	292 (2)	487 (2)	1036 (3)	42
H(23A)	403 (2)	363 (2)	934 (3)	45
H(23B)	347 (3)	394 (2)	804 (3)	45

parameters for all non-hydrogen atoms were refined by full-matrix least-squares analysis using the reflections for which the observed intensity was greater than twice the corresponding standard deviation. The hydrogen atom positions were located in electron density difference maps, and they were refined isotropically. Weights used were $1\sigma_F^2$.[31] Using observed data, the final reliability indexes werer $R = 4.8$, $R_w = 7.7\%$, $S = 2$, and $(\delta/\sigma)_{av} = 0.10$. Atomic scattering factors were taken from the *International Tables for X-ray Crystallography*[32] for neutral atoms and anomalous-dispersion corrections for non-hydrogen atoms were taken from Cromer and Liberman.[33] All calculations except for MULTAN were performed with XRAY 76.[34]

The final coordinates and isotropic atomic displacement for all the atoms are given in Tables I and II. Tables of bond lengths and angles and molecular packing patterns are available from W.L.D. upon request.

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Determination of Enantiomeric Purity of Polar Substrates with Chiral Lanthanide NMR Shift Reagents in Polar Solvents[1]

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The proton NMR spectra of 19 1,2- and 1,3-dioxygenated compounds were studied in deuteriated acetonitrile, acetone, and chloroform in the presence of chiral lanthanide NMR shift reagents tris(3-((heptafluoropropyl)-hydroxymethylene)-*d*-camphorato)europium(III) (1) and tris(((trifluoromethyl)hydroxymethylene)-*d*-camphorato)europium(III) (2). Enantiotopic O*H*, C*H*, and CH_3 NMR resonances were best resolved in acetonitrile; line broadening obscured the scalar coupling. Enantiomeric excesses as high as 98% can be determined for 16 of these compounds in this polar solvent.

Chiral synthons are often smaller polar molecules, and it is useful to have a simple method of determining their optical purity. Methods based on chiral lanthanide shift reagents often fail with these substances[2] for several reasons. They may be contaminated with water and sparingly soluble in the nonpolar solvents normally used with shift reagents ($CDCl_3$, CD_2Cl_2). In these solvents, their strong binding to the lanthanide ion (often a reflection of chelation by multiple polar functions) gives broad resonances and, as a consequence, poor resolution between enantiotopic resonances in the NMR spectrum.[3] We have re-

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(2) For references to non lanthanide based methods, see: Luchinat, C.; Roelans, S. *J. Am. Chem. Soc.* **1986**, *108*, 4873-4878.

(3) Sullivan, G. R. *Top. Stereochem.* **1979**, *10*, 287-329. Fraser, R. R. *Asymmetric Synth.* **1983**, *1*, 173-196. McCreary, M. D.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038-1054.

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