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Steroid Total Synthesis. IX.[1] Alternative Routes to (±)- and (+)-Estr-4-ene-3,17-dione and (±)-13β-Ethylgon-4-ene-3,17-dione *via* Novel Nitrile Intermediates

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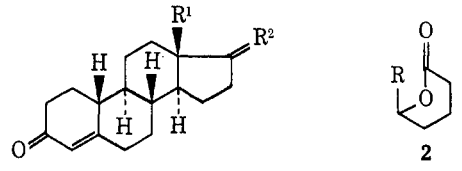
Total syntheses of (±)-estr-4-ene-3,17-dione [(±)-**1a**] and (±)-13β-ethylgon-4-ene-3,17-dione [(±)-**1b**] are described using the known and readily available compound 2,2-di(3-cyanopropyl)-1,3-dioxolane (**5**) as a starting material. The key step in the sequence involves condensation of amine **10** (derived from **5** *via* δ-lactone **9**) with 2-methyl- or 2-ethyl-1,3-cyclopentanedione giving mixtures of the racemic dienes **12a–13a** and **12b–13b** in which the trans isomers **12a** and **12b** predominate. In the optically active series, (+)-estr-4-ene-3,17-dione [(+)-**1a**] was synthesized *via* resolution of base **11** giving the diastereomer **23**. Condensation of **23** or the related ketone **26** with 2-methyl-1,3-cyclopentanedione afforded predominantly the trans diene (−)-**12a** possessing the natural C_{13} configuration. Conversion of the dienes **12** to the title 19-nor steroids was efficiently achieved in 8 stages *via* the intermediates **14–19**. Treatment of the triketone intermediates **15a** and **15b** with *p*-toluenesulfonic acid gave rise to the novel hetero steroids **20a, 20b** and **21a, 21b**.

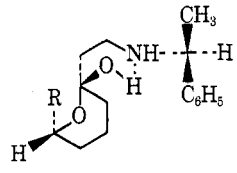
Previous publications from our laboratories have described novel total syntheses of (±)- and (−)-17β-hydroxyde-*A*-androst-9-en-5-one,[2,3] (−)-9β,10α-testosterone,[4] (±)-13β-ethyl-17α-ethynyl-17β-hydroxygon-4-en-3-one (**1c**),[5] (+)- and (±)-estr-4-ene-3,17-dione (**1a**),[1,6-8] and (±)-13β-ethylgon-4-ene-3,17-dione (**1b**).[6] The key intermediates leading to the important optically active steroids are the dienes **4**[1,4,7] which are formed upon condensation of the Mannich bases **3** (or certain related 4-hydroxyalkyl vinyl ketone precursors obtained from the δ-lactones **2**) with 2-methyl-1,3-cyclopentanedione. These reactions, which occur with substantial asymmetric induction give predominantly the trans dienes possessing the natural C_{13} configuration. In this paper we wish to describe a related route to the 19-nor steroid (+)-**1a** *via* the intermediates **2–4** [R = $(CH_2)_3CN$] as well as model studies leading to (±)-**1a** and (±)-**1b** (Chart I). A novel feature of the present work involves the efficient generation of nine carbon atoms (C_1–C_3 and C_5–C_{10}) of the steroid molecule starting from γ-butyrolactone and sodium cyanide.

CHART I

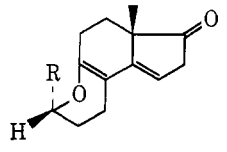


2

1a, $R^1 = CH_3$; $R^2 = O$
b, $R^1 = C_2H_5$; $R^2 = O$
c, $R^1 = C_2H_5$; $R^2 = -OH$, $\cdots C{\equiv}CH$



3



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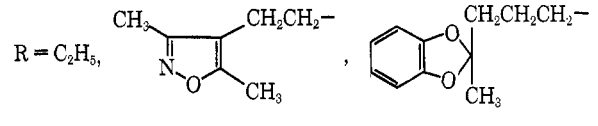
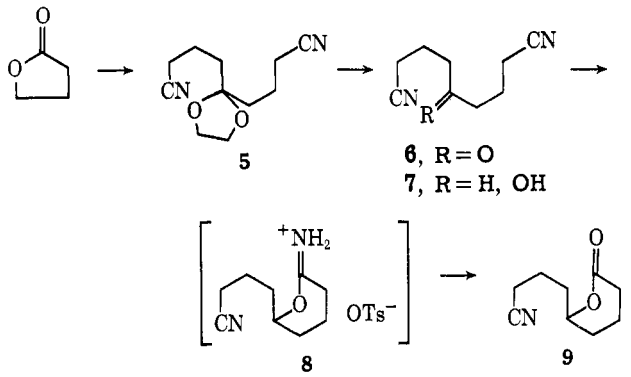


Results and Discussion

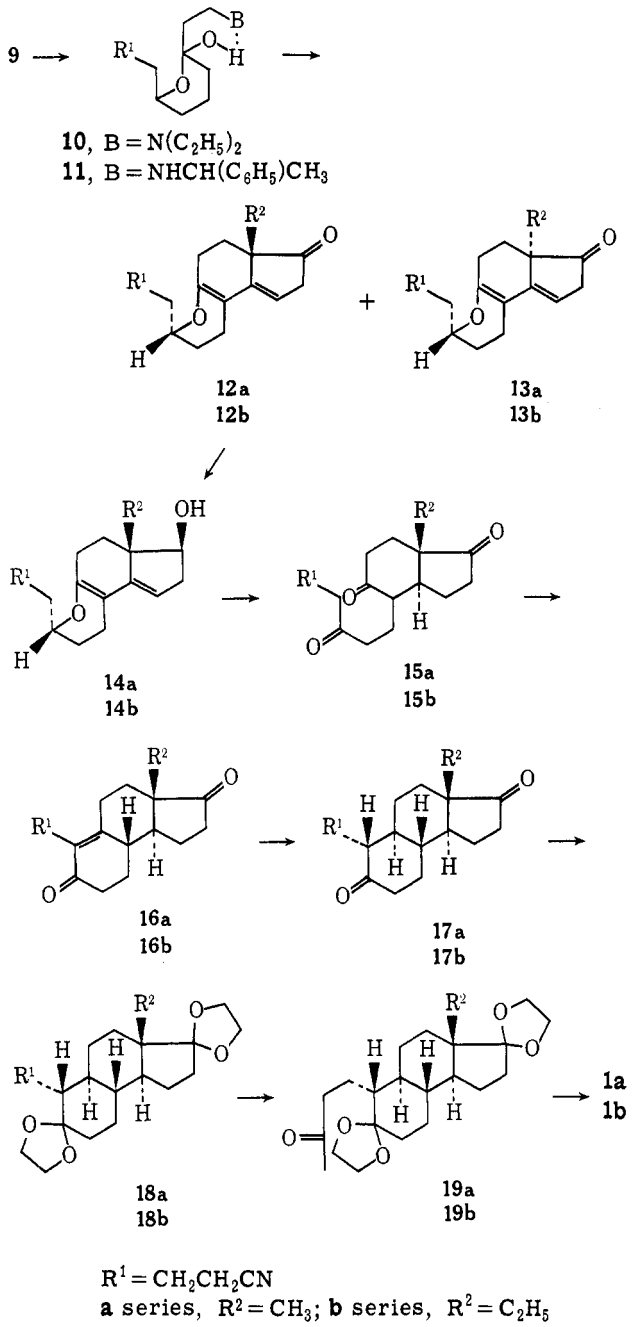
In 1962, Hartley[9] reported a synthesis of 2,2-di(3-cyanopropyl)-1,3-dioxolane (**5**) (Scheme I) in high yield by reaction of 1,7-dichloroheptan-4-one ethylene ketal with sodium cyanide. The required dichloro ketone is, in turn, readily available from γ-butyro-

(1) Part VIII: M. Rosenberger, R. Borer, R. Mueller, and G. Saucy, *Helv. Chim. Acta*, in press.
(2) Part I: G. Saucy, R. Borer, and A. Fürst, *ibid.*, **54**, 2034 (1971).
(3) Part II: G. Saucy and R. Borer, *ibid.*, **54**, 2121 (1971).
(4) Part III: G. Saucy and R. Borer, *ibid.*, **54**, 2517 (1971).
(5) Part IV: M. Rosenberger, T. P. Fraher, and G. Saucy, *ibid.*, **54**, 2857 (1971).
(6) Part V: J. W. Scott and G. Saucy, *J. Org. Chem.*, **37**, 1652 (1972).
(7) Part VI: J. W. Scott, R. Borer, and G. Saucy, *ibid.*, **37**, 1659 (1972).
(8) Part VII: M. Rosenberger, A. Duggan, and G. Saucy, *Helv. Chim. Acta*, **55**, 1333 (1972).
(9) D. Hartley, *J. Chem. Soc.*, 4722 (1962).

SCHEME I



SCHEME II



lactone.[10] We reasoned that **5** would be a valuable starting material for the production of 19-nor steroids (using appropriate modifications of the previously reported schemes)[1,6-8] if its conversion into the lactone **9** [2, R = $(CH_2)_3CN$] could be readily accomplished. It was hoped that utilization of the cyanoethyl moiety in **9** as an A-ring synthon (C_1–C_3) would eliminate the often troublesome requirements imposed by protected or disguised carbonyl functions. Furthermore, the nitrile function appeared to offer sufficient stability to survive the reaction conditions required throughout the synthetic scheme and would allow facile conversion to a methyl ketone by, for example, reaction with methyllithium at a suitable stage late in the sequence.

The required lactone **9** was synthesized as shown in Scheme I. Acid hydrolysis of ketal **5** gave the dicyano ketone **6** which was subsequently reduced with sodium borohydride affording the alcohol **7**. Selective transformation of only one of the two equivalent nitrile functions in **7** was most conveniently achieved by treatment of this material with 1 equiv of *p*-toluenesulfonic acid monohydrate in refluxing toluene. In this way, the lactone **9** was readily produced in an overall yield of 42% based on γ-butyrolactone. The facile conversion of **7** to **9** most likely involves the initial formation of the cyclic imino ether salt **8** which then hydrolyzes to the lactone and ammonium *p*-toluenesulfonate.

The 19-nor steroids (±)-**1a** and (±)-**1b** were produced as shown in Scheme II. Reaction of **9** with vinylmagnesium chloride at −50 to −60° [3] followed by immediate treatment of the resultant vinyl ketone with diethylamine gave the Mannich base (±)-**10** in 81% yield. Under these conditions, the nitrile function was untouched by the Grignard reagent even though an excess of the latter was employed. By substituting (*S*)-(−)-α-methylbenzylamine for diethylamine in this sequence, a mixture of diastereomeric Mannich bases **11** was obtained which could be resolved[4] and used for the synthesis of (+)-**1a** (see below).

Condensation of amine **10** with 2-methyl-1,3-cyclopentanedione in refluxing toluene–acetic acid[2] afforded a mixture of the dienes (±)-**12a** and (±)-**13a** in 85% yield, recrystallization of which allowed isolation of the major (trans) isomer (±)-**12a** in pure form. Further transformations were performed using the major isomer so obtained.[11] Thus, reduction with sodium borohydride furnished the alcohol (±)-**14a** which by a sequence[2,3] involving regio- and stereoselective catalytic hydrogenation [14,15-carbon–carbon double bond (steroid numbering)] then hydration and oxidation[12] subsequently gave the oily triketone (±)-**15a**. Cyclization of the latter material was best accomplished using a catalytic amount of potassium hydroxide. In this way the tricyclic enedione (±)-**16a** was secured in 46.5% overall yield based on the diene (±)-**12a**.

By an analogous set of transformations, the homologous enedione (±)-**16b** was produced starting from Mannich base **10** and 2-ethyl-1,3-cyclopentanedione[13] *via* the racemic intermediates **12b**–**15b**. In this case, the diene mixture (±)-**12b**–(±)-**13b** was noncrystalline and was used without separation.[11]

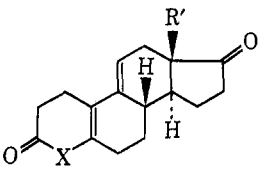
(10) O. E. Curtis, Jr., J. M. Sandri, R. E. Crocker, and H. Hart, *Org. Syn.*, **38**, 19 (1958).

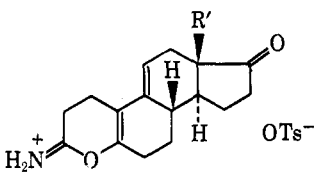
(11) For the purpose of synthesizing racemic 19-nor steroids the separation of these dienes is unnecessary since both lead ultimately to the same racemic intermediates **16a** and **16b**.

(12) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, **39** (1946).

(13) H. Schick, G. Lehmann, and G. Hilgetag, *Angew. Chem.*, **79**, 378 (1967).

When the triketonitriles (±)-**15a** and (±)-**15b** were cyclized under the influence of *p*-toluenesulfonic acid monohydrate in refluxing toluene, the aza steroids (±)-**20a** and (±)-**20b** and oxa steroids (±)-**21a** and (±)-**21b** were isolated in addition to the enediones (±)-**16a** and (±)-**16b**. These hetero steroids probably arise from further acid catalyzed reactions of the enediones. In fact, when (±)-**16a** was heated with *p*-toluenesulfonic acid monohydrate, (±)-**20a** and (±)-**21a** were produced in 24 and 47% yields, respectively. The synthesis of dihydro-2-pyridones (*e.g.*, **20**) from δ-ketonitriles under acidic conditions is well known.[14-16] The formation of the oxa steroids probably involves facile enolization of the α,β-unsaturated ketone function in **16** leading to an imino ether salt such as **22** which then hydrolyzes to the isolated diene lactone.





22

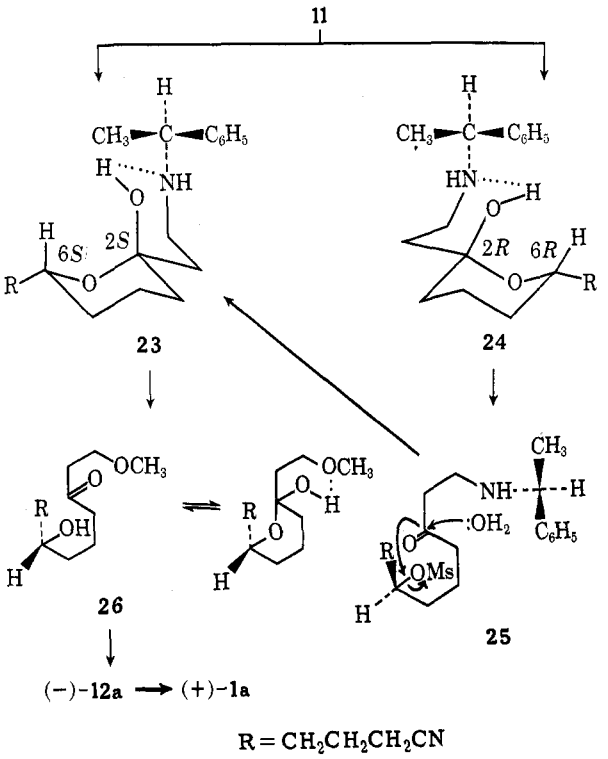
20a, X = NH; R′ = CH_3
b, X = NH; R′ = C_2H_5
21a, X = O; R′ = CH_3
b, X = O; R′ = C_2H_5

Catalytic hydrogenation of the enediones (±)-**16a** and (±)-**16b** over palladium on carbon in the presence of triethylamine[6] gave the expected saturated diketonitriles (±)-**17a** and (±)-**17b**. Conversion of these materials to the bisketals (±)-**18a** and (±)-**18b** was followed by reaction with methyllithium affording the known[6] keto bisketals (±)-**19a** and (±)-**19b**. Finally, exposure of the latter substances to refluxing methanolic hydrochloric acid yielded the desired diones (±)-**1a** and (±)-**1b** in 40 and 47% overall yields, respectively, based on the tricyclic diketones (±)-**16a** and (±)-**16b**.

In order to synthesize (+)-**1a**, the Mannich base **11** was resolved by crystallization of the oxalic acid salt. This led to the oxalate of the oily 2*S*,6*S* diastereomer **23**[17] [**3**, R = $(CH_2)_3CN$] (Scheme III) in 21–27% weight yield based on **9** (42–54% of theory). From the mother liquor of this recrystallization the 2*R*,6*R* base **24** was obtained in crystalline form. In an effort to increase the yield of the desired base **23**, an inversion cycle[1] was employed. Thus, treatment of **25** with a mixture of methanesulphonyl chloride, methanesulfonic acid and pyridine led to the unstable *O*-mesylate **25** which usually was not isolated. Under these conditions N-mesylation was not observed. When the mesylation mixture was simply treated with water and heated, stereochemical inversion occurred, possibly as shown giving the base **23**. Incorporation of this inversion sequence allowed the isolation of **23** oxalic acid salt in an overall yield of 44% based on lactone **9**.

Following prior art,[4] base **23** was treated with benzaldehyde and sodium bicarbonate in refluxing methanol giving the β-methoxy ketone **26** (mixture of keto and hemiketal forms) in 92% yield as well as the Schiff base derived from α-methylbenzylamine and benzaldehyde. Condensation[4] of **26** with 2-methyl-1,3-cyclopentanedione in refluxing toluene–acetic acid[2] then furnished the mixture of dienes **12a** and **13a** in optically active form.[18] By direct crystallization, the major (trans) isomer (−)-**12a** [**4**, R = $(CH_2)_3CN$] was isolated in 38% yield based on **24**. The minor isomer **13a**, of unnatural C_{13} configuration, was never obtained in pure form. The mixture of dienes **12a** and **13a** could also be obtained by reaction of **23** directly with 2-methyl-1,3-cyclopentanedione. In a sequence which completely parallels that employed in the racemic series, the diene (−)-**12a** was finally converted to (+)-estr-4-ene-3,17-dione [(+)-**1a**][7] in an overall yield of 39.6%, *via* the optically active intermediates **14a**–**19a**.

SCHEME III



R = $CH_2CH_2CH_2CN$

Experimental Section[19]

5-Oxoazeleonitrile (**6**).—A solution of 347.4 g (1.67 mol) of the dicyano ketal **5**[9] in 1.5 l. of acetone was cooled to 10° and treated with 1 l. of cold (10°) 3 *N* aqueous hydrochloric acid. The mixture was allowed to stand at room temperature for 18 hr then concentrated to a volume of approximately 1.5 l. at 40° and aspirator pressure. The organic materials were isolated with

(14) A. I. Meyers and G. Garcia-Munoz, *J. Org. Chem.*, **29**, 1435 (1964).
(15) J. J. Vill, T. R. Steadman, and J. J. Godfrey, *ibid.*, **29**, 2780 (1964).
(16) N. P. Shusherina, A. V. Golovin, and R. Ya. Levina, *Zh. Org. Khim.*, **30**, 1762 (1960).
(17) The configuration of this material (which leads ultimately to **1a** of natural configuration) is assigned by analogy with similarly produced optically active Mannich bases from the previous work; see ref 3, 4, and 7.
(18) The mechanism of this crucial, stereoselective annelation reaction has been discussed previously; see ref 4.
(19) Unless otherwise noted, reaction products were isolated by addition of brine and extraction with the specified solvent. Organic solutions were then washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated at water aspirator pressure at 40–50°. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. All reactions except hydrogenations were carried out under an atmosphere of nitrogen. Column chromatography was performed using Merck (Darmstadt) silica gel 0.05–0.2 mm. Varian A-60 or HA-100 spectrometers were used to obtain the pmr spectra. Infrared spectra were recorded on a Beckman IR-9 spectrophotometer. The uv spectra were recorded on a Cary Model 14M spectrophotometer. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Thin layer chromatography was performed using Brinkmann silica gel G plates with uv indicator. Plates were developed with 1:1 benzene–ethyl acetate. Spots were detected with uv light, iodine vapor, or *p*-toluenesulfonic acid spray followed by heating.

methylene chloride giving 276 g of oily ketodinitrile **6**. A sample of this material on distillation yielded pure **6**, bp 137–140° (0.05 mm), as a colorless liquid: ir ($CHCl_3$) 2250 (C≡N) and 1710 cm^{-1} (ketone C=O).

Anal. Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 66.08; H, 7.46; N, 17.07.

5-Hydroxyazeleonitrile (7).—A solution of 276 g (1.67 mol) of crude ketodinitrile **6** in 500 ml of methanol and 500 ml of water was added to a cooled (5°), stirred solution of 33 g (0.873 mol) of sodium borohydride in 300 ml of water. The temperature was held at 5–10° during the addition. After addition was complete, the mixture was stirred at room temperature for 90 min. Dilute aqueous sulfuric acid solution (4 *N*) was added to the reaction mixture with cooling (10°) until pH 2–3 was obtained. The organic materials were isolated with methylene chloride giving 272 g (98%) of hydroxydinitrile **7** as a colorless, mobile liquid. A sample of this material on evaporative distillation gave an analytical specimen: bp 145–175° (bath temperature) (0.01 mm); ir ($CHCl_3$) 3625, 3500 (OH), and 2250 cm^{-1} (C≡N).

Anal. Calcd for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.92; H, 8.35; N, 16.68.

(±)-8-Cyano-5-hydroxyoctanoic Acid Lactone (9).—A solution of 272 g (1.64 mol) of crude hydroxydinitrile **7** in 1.5 l. of toluene was treated with 312 g (1.64 mol) of *p*-toluenesulfonic acid monohydrate and the mixture was stirred and heated at reflux for 1 hr. The starting materials dissolved and were replaced by a precipitate of ammonium tosylate which, after cooling, was filtered with suction and washed with fresh toluene. The combined filtrate and washes were washed with water, dried and concentrated *in vacuo*. The residue on distillation furnished pure lactone **9** (214 g, 78.2%): bp 162–165° (0.2 mm); ir ($CHCl_3$) 2250 (C≡N), 1730 (δ-lactone C=O), and 1250 cm^{-1}.

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.63; H, 7.89; N, 8.18.

(±)-2-(2-Diethylaminoethyl)-6-(3-cyanopropyl)tetrahydropyran-2-ol (10).—A stirred solution of 8.35 g (0.05 mol) of lactone **9** in 40 ml of dry THF was cooled to −70° and treated over 14 min with 38 ml (0.076 mol) of a 2 *M* solution of vinylmagnesium chloride in THF. The mixture was stirred for 6 min at −50°, cooled to −65°, and decomposed first with 2 ml of methanol and subsequently with 50 ml of 5% aqueous ammonium chloride solution. Sufficient acetic acid was added to yield two clear layers yet keeping the pH above 7.

The organic layer was separated and the aqueous layer was extracted with THF. The combined THF solutions were treated with 10 ml of diethylamine and left at room temperature for 1.5–2 hr. Removal of solvents *in vacuo* yielded the crude, oily Mannich base (17 g).

This material was treated with 50 ml of 10% aqueous acetic acid and 20 ml of ether. The aqueous layer was reextracted with 20 ml of additional ether and the combined ether extracts were reextracted with 10% aqueous acetic acid then discarded. The combined aqueous acid extract was made alkaline with 10% aqueous sodium carbonate solution and the product was isolated by extraction with methylene chloride affording the pure product **10** (10.84 g, 81%) as a mobile, pale yellow oil: ir ($CHCl_3$) 3150, 3450 (bonded OH and NH), 2250 (C≡N), 1710 cm^{-1} (w, C=O of open form).

Anal. Calcd for $C_{15}H_{28}N_2O_2$: C, 67.12; H, 10.52; N, 10.44. Found: C, 67.15; H, 10.37; N, 10.28.

(±)-*trans*-3-(3-Cyanopropyl)-6a-methyl-1,2,3,5,6,6a-hexahydrocyclopenta[*f*][*l*]benzopyran-7(8*H*)-one [(±)-12a].—A solution of 18.92 g (0.0706 mol) of Mannich base **10**, 8.72 g (0.0778 mol) of 2-methyl-1,3-cyclopentanedione, 64 ml of glacial acetic acid, and 253 ml of toluene was stirred and heated at reflux for 1.5 hr. After cooling, the solution was washed twice with water, once with 0.5 *N* aqueous HCl, twice with saturated aqueous sodium bicarbonate, then dried, filtered, and concentrated *in vacuo* giving 16.3 g (85.4%) of orange, crystalline diene mixture (±)-**12a** and (±)-**13a**. Recrystallization from 20 ml of ethanol gave 11.54 g (60.4%) of pale orange crystals, mp 95–99° [mainly (±)-12a]. By further recrystallization of a sample from ethanol, an analytical specimen of (±)-**12a** was obtained as pale yellow crystals: mp 100–101.5°; uv max (95% EtOH) 253 nm (ε 19,500); ir ($CHCl_3$) 2250 (C≡N), 1730 (C=O), 1630 cm^{-1} (C=C); nmr ($CDCl_3$) δ 5.47 (t, 1, J = 2 Hz, HC=C), 3.85 (m, 1, HCO), 1.14 ppm (s, 3, C_{6a} CH_3); mass spectrum m/e 271 (M^+).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.36; H, 7.75; N, 5.03.

(±)-*trans-anti*-6-(2-Cyanoethyl)-3a-methyl-1,2,3a,4,5,9,9a,9b-octahydro-3*H*-benz[*e*]indene-3,7(8*H*)-dione [(±)-16a].—A solution of 6 g (0.0222 mol) of diene (±)-**12a** in 35 ml of benzene was added dropwise, over a 10 min period to an ice-cold solution of 0.864 g (0.0228 mol) of sodium borohydride in 50 ml of ethanol and 5 ml of water. The resulting mixture was stirred with ice-bath cooling for 25 min then the cooling bath was removed and the mixture was stirred at ambient temperature for an additional 15 min. Isolation with ether gave 6 g of yellow, crystalline alcohol (±)-**14a**: ir ($CHCl_3$) 3450, 3600 (OH), 2250 (C≡N), 1640 cm^{-1} (C=C).

A solution of this alcohol in 35 ml of toluene and 25 ml of THF was hydrogenated over 1 g of preequilibrated 5% palladium on carbon[20] at room temperature and 1 atm for 23 hr. A total of 543 ml of hydrogen was consumed (555 ml theory). The catalyst was filtered with suction on a pad of Celite and the filter cake was washed well with toluene. The combined filtrate and washes were concentrated at reduced pressure giving 6.65 g of pale yellow foam: ir (film) 3480 (OH), 2250 (C≡N), 1680 cm^{-1} (enol ether).

This material was dissolved in 165 ml of acetone and treated with 15 ml of 0.5 *N* aqueous sulfuric acid. The resulting solution was stirred at room temperature for 3.25 hr, then cooled (ice bath), and treated with 16.5 ml of Jones reagent[12] dropwise, over 15 min. The ice bath was removed and the resulting red mixture was stirred at room temperature for 3.25 hr. After decomposition of the excess oxidant with sodium bisulfite, the product was isolated with benzene (the organic solution was additionally washed with saturated aqueous sodium bicarbonate solution) giving 5.93 g (92.5%) of triketone (±)-**15a** as an orange oil: ir (film) 2250 (C≡N), 1745 (cyclopentanone C=O), 1715 cm^{-1} (cyclohexanone and aliphatic C=O).

A solution of 3.983 g (0.01 mol) of this triketone in 20 ml of methanol was treated with 10 ml of 0.1 *M* methanolic potassium hydroxide solution. The resulting dark brown solution was stirred and heated at reflux for 2 hr. After cooling, the product was isolated with methylene chloride giving 2.8 g (93.8%) of crude enedione (±)-**16a** as a brown solid. Recrystallization from ethanol gave 1.5 g (50.2%) of pale yellow crystals, mp 105–107°. The analytical specimen was obtained as colorless crystals, mp 106–107°, by further recrystallization of a sample from ethanol: ir ($CHCl_3$) 2250 (C≡N), 1740 (cyclopentanone C=O), 1665 (cyclohexenone C=O), 1605 cm^{-1} (C=C); uv max (95% EtOH) 245 nm (ε 15,640); nmr ($CDCl_3$) δ 1.03 ppm (s, C_{3a} CH_3).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.51; H, 7.99; N, 5.08.

(±)-*trans-anti-trans-anti*-6-(2-Cyanoethyl)-3a-methyl-1,2,3a,4,5,5a,8,9,9a,9b-decahydrobenz[*e*]indene-3,7(6*H*)-dione [(±)-17a].—A solution of 1.03 g (3.82 mmol) of enedione (±)-**16a** in 25 ml of dry THF and 0.7 ml of triethylamine was stirred in an atmosphere of hydrogen over 0.25 g of preequilibrated 5% palladium on carbon.[20] After 40 min, 102 ml of hydrogen was absorbed (96 ml theory) and the hydrogenation was stopped. The catalyst was filtered and washed with ether and the combined filtrate and washings were concentrated at reduced pressure giving 1 g of colorless, solid residue. This was recrystallized from ethanol giving 0.805 g (77.4%) of colorless crystals, mp 130–132°. An analytical specimen was obtained, mp 132–133°, by further recrystallization from ethanol: ir ($CHCl_3$) 2250 (C≡N), 1740 (cyclopentanone C=O), 1710 cm^{-1} (cyclohexanone C=O); nmr ($CDCl_3$) δ 0.98 ppm (s, C_{3a} CH_3); mass spectrum m/e 273 (M^+).

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.49; H, 8.49; N, 5.05.

(±)-*trans-anti-trans-anti*-3,3,7,7-Bis(ethylenedioxy)-3a-methyl-6-(2-cyanoethyl)perhydro-1*H*-benz[*e*]indene [(±)-18a].—A solution of 0.1 g (0.366 mmol) of diketone (±)-**17a** in 5 ml of dry THF was treated with 0.226 g (3.66 mmol) of ethylene glycol, 0.2 ml of trimethyl orthoformate and 0.01 ml of concentrated sulfuric acid. The resulting solution was stirred at room temperature for 1.5 hr then poured into excess 10% aqueous sodium hydroxide solution. The product was isolated with ether giving 0.133 g of colorless, crystalline bisketal (±)-**18a**.

This material was combined with the product from an identical run (0.111 g, 0.244 g total) and chromatographed on 25 g of

(20) A 5% palladium-on-carbon catalyst prepared at F. Hoffmann-La Roche and Co., AG, Basle, Switzerland, and designated AK-4 was employed for this hydrogenation.

silica gel. The fractions eluted with 1:1 benzene–ether gave 0.229 g (86.8%) of pure (±)-**18a** as a colorless solid. Two recrystallizations from ether gave colorless crystals: mp 118.5–120.5°; ir ($CHCl_3$) 2250 (C≡N), 1160, 1105, 1050 cm^{-1}; nmr ($CDCl_3$) δ 3.94, 3.86 (2 s, 8, OCH_2CH_2O), 0.87 ppm (s, C_{3a} CH_3); mass spectrum *m/e* 361 (M^+).

Anal. Calcd for $C_{21}H_{31}NO_4$: C, 69.77; H, 8.65; N, 3.88. Found: C, 69.87; H, 8.39; N, 3.86.

(±)-*trans-anti-trans-anti*-3,3,7,7-Bis(ethylenedioxy)-3a-methyl-6-(3-oxo-1-butyl)perhydro-1*H*-benz[*e*]indene [(±)-19a].—An ethereal methyllithium solution (4.3 ml, 2 *M*, 8.6 mmol) was cooled to −10° (ice–salt bath) and stirred while a solution of 0.711 g (1.97 mmol) of bisketal nitrile (±)-**18a** in 15 ml of anhydrous ether and 5 ml of anhydrous THF was added over a 3-min period. The reaction mixture was stirred at −5° for 1 hr then 10 ml of water was added and stirring was continued at room temperature for 30 min. Isolation with ether gave 0.719 g (96.5%) of essentially pure keto bisketal (±)-**19a** as a colorless solid.

A sample was chromatographed on silica gel and recrystallized from ether giving fluffy white crystals: mp 122–123° (lit.[6] mp 126.5–128°); ir ($CHCl_3$) 1715 (ketone C=O), 1160, 1105, 1050, 1040, 950 cm^{-1}.

(±)-Estr-4-ene-3,17-dione [(±)-1a].—A solution of 0.538 g (1.47 mmol) of bisketal (±)-**19a** in 20 ml of methanol and 6 ml of 4 *N* aqueous hydrochloric acid was stirred and heated at reflux for 4 hr then cooled. The product was isolated with ether giving 0.352 g (87%) of colorless, crystalline product. Recrystallization from aqueous methanol gave 0.254 g (62.7%) of colorless crystals: mp 155–156.5° (lit.[6] mp 157–159.5°, lit.[8] mp 155–157°); uv max (95% EtOH) 240 nm (ε 17,400). This material was identical by ir and tlc analysis with a sample of (±)-**1a** prepared previously.[8]

(±)-4-Azaestra-5(10),9-diene-3,17-dione [(±)-20a].—A solution of 2.853 g (0.01 mol) of crude triketone (±)-**15a** and 0.637 g of *p*-toluenesulfonic acid monohydrate in 130 ml of toluene was stirred and heated at reflux, using a Dean-Stark trap for 4.5 hr after vigorous refluxing began. The mixture was allowed to stir at room temperature for 13.5 hr, then washed twice with saturated aqueous sodium bicarbonate solution. The combined washings were back extracted twice with methylene chloride. The combined organic solutions were dried, filtered, and concentrated *in vacuo* giving 2.728 g of an orange semisolid residue.

This material was triturated with ethyl acetate and the solid was suction filtered and washed until essentially colorless with ethyl acetate giving 0.708 g (26.4%) of off-white, solid (±)-**20a**, mp 259–262° dec. The combined filtrate and washings were concentrated at reduced pressure and the residue chromatographed as described in the following experiment.

A 0.3-g sample of the dienol lactam prepared in this manner was recrystallized from acetonitrile giving a colorless solid: mp 261–264° dec; ir ($CHCl_3$) 3425, 3225 (NH), 1735 (cyclopentanone C=O), 1680 (lactam C=O), 1650 cm^{-1} (C=C); uv max (95% EtOH) 216 nm (ε 7280), 284 (14,360); nmr ($CDCl_3$) δ 8.65 (m, 1, NH), 5.46 (m, 1, C_{11} H), 0.90 ppm (s, 3, C_{13} CH_3); mass spectrum *m/e* 271 (M^+).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.36; H, 8.02; N, 5.20.

(±)-4-Oxaestra-5(10),9-diene-3,17-dione [(±)-21a].—The residue (2.02 g) from the preceding experiment [after removal of (±)-**20a**] was chromatographed on 100 g of silica gel. Elution with 9:1 benzene–ether gave 0.223 g of semicrystalline material rich in dienol lactone (±)-**21a**. The analytical specimen was obtained by several recrystallizations from acetonitrile as colorless prisms: mp 167–169°; ir ($CHCl_3$) 1770 (lactone C=O), 1740 (cyclopentanone C=O), 1665 (C=C), 1160, 1120 cm^{-1}; uv max (95% EtOH) 254 nm (ε 12,300), sh 230 (ε 9400); nmr ($CDCl_3$) δ 5.53 (m, 1, C_{11} H), 0.90 ppm (s, 3, C_{13} CH_3); mass spectrum *m/e* 272 (M^+).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.79; H, 7.51.

The fractions eluted with 4:1 benzene–ether gave 0.866 g (32.3%) of crystalline enedione (±)-**16a**. This was recrystallized from ethanol giving 0.681 g of pale yellow solid, mp 105–107°.

Conversion of Dione (±)-16a to Aza Steroid (±)-20a and Oxa Steroid (±)-21a.—A mixture of 1 g (3.69 mmol) of enedione (±)-**16a**, 0.7 g (3.69 mmol) of *p*-toluenesulfonic acid monohydrate and 40 ml of xylene was stirred and heated at reflux for 5 hr. After cooling the resultant slurry was filtered and the solid was washed with methylene chloride and dried giving 0.534 g (76.6%) of ammonium tosylate.

The filtrate and washes were combined and washed with aqueous sodium bicarbonate then dried, filtered and concentrated *in vacuo* giving 1 g of semisolid residue. This material was chromatographed on 50 g of silica gel. Elution with 9:1 benzene–ether gave 0.467 g (46.7%) of crystalline lactone (±)-**21a**. This material was identical (tlc) to the lactone produced in the preceding experiment.

Elution with ethyl acetate afforded 0.242 g (24.2%) of crystalline lactam (±)-**20a** which was identical (tlc) to the lactam produced in the preceding experiment.

(±)-*trans*- and -*cis*-3-(3-Cyanopropyl)-6a-ethyl-1,2,3,5,6,6a-hexahydrocyclopenta[*f*][*l*]benzopyran-7(8*H*)-one [(±)-12b and (±)-13b].—An 18.0 g (0.143 mol) sample of 2-ethylcyclopentane-1,3-dione[13] was dissolved in 500 ml of 4:1 toluene–glacial acetic acid and treated with a solution of 20.15 g (0.075 mol) of Mannich base **10** in 200 ml of 4:1 toluene–glacial acetic acid. The resulting solution was stirred and heated under reflux for 0.5 hr then water was removed azeotropically for 1.5 hr using a Dean-Stark trap. After cooling to room temperature, the mixture was diluted with 100 ml of toluene and washed with water, and saturated brine then dried, filtered, and concentrated in *vacuo* giving 20.38 g (93.5%) of an orange oil.

From an experiment on a smaller scale, using the same procedure as above, the crude product was purified by chromatography on silica gel. Elution with 9:1 and 4:1 benzene–ether gave the pure diene mixture: ir ($CHCl_3$) 2250 (C≡N), 1730 (cyclopentanone C=O), 1640 cm^{-1} (C=C); uv max (95% EtOH) 254 nm (ε 12,650); nmr ($CDCl_3$) δ 5.51 (t, 1, *J* = 2 Hz, CH=C), 3.80 (m, 1, C_3 H), 2.94 (m, 2, C_8 H), 0.83 ppm (t, 3, *J* = 8 Hz, C_{6a} CH_2CH_3).

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.50; H, 7.88; N, 4.76.

(±)-*trans-anti*-6-(2-Cyanoethyl)-3a-ethyl-1,2,3a,4,5,9,9a,9b-octahydro-3*H*-benz[*e*]indene-3,7(8*H*)-dione [(±)-16b].—The crude diene mixture [(±)-**12b** and (±)-**13b**] from the preceding experiment (20.38 g) dissolved in 120 ml of benzene was added to a stirred solution of 6 g (0.159 mol) of sodium borohydride in 150 ml of ethanol and 15 ml of water at 0°. The reaction mixture was stirred at 0° for 30 min then at room temperature for 1 hr. The product was isolated with benzene giving 21.7 g of yellow-orange oil [mainly (±)-**14b** but containing some of the C_{3a} epimer]: ir (film) 3450 (OH), 2250 (C≡N), 1650 cm^{-1} (C=C).

This material was dissolved in 500 ml of toluene and hydrogenated over 4 g of 5% palladium on carbon[20] at room temperature and 1 atm for 6 hr. A total of 1725 ml of hydrogen was absorbed during this period. The catalyst was filtered with suction through Celite and the filter cake was washed well with fresh toluene. The combined filtrate and washings were concentrated at reduced pressure giving 20.15 g of yellow oil: ir (film) 3475 (OH), 2250 (C≡N), 1680 cm^{-1} (enol ether).

This crude enol ether was dissolved in 200 ml of acetone containing 25 ml of 1 *N* aqueous sulfuric acid. The solution was stirred at room temperature for 1 hr then the reaction mixture was cooled to 0–5° (ice bath) while 80 ml of Jones reagent[12] was added dropwise over 20 min. After stirring at room temperature for 3 hr, the excess oxidizing agent was decomposed with sodium bisulfite solution. Isolation of the product with benzene (the organic solution was additionally washed with saturated aqueous sodium bicarbonate solution) gave 14.2 g (66%) of oily trione (±)-**15b**: ir (film) 2250 (C≡N), 1740 (cyclopentanone C=O), 1715 cm^{-1} (aliphatic and cyclohexanone C=O).

A 6.0 g sample of this triketone was dissolved in 50 ml of methanol and 25 ml of 0.1 *N* methanolic potassium hydroxide then the reaction mixture was stirred and heated at reflux for 1.5 hr. The methanol was evaporated at reduced pressure and the product was isolated with benzene giving 5.3 g of dark red, oily, crude (±)-**16b**: uv max (95% EtOH) 246 nm (ε 10,300), 300 (915).

This material was chromatographed on 250 g of silica gel. The fractions eluted with 4:1 and 2:1 benzene–ether which were homogeneous on tlc analysis gave 2.55 g of pale yellow oil. The other fractions (1.10 g) showed the presence of a more polar impurity.

One of the purer fractions was rechromatographed on silica gel giving a colorless oil with the following physical properties: ir ($CHCl_3$) 2255 (C≡N), 1740 (cyclopentanone C=O), 1670 cyclohexenone C=O), 1600 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.86

ppm (t, 3, J = 8 Hz, $C_{3a}CH_2CH_3$); uv max (95% EtOH) 245 nm (ϵ 12,600).

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.79; H, 7.99; N, 4.91.

(±)-*trans-anti-trans-anti*-6-(2-Cyanoethyl)-3a-ethyl-1,2,3a,4,-5,5a,8,9,9a,9b-decahydrobenz[*e*]indene-3,7(6*H*)-dione [(±)-17b].—A 1.15-g (4.04 mmol) sample of pure enedione (±)-**16b** was dissolved in 40 ml of dry THF containing 1 ml of triethylamine and hydrogenated over 0.2 g of 5% palladium on carbon[20] at room temperature and 1 atm for 2.5 hr. The hydrogen uptake amounted to 121 ml. The catalyst was filtered through Celite and the filtrate was concentrated at reduced pressure giving 1.14 g of colorless oil.

This material was chromatographed on 50 g of silica gel. The fractions eluted with 9:1, 4:1, and 2:1 benzene–ether afforded 0.906 g (78.5%) of colorless crystals. Recrystallization from 2-propanol gave the analytical specimen of (±)-**17b** as colorless crystals: mp 118.5–121°; ir ($CHCl_3$) 2250 (C≡N), 1740 (cyclopentanone C=O), 1715 cm^{-1} (cyclohexanone C=O).

Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.40; H, 9.07; N, 4.87.

(±)-*trans-anti-trans-anti*-3,3,7,7-Bis(ethylenedioxy)-3a-ethyl-6-(2-cyanoethyl)perhydro-1*H*-benz[*e*]indene [(±)-18b].—A 0.2 g (0.695 mmol) sample of dione (±)-**17b** was dissolved in 5 ml of dry THF and treated with 0.5 ml of ethylene glycol, 0.5 ml of trimethyl orthoformate and 0.01 ml of concentrated sulfuric acid. The resulting solution was stirred at room temperature for 5.5 hr. After addition of several drops of triethylamine then 2 ml of 10% aqueous sodium hydroxide, the product was isolated with benzene giving 0.264 g (100%) of crude (±)-**18b** as a beige powder. Recrystallization from 2-propanol gave 0.214 g of colorless crystals: mp 127.5–129.5°; ir ($CHCl_3$) 2250 (C≡N), 1160, 1100, 1050 cm^{-1}; nmr ($CDCl_3$) δ 3.96, 3.86 ppm (2 s, 8, OCH_2CH_2O).

Anal. Calcd for $C_{22}H_{33}NO_4$: C, 70.37; H, 8.86; N, 3.73. Found: C, 70.32; H, 8.56; N, 3.52.

(±)-*trans-anti-trans-anti*-3,3,7,7-Bis(ethylenedioxy)-3a-ethyl-6-(3-oxo-1-butyl)perhydro-1*H*-benz[*e*]indene [(±)-19b].—A solution of 0.164 g (0.437 mmol) of nitrile (±)-**18b** in 25 ml of anhydrous ether was added dropwise from a syringe to a solution of 2 ml of 2 M ethereal methyllithium in 5 ml of anhydrous ether at −15°. The mixture was stirred at −10° for 1.75 hr then decomposed by the addition of 2 ml of water at 0°. After stirring at room temperature for 1.5 hr the product was isolated with ether giving 0.165 g (97%) of (±)-**19b** as a beige solid.

This material was recrystallized from 2-propanol giving 0.082 g of colorless, fluffy crystals: mp 116–119° (lit.[6] mp 117.5–119.5°); ir ($CHCl_3$) 1710 (ketone C=O), 1155, 1100, 1055 cm^{-1}.

(±)-13β-Ethylgon-4-ene-3,17-dione [(±)-1b].—A solution of 0.124 g (0.33 mmol) of ketone (±)-**19b** in 7 ml of methanol and 2 ml of 4 N aqueous hydrochloric acid was refluxed for 4 hr. After cooling to room temperature, the product was isolated with benzene giving 0.110 g of crude, yellow, crystalline (±)-**1b**.

This material was chromatographed on 5 g of silica gel. The fractions eluted with 2:1 and 1:1 benzene–ether gave 0.083 g (92%) of pale yellow crystalline material. Recrystallization from methanol afforded 0.056 g (62%) of pure (±)-**1b** as colorless crystals: mp 156–159° (lit.[6] mp 158–161°); ir ($CHCl_3$) 1735 (cyclopentanone C=O), 1670 (conjd ketone C=O), 1625 cm^{-1} (C=C); uv max (95% EtOH) 240 nm (ϵ 18,000). This material was identical by ir and tlc analysis with a sample of (±)-**1b** prepared previously.[6]

(±)-13-Ethyl-4-azagona-5(10),9-diene-3,17-dione [(±)-20b].—A 4.0-g (0.0132 mol) sample of the crude triketone (±)-**15b** was dissolved in 200 ml of toluene and 0.90 g of *p*-toluenesulfonic acid monohydrate was added. The mixture was stirred and brought to reflux over 1 hr then heated at reflux with azeotropic removal of water (Dean-Stark trap) for 4 hr. After cooling to room temperature, the reaction mixture was washed with saturated aqueous sodium bicarbonate and saturated brine. The organic solution was dried, filtered and concentrated *in vacuo* giving 3.5 g of an orange semisolid residue.

This material was triturated with ethyl acetate and the solid was filtered off and washed well with ethyl acetate until nearly colorless giving 0.674 g (18%) of an off-white powder. Recrystallization from methanol–chloroform afforded 0.593 g of colorless crystals: mp 275–286° dec; ir ($CHCl_3$) 3400, 3225 (NH), 1730 (cyclopentanone C=O), 1680 (lactam C=O), 1650 cm^{-1} (C=C); uv max (95% EtOH) 212 nm (ϵ 7280), 282 (14,020); nmr ($CDCl_3$) δ 8.25 (s, 1, NH), 5.40 (m, 1, $C_{11}H$), 0.80 ppm (t, 3, J = 8 Hz, CH_2CH_3).

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 9.90. Found: C, 75.91; H, 8.06; N, 9.99.

The combined filtrate and washings from the above purification were concentrated *in vacuo* and the residue was purified as in the following experiment.

(±)-13-Ethyl-4-oxagona-5(10),9-diene-3,17-dione [(±)-21b].—The residue (2.8 g) from the preceding experiment was chromatographed on 140 g of silica gel. The fractions eluted with 9:1 benzene–ether gave 0.32 g (8.5%) of yellow powder. Recrystallization from 2-propanol afforded 0.161 g of beige, crystalline (±)-**21b**: mp 142.5–145.0°; ir ($CHCl_3$) 1770 (lactone C=O), 1735 (cyclopentanone C=O), 1662 (C=C), 1150, 1120 cm^{-1}; uv max (95% EtOH) 253 nm (ϵ 12,380), 228 (sh, 9440); nmr ($CDCl_3$) δ 5.47 ppm (m, 1, $C_{11}H$).

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.62; H, 7.59.

The fractions eluted with 4:1 and 2:1 benzene–ether gave 0.95 g (25.2%) of pale yellow oil. The ir spectrum and tlc mobility of this material were identical to those of enedione (±)-**16b**. Four other fractions gave 0.63 g of pale yellow oil showing two spots (1:1 mixture) on tlc analysis, the faster moving of which corresponded to (±)-**16b**.

(2*S*,6*S*)-2-{2-[(*S*)-α-Phenethylamino]ethyl}-6-(3-cyanopropyl)-tetrahydropyran-2-ol (23).—A 16.7-g (0.1 mol) sample of lactone **9** was treated with 76 ml (0.16 mol) of 2.1 M vinylmagnesium chloride solution in THF using the procedure described above for the synthesis of Mannich base **10**. After the same work-up, the THF extracts (containing the vinyl ketone intermediate) were treated with 12.1 g (0.1 mol) of *l*-(−)-α-methylbenzylamine and left at room temperature for 3 hr. The solvents were removed *in vacuo* and the residue was dissolved in a mixture of 125 ml of acetone and 125 ml of 1.5 N aqueous sulfuric acid solution. After 15 min at room temperature this mixture was extracted with *n*-hexane and the hexane extract was reextracted with 1:1 acetone–aqueous sulfuric acid (1N).

The combined acid aqueous extract was made alkaline with 10% aqueous sodium carbonate solution and the precipitated Mannich base mixture **11** was isolated by ether extraction giving 28.5 g of oily product. This material was dissolved in 65 ml of acetone, added to a solution of 9.2 g of anhydrous oxalic acid in 65 ml of acetone, and left at room temperature for 24 hr. The solids were filtered with suction, washed with 25 ml of acetone and 60 ml of 1:1 acetone–isopropyl ether and dried under high vacuum. The white solid was recrystallized from 50 ml of acetonitrile to yield 9.33 g (46%) of pure **23** oxalate: mp 108–12° (hot stage); $[\alpha]^{25}D$ −36.6° (*c* 2.26, CH_3OH). The analytical specimen, obtained by several recrystallizations of a sample from acetone showed mp 108–109° (capillary); $[\alpha]^{25}D$ −35.28° (*c* 1, CH_3OH).

Anal. Calcd for $C_{19}H_{28}N_2O_2 \cdot C_2H_2O_4$: C, 62.05; H, 7.44; N, 6.89. Found: C, 62.37; H, 7.65; N, 6.84.

To a suspension of 6.1 g of this salt in 60 ml of water, sodium carbonate was added until the mixture showed pH 9. The free base was then isolated by ether extraction giving 4.65 g of the free base **23** as a light yellow oil: $[\alpha]^{25}D$ −20.39° (*c* 1, C_6H_6); ir ($CHCl_3$) 3100 (bonded OH, NH), 2250 cm^{-1} (C≡N).

Anal. Calcd for $C_{19}H_{28}N_2O_2$: C, 72.11; H, 8.92; N, 8.85. Found: C, 72.17; H, 8.85; N, 9.05.

(2*R*,6*R*)-2-{2-[(*S*)-α-Phenethylamino]ethyl}-6-(3-cyanopropyl)-tetrahydropyran-2-ol (24).—The mother liquor from the first crystallization of **23** oxalate (obtained from a preparation similar to that described in the preceding experiment) was concentrated *in vacuo*. The residue was diluted with water and made alkaline with aqueous sodium carbonate solution. The liberated base was isolated by extraction with ether. A 135-g sample of this material was percolated through a column of grade III alumina (500 g) in 1:1 hexane–ethyl acetate (2.2 l.). The eluate was concentrated *in vacuo* and the residue (110 g) was recrystallized twice from isopropyl ether giving 27 g of pure base **24**: mp 62–63°; $[\alpha]^{25}D$ −52.4° (*c* 1.37, C_6H_6); ir ($CHCl_3$) 3150 (NH, OH), 2250 cm^{-1} (C≡N); nmr ($CDCl_3$) δ 7.40 (s, 5, C_6H_5), 3.85 (m, 1, >CHO), 1.35 ppm (d, 3, J = 6 Hz, $CH_3CH<$); mass spectrum m/e 316 (M^+).

Anal. Calcd for $C_{19}H_{28}N_2O_2$: C, 72.11; H, 8.92; N, 8.85. Found: C, 72.15; H, 8.83; N, 8.79.

Mannich Base 23 Oxalate Using an Inversion Cycle.—The crude oily diastereomeric base mixture **11** (75.3 g), obtained as described above from 41.8 g (0.25 mol) of lactone **9**, was dissolved

in 167 ml of acetone and treated with a solution of 25.7 g (0.286 mol) of anhydrous oxalic acid in 167 ml of acetone. The resulting solution was seeded with the oxalate of **23** and kept at room temperature for 3 hr and 4° for 40 hr. The solids were filtered, washed with 1:1 isopropyl ether–acetone (200 ml) and dried giving 50.6 g of salt. Recrystallization from 240 ml of acetonitrile yielded 33.15 g of pure **23** oxalate: mp 106–109°; $[\alpha]^{25}D$ −34.0° (*c* 2.15, CH_3OH).

The mother liquor from the first crystallization was concentrated *in vacuo* and the residue was dissolved in 100 ml of water and extracted with ether (ether solutions discarded). The aqueous solution was made alkaline (pH 9) with 10 *N* aqueous sodium hydroxide and the liberated base was isolated by ether extraction giving 29.5 g of crystalline product rich in **24**.

This material was dissolved in 250 ml of THF and treated at −10° with a solution (prepared at 0°) of 7.35 ml of methanesulfonic acid in 40 ml of THF. After the addition of 74 ml of pyridine, the mixture was cooled to −20° and stirred while 48 ml of methanesulfonyl chloride was added over a 10-min period. The reaction mixture was kept at room temperature for 5 hr then 250 ml of water was added and the resulting mixture was heated at reflux for 3 hr. After cooling, the mixture was made alkaline (pH 9) with 10 *N* aqueous sodium hydroxide and the organic layer was separated. The aqueous phase was extracted with methylene chloride. By isolation in the usual manner, there was obtained 29.6 g of dark brown, oily Mannich base **23** from the combined organic solutions.

This material was dissolved in 66 ml of acetone and treated with a solution of 10 g of anhydrous oxalic acid in 66 ml of acetone. The solution was seeded with **23** oxalate and kept at 4° for 24 hr. The resulting solid was filtered and recrystallized from 88 ml of acetonitrile yielding 12.28 g of pure **23** oxalate: mp 110–115°; $[\alpha]^{25}D$ −34.5° (*c* 2.04, CH_3OH). The total amount of 45.43 g of **23** oxalate produced by this sequence corresponds to a 44.5% yield based on lactone **9**.

In a separate experiment, the mesylate intermediate **25** was isolated before the hydrolysis–inversion step by careful basification of the mesylation mixture with 10% aqueous sodium carbonate followed by extraction with methylene chloride. This afforded an unstable oil which showed the following spectral properties: ir ($CHCl_3$) 3350 (NH), 2250 (C≡N), 1718 (ketone C=O), 1340, 1150 cm^{-1} (SO_2O); nmr ($CDCl_3$) δ 7.3 (s, 5, C_6H_5), 4.18 (m, 1, NH exchangeable with D_2O), 3.00 (s, 3, CH_3SO_2), 1.42 ppm (d, 3, *J* = 6 Hz, CH_3CH).

(3*S*,6a*S*)-(−)-3-(3-Cyanopropyl)-6a-methyl-1,2,3,5,6,6a-hexahydrocyclopenta[*f*][*l*]benzopyran-7(8*H*)-one [(−)-12a].—A mixture of 4.55 g (0.0144 mol) of the free base derived from pure **23** oxalate, 110 ml of methanol, 0.46 g of sodium bicarbonate, and 2.0 g of freshly distilled benzaldehyde was stirred and heated at reflux for 8.5 hr. The reaction mixture was then concentrated to a volume of 10 ml and the products were isolated with methylene chloride giving 6.4 g of an oil. This material was chromatographed on 65 g of silica gel. Elution with ether, 4:1 and 2:1 ether–ethyl acetate afforded 3.07 g (92%) of pure β-methoxy ketone **26** as an oil: ir (film) 3470 (OH), 2250 (C≡N), 1720 cm^{-1} (ketone C=O).

In subsequent experiments the Schiff base of benzaldehyde and α-methylbenzylamine was isolated by dilution of the cooled reaction mixture with an equal volume of water followed by extraction with hexane. The product **26** was then isolated by saturation of the aqueous methanol phase with sodium chloride and extraction with methylene chloride.

A mixture of 2.27 g (0.01 mol) of **26**, 1.35 g (0.012 mol) of 2-methylcyclopentane-1,3-dione, 40 ml of toluene, and 20 ml of glacial acetic acid was stirred and heated at 110° for 5 hr. The bath temperature was then raised to 140° for 1 hr during which time azeotropic distillation of water into a Dean–Stark trap was carried out. The cooled mixture was washed with water, saturated aqueous sodium bicarbonate, and brine then dried, filtered, and concentrated *in vacuo* yielding 2.8 g of an orange, crystalline mixture of optically active dienes **12a** and **13a** which was chromatographed on 250 g of silica gel. The fractions eluted with 19:1 benzene–ether furnished 2.02 g of solid: mp 72–96°; $[\alpha]^{25}D$ −150.86° (*c* 0.92, $CHCl_3$).

This material was recrystallized from 2-propanol giving 1.02 g (37.7%) of pure (−)-**12a**: mp 101–104°; $[\alpha]^{25}D$ −182.0° (*c* 1.0, $CHCl_3$). A sample was recrystallized several times to afford the analytical specimen as pale yellow solid: mp 102–104°; $[\alpha]^{25}D$ −184.42° (*c* 1.03, $CHCl_3$); ir ($CHCl_3$) 2250 (C≡N), 1740 (cyclopentanone C=O) and 1640 cm^{-1} (C=C); uv max (95% EtOH) 254 nm (ε 18,800); nmr ($CDCl_3$) δ 5.41 (t, 1, *J* = 2 Hz, HC=), 3.78 (m, 1, C_3H), 1.10 ppm (s, 3, C_{3a} CH_3).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80. Found: C, 75.17; H, 7.95.

In another experiment, a mixture of 10 g (0.0246 mol) of **23** oxalic acid salt, 200 ml of toluene, 90 ml of glacial acetic acid, 10 ml of water, 40 ml of pyridine, and 3.5 g (0.031 mol) of 2-methyl-1,3-cyclopentanedione was stirred and heated at reflux for 16 hr. A Dean-Stark trap was then inserted into the system and heating at reflux was continued for 40 min with water removal. After cooling, the reaction mixture was diluted with toluene then washed successively with water, 1 *N* aqueous sulfuric acid and 10% aqueous sodium carbonate solution. After drying of the organic layer and removal of the solvents *in vacuo* there was obtained 6.2 g of red solid product. Two recrystallizations from 2-propanol gave 2.3 g (34.6%) of reddish crystals of (−)-**12a**: mp 102–103°; $[\alpha]^{25}D$ −178.0° (*c* 2.14, $CHCl_3$).

(+)-*trans-anti*-6-(2-Cyanoethyl)-3aβ-methyl-1,2,3a,4,5,9,9a,-9b-octahydro-3*H*-benz[*e*]indene-3,7(8*H*)-dione [(+)-16a].—A solution of 27.1 g (0.1 mol) of dienone (−)-**12a** in 150 ml of toluene was added over 35 min to a cold (5°), stirred solution of 2.5 g (0.066 mol) of sodium borohydride in 20 ml of water and 80 ml of ethanol. After the mixture had stirred for 40 min at room temperature, brine was added and the toluene layer was removed. The aqueous layer was extracted twice more with toluene; then the toluene solutions were combined, washed with brine, and dried. After filtration, the toluene solution [400-ml total volume containing alcohol (−)-**14a**] was treated with 2 ml of triethylamine and 2.5 g of 5% palladium on carbon[20] and stirred in an atmosphere of hydrogen for 5.24 hr (2.53 l. of hydrogen consumed). The catalyst was filtered and the filtrate was concentrated *in vacuo* to yield 30 g of colorless glass: ir (film) 3620 (OH), 2250 (C≡N), 1680 cm^{-1} (enol ether).

This material was dissolved in 300 ml of acetone and treated with 30 ml of 1 *N* aqueous sulfuric acid. After standing at room temperature for 1 hr, the solution was cooled to −5° and stirred while a freshly prepared solution of 30 g of sodium dichromate dihydrate and 21.3 ml of concentrated sulfuric acid diluted to 75 ml with water was added over 8 min. The resulting mixture was stirred at 0–2° for 30 min, then allowed to warm to room temperature, and stirred at room temperature for 2 hr. After decomposition with aqueous sodium bisulfite solution and brine, the product was isolated with toluene in the usual manner (the combined organic extracts were additionally washed with saturated aqueous sodium carbonate solution) giving 27 g of crude, optically active triketone **15a**.

Without further purification, this material was dissolved in 50 ml of methanol and treated with a solution of 1.32 g (0.02 mol) of potassium hydroxide in 100 ml of methanol. After stirring and heating under reflux for 40 min, the mixture was cooled and diluted with brine and the product isolated with toluene affording 24.2 g of crude enedione (+)-**16a**. Recrystallization from 2-propanol yielded 13.3 g (49.2%) of solid: mp 112–114°; $[\alpha]^{25}D$ +54.0° (*c* 1.0, $CHCl_3$). An analytical specimen was obtained by further recrystallization of a sample from 2-propanol as colorless crystals: mp 116–119°; $[\alpha]^{25}D$ +53.9° (*c* 0.9, $CHCl_3$); ir ($CHCl_3$) 2250 (C≡N), 1740 (cyclopentanone C=O), 1665 (cyclohexenone C=O), 1605 cm^{-1} (C=C); uv max (95% EtOH) 245 nm (ε 13,400); nmr ($CDCl_3$) δ 1.04 ppm (s, C_{3a} CH_3).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 74.98; H, 7.71; N, 5.00.

Concentration of the mother liquor from the above crystallization gave 9.2 g of material which was reoxidized and cyclized as above to give an additional 4.3 g of (+)-**16a**: mp 112–114°; $[\alpha]^{25}D$ +55.6° (total yield 17.6 g, 65%).

The intermediate alcohol (−)-**14a** was isolated from a similar preparation:

(3*S*,6a*S*,7*S*)-(−)-3-(3-Cyanopropyl)-6a-methyl-1,2,3,5,6,6a,7,-8-octahydrocyclopenta[*f*][*l*]benzopyran-7-ol [(−)-14a].—Pale yellow crystals were obtained from 2-propanol at −15°: mp 116–119°; $[\alpha]^{25}D$ −194.57° (*c* 1.01, $CHCl_3$); ir ($CHCl_3$) 3650 (OH), 2250 (C≡N), 1640 cm^{-1} (C=C); uv max (95% EtOH) 254 nm (ε 19,300); nmr ($CDCl_3$) δ 5.01 (m, 1, HC=), 3.93 (m, HCO), 3.73 (m, HCO), 0.93 ppm (s, 3, C_{6a} CH_3).

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48. Found: C, 74.55; H, 8.61.

(+)-Estr-4-ene-3,17-dione [(+)-1a].—A solution of 2.71 g (0.01 mol) of enedione (+)-**16a** in 30 ml of THF containing 1% triethylamine was treated with 0.25 g of 5% palladium on car-

bon[20] and stirred in an atmosphere of hydrogen for 5.75 hr (267 ml hydrogen consumed). The catalyst was filtered and the filtrate was concentrated *in vacuo* giving 2.8 g of dione (+)-**17a**.

This material was dissolved in 30 ml of THF and treated with 2.5 ml of ethylene glycol and 2.5 ml of trimethyl orthoformate. After the mixture cooled to 5°, 0.1 ml of concentrated sulfuric acid was added and the solution was kept at room temperature for 1 hr. Sequential addition of 3 ml of triethylamine, 10 ml of 2 *N* aqueous sodium hydroxide and brine was followed by isolation of the product with toluene. This gave 3.61 g of crystalline bisketal (+)-**18a**.

Without purification, this material was dissolved in 70 ml of anhydrous ether and added over 10 min to 23 ml of stirred, cold (−20°) 1.75 *M* ethereal methyllithium solution. After stirring at room temperature for 30 min, the mixture was again cooled and decomposed with water. Isolation of the product with ether yielded 3.8 g of crude keto bisketal (−)-**19a**.

This material was dissolved in 30 ml of methanol and 20 ml of 2 *N* aqueous hydrochloric acid was added. After heating at reflux for 2 hr, the methanol was removed *in vacuo* and the product was isolated with toluene giving 2.71 g of crude (+)-**1a**. Recrystallization from methylene chloride–isopropyl ether gave 1.65 g (60.6%) of colorless crystals: mp 167–171°; $[\alpha]^{25}D$ +140.0° (*c* 1.00, $CHCl_3$) {lit.[7] mp 172–173°; $[\alpha]^{25}D$ +139.5° (*c* 0.95, $CHCl_3$)}; uv max (95% EtOH) 240 nm (ε 17,000); ir ($CHCl_3$) 1740 (cyclopentanone C=O), 1665 (conjd ketone C=O), 1620 cm^{-1} (C=C). This material was identical with an authentic sample of (+)-**1a** by tlc and ir analysis.

The intermediates (+)-**17a**, (+)-**18a**, and (−)-**19a** were isolated from a similar preparation.

(+)-*trans-anti-trans-anti*-**6-(2-Cyanoethyl)-3aβ-methyl-1,2,3a,4,5,5a,8,9,9a,9b-decahydrobenz[*e*]indene-3,7(6*H*)-dione** [(+)-**17a**].—Colorless crystals were obtained from 2-propanol: mp 135–136°; $[\alpha]^{25}D$ +78.91° (*c* 1.03, $CHCl_3$); ir ($CHCl_3$) 2250 (C≡N), 1740 (cyclopentanone C=O), 1710 cm^{-1} (cyclohexanone C=O); nmr ($CDCl_3$) 0.97 ppm (s, C_{3a} CH_3).

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.60; H, 8.79; N, 5.13.

(+)-*trans-anti-trans-anti*-**3,3,7,7-Bis(ethylenedioxy)-3aβ-methyl-6-(2-cyanoethyl)perhydro-1*H*-benz[*e*]indene** [(+)-**18a**].—A colorless solid was obtained from 2-propanol: mp 130–131°; $[\alpha]^{25}D$ +0.67° (*c* 1.04, $CHCl_3$); ir ($CHCl_3$) 2250 cm^{-1} (C≡N); nmr ($CDCl_3$) δ 3.96, 3.86 (2 s, 8, OCH_2CH_2O), 0.88 ppm (s, C_{3a} CH_3).

Anal. Calcd for $C_{21}H_{31}NO_4$: C, 69.77; H, 8.65; N, 3.88. Found: C, 69.93; H, 8.50; N, 3.91.

(−)-*trans-anti-trans-anti*-**3,3,7,7-Bis(ethylenedioxy)-3aβ-methyl-6-(3-oxo-1-butyl)perhydro-1*H*-benz[*e*]indene** [(−)-**19a**].—A colorless solid was obtained: mp 77–81°; $[\alpha]^{25}D$ −6.2° (*c* 1.0, $CHCl_3$) (lit.[7] mp 83.5–86.5°; $[\alpha]^{25}D$ −16.0° (*c* 1.17, C_6H_6)); ir ($CHCl_3$) 1720 cm^{-1} (ketone C=O).

(+)-**4-Azaestra-5(10),9-diene-3,17-dione** [(+)-**20a**].—This material was prepared by treatment of crude, optically active triketone **15a** (4.6 g; 0.016 mol) with *p*-toluenesulfonic acid monohydrate (1.0 g) in toluene (200 ml) as described above for the racemic modification. Trituration of the crude product (4.0 g) with ethyl acetate afforded 0.62 g (13.4%) of colorless solid lactam: mp 282–285° dec; $[\alpha]^{25}D$ +431.2° (*c* 1.0, $CHCl_3$). Recrystallization from methanol gave 0.45 g of pure (+)-**20a**: mp 283–287°d; $[\alpha]^{25}D$ +434.9° (*c* 0.93, $CHCl_3$); ir ($CHCl_3$) 3400, 3240 (NH), 1740 (cyclopentanone C=O), 1680 (lactam C=O), 1650 cm^{-1} (C=C); uv max (95% EtOH) 213 nm (ε 7500), 281 (13,640); nmr ($CDCl_3$) δ 8.36 (s, 1, NH), 5.42 (m, 1, C_{11} H), 0.90 ppm (s, 3, C_{13} CH_3).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.37; H, 7.86; N, 5.03.

Chromatography of the material remaining after removal of lactam (+)-**20a** gave the enedione (+)-**16a**, eluted with 4:1 and 2:1 benzene–ethyl acetate.

(+)-**4-Oxaestra-5(10),9-diene-3,17-dione** [(+)-**21a**].—A mixture of 1.0 g (3.69 mmol) of enedione (+)-**16a** was treated with 0.7 g (3.69 mmol) of *p*-toluenesulfonic acid monohydrate in 40 ml of xylene as described above in the racemic series. The crude product (0.967 g) was chromatographed on 50 g of silica gel. Elution with 9:1 and 4:1 benzene–ether gave 0.584 g (58.1%) of the crystalline diene lactone (+)-**21a**. Recrystallization from 2-propanol gave colorless crystals: mp 105.5–107.5°; $[\alpha]^{25}D$ +327.23° (*c* 1.06, $CHCl_3$); ir ($CHCl_3$) 1770 (lactone C=O), 1745 (cyclopentanone C=O), 1670 cm^{-1} (C=C); uv max (95% EtOH) 254 nm (ε 11,500), 220 (sh, 8300); nmr ($CDCl_3$) δ 5.50 (m, 1, C_{11} H), 0.89 ppm (s, 3, C_{13} CH_3).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.21; H, 7.47.

Elution with 9:1 chloroform–ethyl acetate gave 0.174 g (17.4%) crystalline diene lactam (+)-**20a**.

Registry No.—(±)-**1a**, 5972-59-8; (+)-**1a**, 734-32-7; (±)-**1b**, 23477-67-0; **6**, 35341-69-6; **7**, 35341-70-9; **9**, 35337-27-0; **10**, 35341-71-0; (±)-**12a**, 35337-28-1; (−)-**12a**, 35378-22-4; (±)-**12b**, 35337-29-2; (±)-**13b**, 35337-30-5; (−)-**14a**, 35378-23-5; (±)-**16a**, 35337-31-6; (+)-**16a**, 35378-24-6; (±)-**16b**, 35378-25-7; (±)-**17a**, 35337-32-7; (+)-**17a**, 35337-33-8; (±)-**17b**, 35337-34-9; (±)-**18a**, 35337-35-0; (+)-**18a**, 35337-36-1; (±)-**18b**, 35427-25-9; (±)-**20a**, 35337-37-2; (+)-**20a**, 35337-38-3; (±)-**20b**, 35337-39-4; (±)-**21a**, 35337-40-7; (+)-**21a**, 35378-26-8; (±)-**21b**, 35341-65-2; **23**, 35341-66-3; **23** oxalate, 35341-67-4; **24**, 35341-68-5.

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