Steroid Total Synthesis. V.[1] (±)-Estr-4-ene-3,17-dione and (±)-13β-Ethylgon-4-ene-3,17-dione[2]

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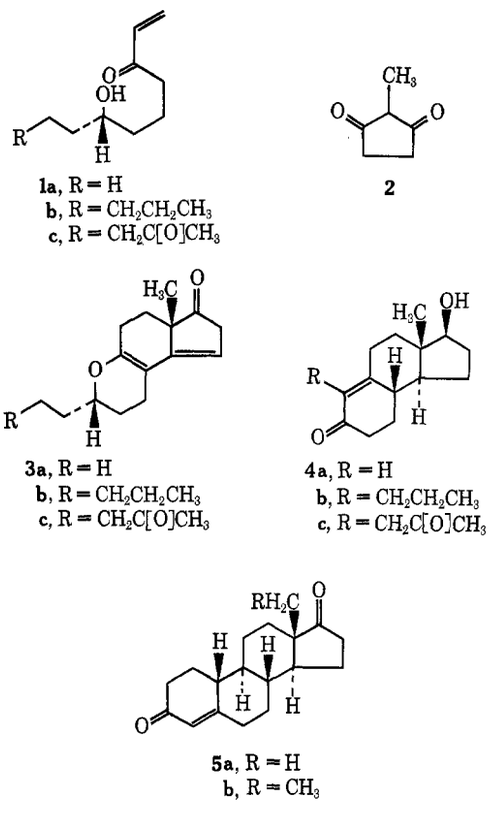
Condensation of (±)-9-(3,5-dimethyl-4-isoxazolyl)-7-hydroxynon-1-en-3-one (**12**), as its Mannich base **18**, with 2-methyl- and 2-ethylcyclopentane-1,3-dione gave mixtures of *trans*- and *cis*-(±)-3-[2-(3,5-dimethyl-4-isoxazolyl)ethyl]-6a-methyl-1,2,3,5,6,6a-hexahydrocyclopenta[*f*][1]benzopyran-7(8*H*)-one (**20a**, **21a**) and (±)-3-[2-(3,5-dimethyl-4-isoxazolyl)ethyl]-6a-ethyl-1,2,3,5,6,6a-hexahydrocyclopenta[*f*][1]benzopyran-7(8*H*)-one (**20b**, **21b**) in which the trans isomers predominated. These dienol ether mixtures were converted in five steps to (±)-19-(3,5-dimethyl-4-isoxazolyl)-de*A*-androst-9-ene-5,17-dione (**26a**) and (±)-19-(3,5-dimethyl-4-isoxazolyl)-18-methyl-de*A*-androst-9-ene-5,17-dione (**26b**). A modified procedure for hydrogenolysis of the isoxazole group and ring closure then gave (±)-estr-4-ene-3,17-dione (**5a**) and (±)-13β-ethylgon-4-ene-3,17-dione (**5b**) in high yield.

Recently, one of us reported[3] the unique asymmetric induction obtained during the condensation of (±)-7-hydroxynon-1-en-3-one (**1a**) with 2-methylcyclopentane-1,3-dione (**2**). One of the two isomers of (±)-3-ethyl-6a-methyl-1,2,3,5,6,6a-hexahydrocyclopenta[*f*][1]benzopyran-7(8*H*)-one was obtained as the predominant product of this reaction. This major component, later shown[4] to be the trans dienol ether **3a**,[5] was readily converted[3] to (±)-17β-hydroxy-de*A*-androst-9-en-5-one (**4a**). The (−) antipode[4] of this compound has been employed as an intermediate in syntheses of retrotestosterone[6] and retroprogesterone.[7]

The trans configuration of the dienol ethers **3** was determined[4] by using the vinyl ketone **1b** of known absolute configuration in the condensation reaction, and converting the resulting dienol ether **3b** to the tricyclic enone **4b**, also of known absolute configuration. It can be seen that, if the vinyl ketone **1b** were substituted by a properly positioned, masked keto function (as in the hypothetical intermediate **1c**), one would obtain the tricyclic enone **4c**, a type of compound employed in an elegant synthesis[8] of 19-nor steroids. In this paper, we wish to report our efforts in this direction, which have culminated in total syntheses of (±)-estr-4-ene-3,17-dione (**5a**)[9] and (±)-13β-ethylgon-4-ene-3,17-dione (**5b**).[10]



1a, R = H
b, R = $CH_2CH_2CH_3$
c, R = $CH_2C[O]CH_3$

2

3a, R = H
b, R = $CH_2CH_2CH_3$
c, R = $CH_2C[O]CH_3$

4a, R = H
b, R = $CH_2CH_2CH_3$
c, R = $CH_2C[O]CH_3$

5a, R = H
b, R = CH_3

Results and Discussion

In choosing the type of masked 3-oxobutyl function to employ in the vinyl ketone **1c**, we were guided by the necessity of having a moiety which would be easy to prepare, stable to the wide variety of reaction conditions[3] involved in the sequence **1c** → **4c** (*vide infra*), and yet easily reconverted to the free ketone. The 3,5-dimethylisoxazole group[11] seemed admirably suited to our needs. Isoxazoles are known[12] to be stable to most reagents but are readily opened by hydrogenation under the proper conditions. We thus set out to synthesize the desired δ-hydroxy vinyl ketone **12**. We have developed two syntheses (outlined in Scheme I) of this compound.

In one approach, the anion of diethyl β-oxopimelate (**7**)[13] was alkylated in benzene with 4-chloromethyl-3,5-dimethylisoxazole (**6**).[14,15] The crude alkylated

(1) Part IV: M. Rosenberger, T. P. Fraher, and G. Saucy, *Helv. Chim. Acta*, **54**, 2857 (1971).

(2) Presented in part at the Joint Chemical Institute of Canada–American Chemical Society Meeting, Toronto, Canada, May 1970.

(3) Part I: G. Saucy, R. Borer, and A. Fiirst, *Helv. Chim. Acta*, **54**, 2034 (1971).

(4) Part II: G. Saucy and R. Borer, *Helv. Chim. Acta*, **54**, 2121 (1971).

(5) All compounds reported in this paper, with the exceptions of **1b**, **3b**, and **4b**, are racemic. Only one enantiomer is shown.

(6) Part III: G. Saucy, and R. Borer, *Helv. Chim. Acta*, **54**, 2517 (1971).

(7) A. M. Krubiner, G. Saucy, and E. P. Oliveto, *J. Org. Chem.*, **33**, 3548 (1968).

(8) L. Velluz, J. Mathieu, and G. Nominé, *Tetrahedron, Suppl. 8*, Part II, 495 (1966).

(9) K. K. Koshoev, S. N. Ananchenko, and I. V. Torgov, *Khim. Prir. Soedin.*, 180 (1965); *Chem. Abstr.*, **63**, 13346f (1965).

(10) H. Smith, Belgian Patent 608,370 (1961).

(11) G. Stork, S. Danishefsky, and M. Ohashi, *J. Amer. Chem. Soc.*, **89**, 5459 (1967).

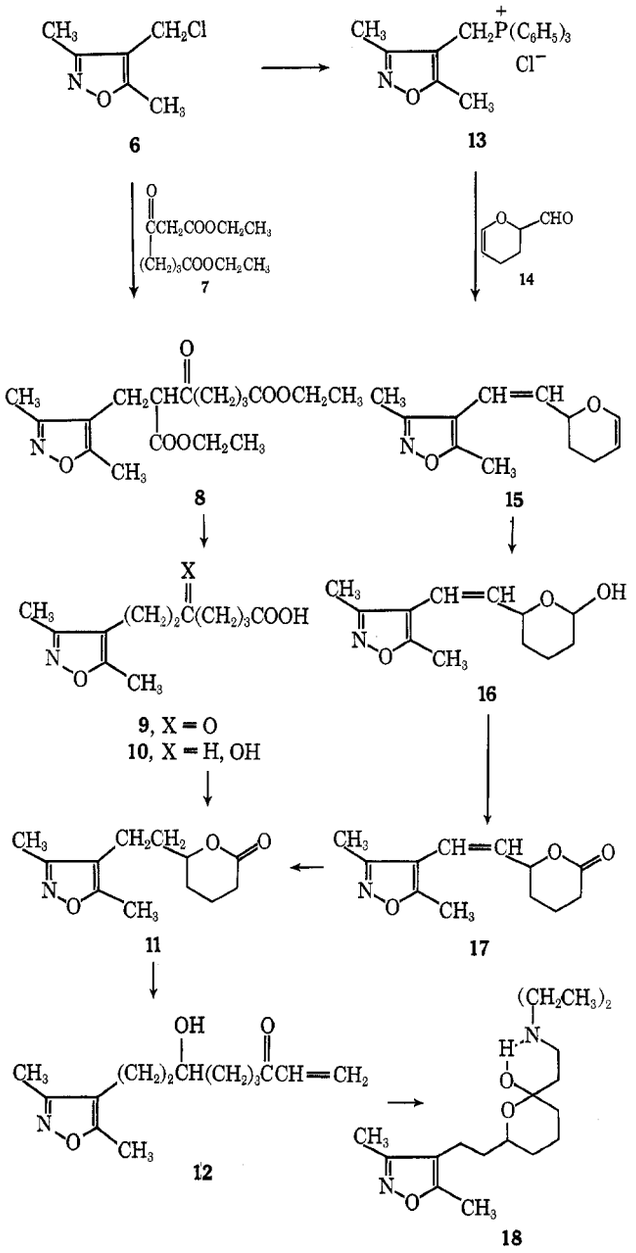
(12) For general reviews of isoxazole preparations and reactions, see (a) N. K. Kochetkov and S. D. Sokolov in "Advances in Heterocyclic Chemistry," Vol. 2, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963, pp 365–422; (b) A. Quilico, "The Chemistry of Heterocyclic Compounds," Vol. 17, A. Weissberger, Ed., Interscience, New York, N. Y., 1963, pp 1–230.

(13) M. Guha and D. Nasipuri, *Org. Syn.*, **42**, 41 (1962).

(14) N. K. Kochetkov, E. D. Khomutova, and M. V. Bazilevskii, *J. Gen. Chem. USSR*, **28**, 2762 (1958).

(15) J. E. McMurry, Ph.D. Thesis, Columbia University, New York, N. Y., 1967.

SCHEME I



diester **8** was saponified with dilute sodium hydroxide solution and was then acidified to effect decarboxylation. It was thus possible to isolate crystalline keto acid **9**, mp 61.5–62°. Usually, however, the noncrystalline acid, purified only by acid–base extraction, was reduced with sodium borohydride. The resulting hydroxy acid **10** was distilled with loss of water to give lactone **11**, mp 61–62.5°, in 32% yield from the diester **7**. Reaction[4] of this lactone with 1.75–2 equiv of vinylmagnesium chloride[16] at −60°[5] gave the vinyl ketone **12**. Since this compound proved to be relatively unstable, it was treated with diethylamine[5] to give the corresponding Mannich base. The infrared spectrum of this compound (hydrogen-bonded hydroxyl absorption at 3100 cm^{-1}, weak carbonyl absorption at 1705 cm^{-1}) indicated that it existed mostly in the bicyclic, internally hydrogen-bonded form **18**. After purification by acid–base extraction, the oily base **18** was obtained in 80–85% yield from the lactone **11**.

The first step of an alternate approach to the lactone **11**, and thus the vinyl ketone **12**, consisted in converting the chloride **6** to the phosphonium salt **13**. Conversion of this salt to the corresponding ylide with methylsulfinyl carbanion,[17] followed by reaction with freshly distilled acrolein dimer (**14**),[18] gave **15** in 82% yield. The Wittig product **15** was treated with dilute sulfuric acid in dioxane to give the hemiacetal **16**. Oxidation[19] of the crude material so produced with activated manganese dioxide gave lactone **17** in 39% yield. Hydrogenation of this unsaturated lactone over palladium on carbon proceeded smoothly to give lactone **11** in 76% yield. The isoxazole ring was not reduced under these conditions.

Condensation of the Mannich base **18** with 2-methylcyclopentane-1,3-dione (**2**)[4] (Scheme II) in a toluene–acetic acid mixture at reflux[3] afforded a mixture of trans and cis dienol ethers **20a** and **21a**. The major component of this mixture, assigned the trans configuration **20a** in analogy with previous work,[3,5] could be isolated in pure form by crystallization. The nmr spectrum of the oily residue from this crystallization indicated that the sample was a mixture of the crystalline trans dienol ether **20a** and a second compound, differing only in the position of the signal of the C-3 proton. This second compound, presumably the cis dienol ether **21a**, could not be isolated in pure form. By integration of the C-3 proton signal of the crude dienol ether mixture, it was possible to estimate that the ratio of trans to cis dienol ethers was approximately 4:1. The extent of asymmetric induction observed with the vinyl ketone **12** was thus considerably less than when the vinyl ketone **1a** was used. We have no explanation for this difference, but presumably it depends upon steric factors in the transition state leading to the dienol ethers.[3]

Reduction of the mixture[20] of dienol ethers **20a** and **21a** with lithium aluminum hydride in tetrahydrofuran gave the trans and cis dienol ether alcohols **22a**.[21] The 7β configuration of the hydroxyl groups is assigned on the basis of our own previous work,[3] as well as literature analogy.[22] Hydrogenation of the crude reduction product over a palladium catalyst[3,23] in tetrahydrofuran at atmospheric pressure gave a mixture showing C-6a methyl signals in the nmr spectrum at δ 0.80 and 0.98 ppm in a ratio of 7:1. No hydrogenolysis of the isoxazole ring was observed when these relatively mild reaction conditions were employed. The major nmr signal was due to the trans anti enol

(16) H. E. Ramsden, J. R. Leebrick, S. D. Rosenberg, E. H. Miller, J. J. Walburn, A. D. Balint, and R. Cserr, *J. Org. Chem.*, **22**, 1602 (1957).

(17) R. Greenwald, M. Chaykovsky, and E. J. Corey, *ibid.*, **28**, 1128 (1963).

(18) G. Büchi and J. E. Powell, Jr., *J. Amer. Chem. Soc.*, **92**, 3126 (1970). We wish to thank Professor Büchi for communicating the experimental details of this work prior to publication.

(19) R. J. Highet and W. C. Wildman, *J. Amer. Chem. Soc.*, **77**, 4399 (1955).

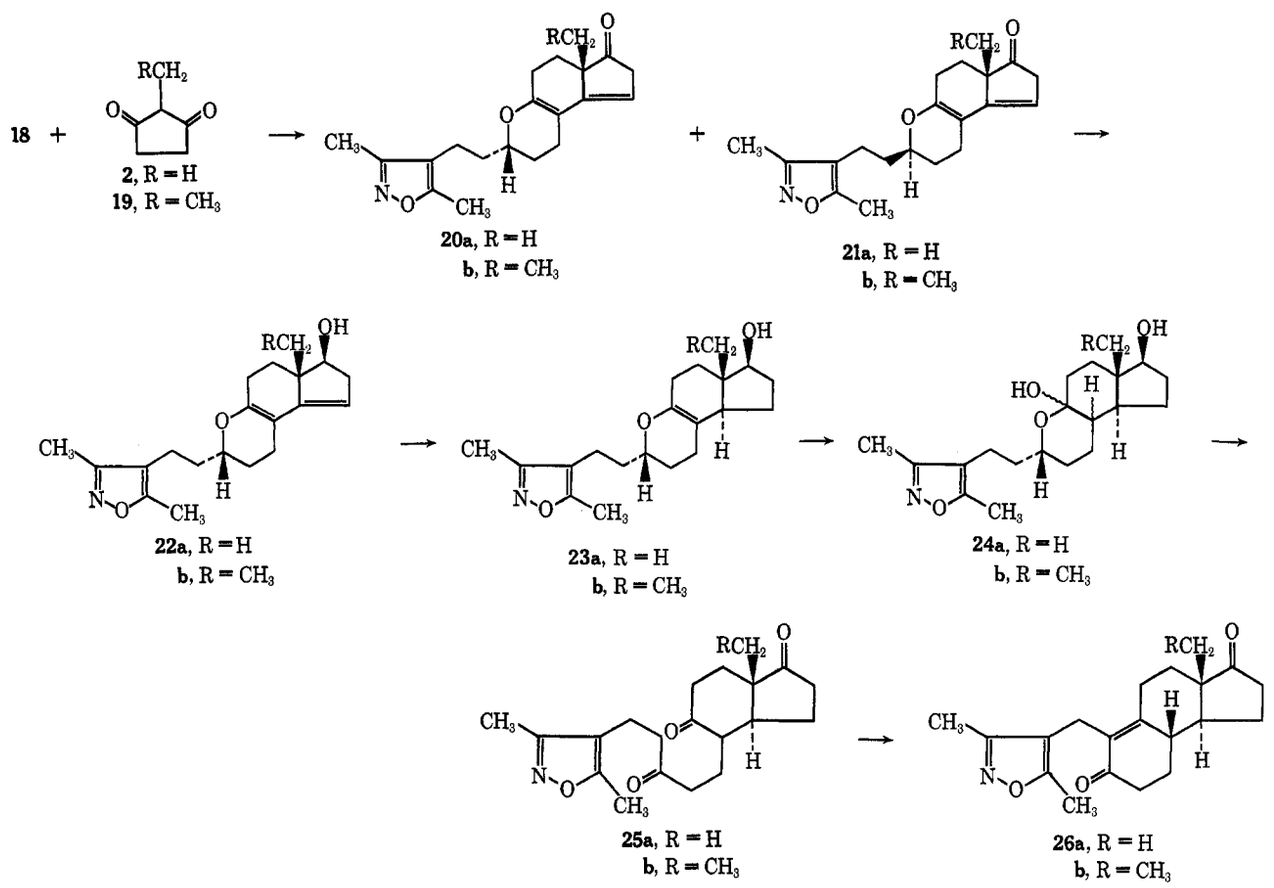
(20) Either the mixture of trans and cis dienol ethers or the pure trans isomer could be carried through the synthesis. Since the original asymmetric center at C-3 is eventually destroyed (*vide infra*), both trans and cis dienol ethers give the same de*A*-androstenone **26a** *when racemic compounds are involved*, as is here the case. For this reason, the isomers were not usually separated.

(21) For convenience, only the trans isomers of compounds **22**, **23**, and **24** are shown.

(22) L. J. Chinn, *J. Org. Chem.*, **27**, 54 (1962).

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

SCHEME II



ether **23a**, while the minor signal may have been due to material having a cis ring fusion. The trans ring fused product had been expected to predominate on the basis of previous analogous reactions.[3] That α-face hydrogenation had occurred was confirmed at the end of the synthesis when the C/D trans steroid **5a** was obtained. The mixture of products from the hydrogenation was hydrated with 1 *N* sulfuric acid in acetone to give the hemiketal **24a** as a mixture of compounds with unknown configurations at C-3a and C-9b. It was not necessary to isolate this mixture; rather, it was oxidized with Jones reagent[24] to give the trione **25a**. This oxidation destroyed the original center of asymmetry (C-7 of the vinyl ketone **12**), again giving a homogeneous compound, rather than the trans–cis mixtures encountered with compounds **20a–24a**.[21] Since the trione **25a** was not crystalline, it was cyclized with methanolic sodium hydroxide solution to give the racemic tricyclic dione (**26a**),[25] mp 141.5–143.5°. This compound was obtained in 33% yield from the lactone **11** when the crude trans–cis dienol ether mixture **20a**, **21a** was used.

Condensation of the Mannich base **18** with 2-ethylcyclopentane-1,3-dione (**19**)[26] in the same manner as described above gave the trans and cis 6a-ethyl dienol ethers **20b** and **21b**. The ratio of isomers was again approximately 4:1, as determined by nmr. This mixture of dienol ethers was converted, *via* intermediates **22b–25b**, to dione **26b**. This compound, mp 111–115.5°, was obtained in 37% yield from the lactone **11**.

To complete the synthesis of (±)-estr-4-ene-3,17-dione[9] (**5a**) and (±)-13β-ethylgon-4-ene-3,17-dione[10] (**5b**), it was necessary only to stereoselectively saturate the Δ^9 double bond of the de*A*-andostenones **26a** and **26b** and elaborate ring A. This was done as shown in Scheme III. Hydrogenation of the enones **26a,b** over palladium on carbon in a 3:1 ethanol–triethylamine mixture gave the expected[8] diones **27a**, mp 137.5–139.5°, and **27b**, mp 143.5–146°. As before, no hydrogenolysis of the isoxazole ring was observed. When the hydrogenation mixture containing the dione **27a** was made alkaline to the extent of 0.1 *N* in potassium hydroxide, a second equivalent of hydrogen was rapidly taken up. The resulting vinylogous amide **28**,[27] upon heating with aqueous base, was converted to (±)-estr-4-ene-3,17-dione (**5a**).[9] The yield from the enone **26a** could not be raised above 45% when this procedure was employed. It seemed to us that the reason for this relatively low yield might lie in the instability of the carbinolamine **28**. Stork[27] has shown that vinylogous amides of this type rapidly dehydrate upon treatment with base to give dihydropyridines, which are susceptible to oxidation and possibly also disproportionation to give pyridines and/or other compounds of no use to us. We theorized that if we prevented cyclization of the initial isoxazole hydrogenolysis product[27] to the carbinolamine form **28**, the yield of steroid

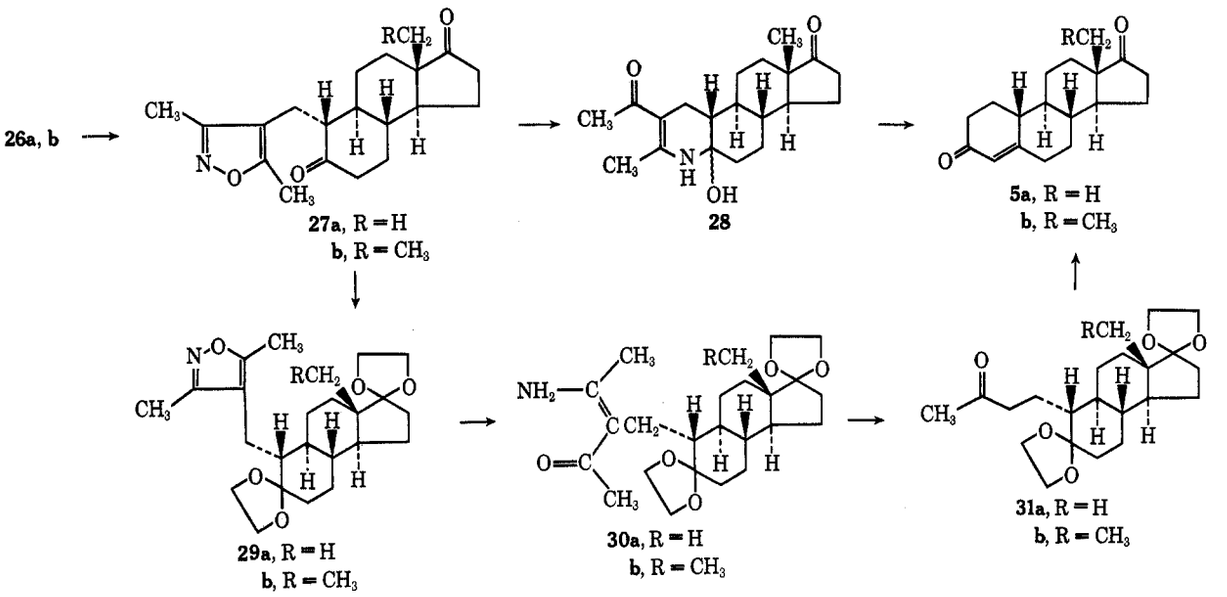
(24) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(25) This compound has been disclosed in Syntex Corp., Netherlands Patents 6,817,384 and 6,817,385 (1969). No physical or spectral data were given.

(26) H. Shick, G. Lehmann, and G. Hilgetag, *Angew. Chem.*, **79**, 378 (1967).

(27) G. Stork and J. E. McMurry, *J. Amer. Chem. Soc.*, **79**, 5463 (1967).

SCHEME III



end product might be significantly higher. This, in fact, proved to be the case.

The hydrogenation of the enone **26a** was carried out as before, and the crude dione **27a** was then ketalized to give the bisketal **29a**, mp 145.5–148°. Hydrogenolysis of this diketal over palladium on carbon in 4% ethanolic potassium hydroxide solution proceeded smoothly. The vinylogous amide **30a** was not isolated. The hydrogenation solution, after removal of the catalyst, was concentrated to approximately one-third its original volume. Addition of 20% aqueous potassium hydroxide solution, followed by heating at reflux, gave the heretofore unknown keto bisketal **31a**, mp 126.5–128°. Heating this material with methanolic hydrochloric acid caused deketalization and cyclization to give the desired steroid **5a**.[9] The yield for the five-step sequence, when none of the intermediates was purified, was 80–85%. In a similar manner, the 18-methyl enone **26b** was converted, *via* the dione **27b**, the diketal **29b** (mp 140–143°), the vinylogous amide **30b**, and the keto diketal **31b** (mp 117.5–119.5°), to (±)-13β-ethylgon-4-ene-3,17-dione[10] (**5b**, mp 158–161°), in 70% yield. The same compound, which may serve as a precursor for the synthesis of *Norgestrel*,[28] had been prepared earlier by a related route.[1]

Experimental Section[29]

(±)-7-(3,5-Dimethyl-4-isoxazolyl)-5-hydroxyheptanoic Acid Lactone (11). A.—In a dry flask under nitrogen, 35 g (0.080 mol) of 55% NaH suspension was washed with pentane to remove the mineral oil and was then suspended in 800 ml of dry benzene. A solution of 180 g (0.785 mol) of diethyl β-oxopimelate (**7**)[13] in 250 ml of benzene was added dropwise over 2.0 hr. The greenish-brown suspension was stirred at 20° for 3.0 hr and then a solution of 117 g (0.80 mol) of 4-chloromethyl-3,5-dimethylisoxazole (**6**)[14,15] in 200 ml of benzene was added over 2.0 hr. The resulting suspension was stirred at 20° overnight and was then heated at reflux for 24 hr. The cooled solution was washed with 2 *N* HCl, H_2O, and saturated brine and was dried (Na_2SO_4). Solvent removal gave the crude alkylated diester **8** as 280 g of light orange oil. A solution of this material in 2 l. of 5% NaOH was stirred at 20° for 4 hr. To the flask was cautiously added 250 ml of 18 *N* H_2SO_4 and the resulting mixture was heated at reflux for 2.0 hr. The solution was cooled, saturated with NaCl, and extracted with ethyl acetate. The organic solutions were washed with saturated brine, dried (Na_2SO_4), and stripped of solvent to give the crude keto acid **9** as 200 g of orange oil. A similarly prepared sample was crystallized twice from ethyl acetate–hexane to give analytically pure 7-(3,5-dimethyl-4-isoxazolyl)-5-oxoheptanoic acid as white microprisms: mp 61.5–62°; uv max (C_2H_5OH) 220 nm (ε 5000); ir ($CHCl_3$) 3500–2500 (acid OH), 1720 (strong, acid and ketone C=O), and 1640 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 2.21 (s, 3) and 2.32 (s, 3, 2 isoxazole-CH_3), and 10.5 ppm (s, 1, COOH).

Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.15; H, 7.29; N, 5.78.

To a solution of the crude keto acid **9** in 1 l. of isopropyl alcohol was slowly added 50 g (1.48 mol) of $NaBH_4$. The resulting mixture was stirred at 20° for 3.0 hr, slowly heated to reflux, and then held at reflux for 1.5 hr. The cooled solution was stripped of solvent, diluted with H_2O, cautiously acidified with 4 *N* HCl, and extracted with benzene. The benzene solutions were washed with saturated brine and dried (Na_2SO_4). Solvent removal gave crude hydroxy acid **10** as 150 g of pale yellow resin. Distillation of this material through a short-path apparatus gave 84 g of pale yellow oil, bp 160–185° (0.25 mm). Crystallization of this material from 400 ml of ether gave 57.2 g (32%) of the lactone **11** as small, white prisms, mp 61–62.5°. A similarly prepared sample was crystallized an additional time from ether to give analytically pure material as white microprisms: mp 61–62.5°; uv max (C_2H_5OH) 220 nm (ε 5350); ir ($CHCl_3$) 1735 (lactone C=O) and 1640 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 2.18 (s, 3) and 2.29 (s, 3, 2 isoxazole-CH_3), and 4.19 ppm (m, 1, >CHOC=O).

Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.59; H, 7.77; N, 6.12.

B.—A solution of 59.6 g (0.40 mol) of 4-chloromethyl-3,5-dimethylisoxazole (**6**)[14,15] and 116 g (0.44 mol) of triphenylphosphine in 1 l. of toluene was heated at reflux under nitrogen for 6.0 hr. The suspension was cooled and filtered. The filtrate was heated at reflux for an additional 20 hr. The precipitate was again removed by filtration and the combined solids were washed with ether and benzene. Crystallization from ethanol–ether gave the phosphonium salt **13** as 149.5 g (91%) of cream-white solid, mp 313–316° dec. A sample from a similar preparation was

(28) (±)-13β-Ethyl-17α-ethinyl-17β-hydroxygon-4-en-3-one: H. Smith, G. A. Hughes, G. H. Douglas, G. R. Wendet, G. C. Buzby, Jr., R. A. Edgren, J. Fisher, T. Foell, B. Gadsby, D. Hartley, D. Herbst, A. B. A. Jansen, K. Ledig, B. J. McLoughlin, J. McMenamin, T. W. Pattison, P. C. Phillips, R. Rees, J. Siddall, J. Siuda, L. L. Smith, J. Tokolics, and D. H. P. Watson, *J. Chem. Soc.*, 4472 (1964).

(29) Melting points were determined on a Kofler hot stage, except for mixture melting points, which were determined in capillaries on a Thomas-Hoover apparatus, and are not corrected. A Varian A-60 spectrometer was used to obtain the nmr spectra and tetramethylsilane was used as the internal standard. Infrared spectra were recorded on a Beckman IR-9 spectrophotometer. The uv spectra were recorded on a Cary Model 14M spectrophotometer.

crystallized again from ethanol–ether to give analytically pure material as small, white prisms: mp 303–305° dec;[30] ir (KBr) 1625 cm^{-1} (isoxazole); nmr (D_2O) δ 1.83 (s, 3, isoxazole-5-CH_3), 2.05 (d, 3, J = 3 Hz, isoxazole-3-CH_3), 4.90 (d, 2, J = 12 Hz, isoxazole-CH_2), and 7.7–8.2 ppm (m, 15, 3-C_6H_5).

Anal. Calcd for $C_{24}H_{23}ClNOP$: C, 70.67; H, 5.68; Cl, 8.69; N, 3.44. Found: C, 70.73; H, 5.69; Cl, 8.66; N, 3.55.

Methylsulfinyl carbanion was prepared under nitrogen in the usual manner[17] from 8.75 g (0.20 mol) of 55% NaH dispersion and 600 ml of dimethyl sulfoxide. The gray-green solution was cooled to 15° and 91.6 g (0.20 mol) of the phosphonium salt **13** was added in one portion. After 5 min, a bright orange precipitate formed in the initially dark red solution. This suspension was stirred at 20° for 45 min. To the mixture was then added, dropwise *via* syringe, 25.0 g (0.223 mol) of acrolein dimer **14** (Shell Chemical Co.; freshly distilled from and into hydroquinone) at such a rate that the temperature remained less than 30° (10–15 min, with water bath cooling). The orange-brown solution was stirred at 25° for 20 min, and then at 60–65° for 3.0 hr.[18] The reaction mixture was cooled, poured onto ice, and slurried until all the dark oil solidified. The suspension was filtered and the filter cake was washed well with pentane. The combined filtrates were washed with H_2O and saturated brine and dried (Na_2SO_4). Solvent removal gave a light orange oil which was distilled from a few milligrams of anhydrous K_2CO_3 to give 33.5 g (82%) of the Wittig product **15** as a colorless liquid, bp 83–85° (0.1 mm). A similarly prepared sample, bp 77–85° (0.2 mm), was submitted for analysis: uv max (hexane) 221 nm (ϵ 8830); ir ($CHCl_3$) 1665 (sh, C=C), 1655 (C=CO–), and 1625 cm^{-1} (isoxazole); nmr (CCl_4) δ 2.16 (s, 3) and 2.34 (s, 3, 2 isoxazole-CH_3), 4.24 (m, 1, CHO–), 4.62 (m, 1, C**H**=CHO–), 5.87 (q, 2, J = 11 Hz, C**H**=C**H**), and 6.30 ppm (d, 1, CH=C**H**O–).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.45; H, 7.44; N, 6.60.

To a solution of 33.5 g (0.163 mol) of the Wittig product **15**, bp 83–85° (0.1 mm), in 400 ml of dioxane was added 400 ml of 1 N H_2SO_4 and the cloudy solution, which soon cleared, was stirred at 20° for 1.0 hr. The mixture was poured into 2 l. of saturated $NaHCO_3$ solution and extracted with ether. The ether extracts were washed with saturated brine and dried (Na_2SO_4). Solvent removal gave the crude hemiacetal **16** as a colorless oil. To a solution of this material in 2 l. of benzene was added 400 g of activated MnO_2 (Sterwin Chemical Co.) and the resulting suspension was stirred at 20° under nitrogen for 40 hr. The mixture was filtered and the solids were carefully washed with fresh benzene. Solvent removal from the filtrates gave 23 g of yellow solid which was crystallized twice from benzene–ether to give 14.30 g (40%) of the unsaturated lactone **17** as a cream-white powder, mp 90–91.5°. A similarly prepared sample was crystallized again from benzene–ether to give the analytical sample as fine, white needles: mp 91–92.5°; uv max 222 nm (ϵ 8100); ir ($CHCl_3$) 1735 (lactone C=O), 1665 (C=C), and 1624 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 2.15 (s, 3) and 2.32 (s, 3, 2 isoxazole-CH_3), 4.77 (t, 1, CHO–), and 5.82 and 6.15 ppm (AB q, 2, C**H**=C**H**).

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.93; H, 6.71; N, 6.06.

To a solution of 16.80 g (76 mmol) of the unsaturated lactone **17**, prepared as described above, in 400 ml of ethyl acetate was added 500 mg of 10% palladium on carbon catalyst and the resulting suspension was hydrogenated at atmospheric pressure and 20°. After 2.0 hr, the uptake of hydrogen had ceased. The catalyst was removed by filtration and washed with fresh ethyl acetate. Solvent removal from the filtrates gave a colorless oil which was crystallized from ether to give 12.07 g (76%) of the lactone **11** as white microprisms, mp 59–62°, which were identical in all respects with the sample prepared in part A.

(±)-*trans*-3-[2-(3,5-Dimethyl-4-isoxazolyl)ethyl]-6a-methyl-1,2,3,5,6,6a-hexahydrocyclopenta[*f*] [1]benzopyran-7(8*H*)-one (20a).—A solution of 10.0 g (44.8 mmol) of the lactone **11** in 150 ml of tetrahydrofuran (freshly distilled from $LiAlH_4$) was cooled in a Dry Ice–isopropyl alcohol bath under nitrogen to −60°. A 25% solution of vinylmagnesium chloride[19] (25 ml, 75 mmol) was added *via* syringe at a rate such that the temperature remained at −50 to −55°. The mixture was stirred at −60° for 15 min, cooled to −70°, and quenched by the slow addition of 5 ml of methanol (temperature < −50°). It was then poured into ice, 24 g of NH_4Cl, and 8 ml of acetic acid. The resulting solution was extracted with ether and the ether solutions were washed with saturated $NaHCO_3$ solution and saturated brine and were dried (Na_2SO_4). After 10 min, 10 ml of diethylamine was added to the etheral solution of the vinyl ketone **12**. The solution was allowed to stand at 20° for 15 min, and was then stripped of solvent to give the crude Mannich base **18** as a yellow oil. This material was taken up in ether and extracted with a total of 100 ml of 1 N HCl followed by 25 ml of H_2O. The aqueous solutions were washed with ether and placed under a layer of ether in an ice bath. The solution was made basic with 3 N NaOH and then extracted with ether. The ether extracts were washed with saturated brine and dried (Na_2SO_4). Solvent removal gave the Mannich base **18** as a pale yellow oil: ir (film) 3400–2700 (NH and OH, hydrogen bonded), 1705 (weak, C=O), and 1640 cm^{-1} (isoxazole).

A solution of 5.30 g (47.2 mmol) of 2-methylcyclopentane-1,3-dione (**2**)[4] in 150 ml of toluene and 50 ml of acetic acid was degassed, placed under nitrogen, and heated at reflux for 5 min. A solution of the Mannich base prepared above in 50 ml of toluene was added, and refluxing was continued for 2.0 hr. The cooled solution was washed with H_2O, saturated $NaHCO_3$ solution, and saturated brine and dried (Na_2SO_4). Solvent removal gave a reddish-orange gum which was filtered through 150 g of Woelm neutral alumina III with benzene to give 12.0 g (81%) of the trans,cis dienol ether mixture (**20a, 21a**) as a light orange solid.

Normally, this mixture was used without further purification. The sample from one experiment was, however, crystallized from ether–hexane and then from ether to give an analytically pure sample of the trans dienol ether **20a** as light yellow prisms: mp 113–116°; uv max (C_2H_5OH) 227 nm (sh, ϵ 10,200) and 252 (18,200); ir ($CHCl_3$) 1740 (cyclopentanone) and 1640 cm^{-1} (C=CC=CO and isoxazole); nmr ($CDCl_3$) δ 1.13 (s, 3, CH_3), 2.21 (s, 3) and 2.32 (s, 3, 2 isoxazole-CH_3), 3.11 (q, 2, =CH-C**H**$_2$C=O), 3.73 (m, 1, >CHOC), and 5.44 ppm (t, 1, =C**H**CH$_2$).

Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.64; H, 7.72; N, 4.57.

In a separate experiment, 2.23 g of lactone **11** was converted to 2.38 g of dienol ether mixture. The nmr of this sample was the same as that of the pure trans isomer **20a**, except that the C-3 proton was two multiplets (total 1 H) at δ 3.73 and 3.85 ppm in a ratio of approximately 4:1. The sample was crystallized twice from isopropyl ether to give 1.545 g of trans dienol ether **20a** as light-orange prisms, mp 111–115°. Concentration of the mother liquors gave 730 mg of orange semicrystalline resin which was shown to contain the trans and cis isomers in a ratio of approximately 45:55. Thus, the original mixture contained 1545 + 0.45(730)/2275 = 83% of trans dienol ether **20a**.

(±)-19-(3,5-Dimethyl-4-isoxazolyl)-de*A*-androst-9-ene-5,17-dione (26a).—A suspension of 1.60 g (41 mmol) of lithium aluminum hydride in 150 ml of freshly distilled tetrahydrofuran was cooled under nitrogen in an ice bath as a solution of 12.0 g of the mixture of trans and cis dienol ethers (**20a, 21a**), the preparation of which is described in the preceding experiment, in 50 ml of tetrahydrofuran was added over 10 min. The suspension was stirred at 0° for another 10 min and then without cooling for 30 min. The mixture was cooled again in an ice bath, carefully hydrolyzed with saturated Na_2SO_4 solution, and dried (Na_2SO_4). The salts were removed by filtration and washed with tetrahydrofuran and chloroform. Solvent removal from the filtrates gave 10.4 g of cream-white solid. Normally, the hydroxy dienol ether **22a** thus prepared was used without purification. However, the material obtained by reduction of the pure trans dienol ether **20a** was crystallized from ether and then from ether–tetrahydrofuran to give analytically pure trans hydroxy dienol ether **22a** as a cream-white crystalline powder: mp 158.5–165° dec; uv max (C_2H_5OH) 230 nm (sh, ϵ 12,000) and 252 (20,000); ir ($CHCl_3$) 3620 and 3450 (OH) and 1640 cm^{-1} (C=CC=CO and isoxazole); nmr ($CDCl_3$) δ 0.96 (s, 3, CH_3), 2.22 (s, 3) and 2.32 (s, 3, 2 isoxazole-CH_3), 3.72 (m, 1, >CHOC), 4.05 (t, 1, >CH-OH), and 5.09 ppm (m, 1, =C**H**CH$_2$).

Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 73.22; H, 8.26; N, 4.03.

The crude hydroxy dienol ether prepared above was dissolved in 350 ml of tetrahydrofuran. To this solution was added 750 mg of 5% palladium on carbon catalyst[23] and the resulting mixture was hydrogenated at atmospheric pressure and room temperature. After 4.0 hr, the uptake of H_2 (1.1 equiv) had ceased. The catalyst was removed by filtration and washed with fresh tetra-

(30) The melting point of this compound depends upon the rate of heating.

hydrofuran. Solvent removal gave the enol ether **23a** as a pale green resin: ir (film) 3150 (OH), 1675 (C=CO–), and 1630 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 0.80 and 0.98 ppm (s, ratio 7:1, CH_3).

A solution of the crude enol ether **23a** in 400 ml of acetone was stirred at 20° with 100 ml of 1 *N* H_2SO_4 for 1.5 hr. This solution of the hemiketal **24a** was cooled in an ice bath as 100 ml of freshly prepared, cold Jones reagent[24] was added over 30 min. The mixture was stirred with cooling for 30 min and then for another 1.5 hr after removal of the cooling bath. It was then poured into H_2O and extracted with benzene. The benzene solutions were washed with saturated $NaHCO_3$ solution and saturated brine and dried (Na_2SO_4). Solvent removal gave the crude trione **25a** as a pale yellow resin. A solution of this material in 100 ml of methanol was degassed, placed under nitrogen, and, after the addition of 1.0 g of KOH, heated at reflux for 1.5 hr. The dark mixture was cooled, poured into H_2O, and extracted with benzene. The benzene extracts were washed with H_2O and saturated brine and dried (Na_2SO_4). Solvent removal gave 8.33 g of orange solid which was filtered through 150 g of Woelm neutral alumina I. Elution with 3:1 benzene–ether gave the enedione **26a** as a cream-white solid. Crystallization from benzene–hexane gave 4.80 g (33% from lactone **11**) of white prisms, mp 141–143.5°. A sample from a similar preparation was crystallized again from benzene–hexane to give analytically pure material: mp 141.5–143.5°; uv max (C_2H_5OH) 226 nm (ϵ 11,300) and 243 (13,350); ir ($CHCl_3$) 1735 (cyclopentanone), 1660 (cyclohexenone), and 1630 cm^{-1} (sh, isoxazole); nmr ($CDCl_3$) δ 1.03 (s, 3, CH_3), 2.14 (s, 3) and 2.27 (s, 3, 2 isoxazole-CH_3), and 3.38 ppm (s, 2, isoxazole-CH_2).

Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.39; H, 7.64; N, 4.38.

(±)-Estr-4-ene-3,17-dione[9] **(5a).**—A solution of 654 mg (2.0 mmol) of the enedione **26a** in 50 ml of 3:1 ethanol–triethylamine containing 60 mg of 10% palladium on carbon catalyst was hydrogenated at atmospheric pressure and room temperature. After 1.0 hr, the uptake of H_2 (50 ml) had ceased. The catalyst was removed by filtration and washed with fresh ethanol. Solvent removal from the filtrates gave the dione **27a** as a colorless foam. This material was taken up in 15 ml of ethylene glycol and 50 ml of benzene containing 400 mg of *p*-toluenesulfonic acid monohydrate. This solution was degassed, placed under nitrogen, and heated at reflux, with azeotropic removal of H_2O (water-jacketed Dean–Stark trap) for 21 hr. The cooled solution was washed with saturated $NaHCO_3$ solution, H_2O, and saturated brine and dried (Na_2SO_4). Solvent removal gave the diketal **29a** as a pale yellow resin. To a solution of this material in 40 ml of ethanol containing 1.5 g of KOH was added 80 mg of 10% palladium on carbon catalyst. The resulting solution was hydrogenated at atmospheric pressure and room temperature. The uptake of hydrogen stopped after 4 hr. The catalyst was removed by filtration and washed with fresh ethanol. The solvent was removed from the filtrates until a residue of approximately 20 ml remained. To this solution of the vinylogous amide **30a** was added 50 ml of 20% aqueous KOH solution. The resulting mixture was degassed, placed under nitrogen, and heated at reflux for 18 hr. The cooled solution was extracted with benzene and the benzene solutions were washed with saturated brine and dried (Na_2SO_4). Solvent removal gave the keto diketal **31a** as a pale yellow solid. To a solution of this material in 30 ml of methanol was added 3 ml of 4 *N* HCl. The resulting solution was heated at reflux under nitrogen for 3.0 hr, cooled, diluted with H_2O, and extracted with benzene. The benzene solutions were washed with saturated $NaHCO_3$ solution and saturated brine and dried (Na_2SO_4). Solvent removal gave 540 mg of pale tan solid which was chromatographed on 25 g of E. Merck 0.05–0.2 mm silica gel. The material eluted with 9:1 and 8:2 benzene–ether was triturated with hot isopropyl ether and then cooled to give 474 mg (85%) of the desired steroid **5a** as white prisms, mp 157–159.5° (lit.[9] mp 156–157°). The ir, nmr, and uv spectra of a similarly prepared sample were identical with those of (+)-estr-4-ene-3,17-dione.[31]

The following intermediates were isolated from a similar preparation.

Isoxazole dione 27a was obtained as white prisms from benzene–hexane: mp 137.5–139.5°; uv max (C_2H_5OH) 223 nm (ϵ 4680) and 292 (65); ir ($CHCl_3$) 1740 (cyclopentanone), 1705 (cyclohexanone), and 1630 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 1.00 (s, 3, CH_3) and 2.26 (s, 3) and 2.41 ppm (s, 3, 2 isoxazole-CH_3).

Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 72.89; H, 7.93; N, 4.34.

Isoxazole diketal 29a was obtained as colorless microprisms from ether: mp 145.5–148°; uv max (C_2H_5OH) 225 nm (ϵ 4500); ir ($CHCl_3$) 1640 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 0.82 (s, 3, CH_3), 2.25 (s, 3) and 2.32 (s, 3, 2 isoxazole-CH_3), and 3.92 ppm (m, 8, 2 –OCH_2CH_2O–).

Anal. Calcd for $C_{24}H_{35}NO_5$: C, 69.03; H, 8.45; N, 3.35. Found: C, 69.34; H, 8.64; N, 3.35.

Keto diketal 31a was obtained as fine, white needles from ether: mp 126.5–128°; no uv max; ir ($CHCl_3$) 1715 cm^{-1} (CH_3CO–); nmr ($CDCl_3$) δ 0.85 (s, 3, CH_3), 2.10 (s, 3, CH_3CO–), and 3.90 ppm (d, 8, J = 4 Hz, 2 –OCH_2CH_2O–).

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 70.11; H, 8.99.

(±)-13β-Ethylgon-4-ene-3,17-dione (5b).—A solution of Mannich base **18** (25.0 g, prepared as described above from 20.0 g of lactone **11**) and 12.6 g (0.01 mol) of 2-ethylcyclopentane-1,3-dione (**19**)[26] in 300 ml of toluene and 100 ml of acetic acid was degassed, placed under nitrogen, and heated at reflux for 2.5 hr, the last 1 hr with azeotropic removal of H_2O (Dean–Stark trap). The solution was cooled under nitrogen, washed with saturated brine, saturated $NaHCO_3$ solution, and saturated brine, and dried (Na_2SO_4). Solvent removal at reduced pressure gave the trans and cis dienol ethers **20b** and **21b** as 26.2 g of orange semisolid.

A suspension of 2.6 g (78 mmol) of $LiAlH_4$ in 300 ml of tetrahydrofuran was cooled in an ice–salt bath under nitrogen as a solution of the dienol ether mixture prepared above in 80 ml of tetrahydrofuran was added dropwise over 30 min. The solution was stirred for an additional 10 min with cooling and then for 2.0 hr at room temperature. The mixture was again cooled in an ice bath and cautiously hydrolyzed with saturated aqueous Na_2SO_4 solution until a light yellow solution containing a white precipitate was obtained. This suspension was filtered and the salts were carefully washed with eight portions of fresh tetrahydrofuran. The filtrates were dried (Na_2SO_4) and stripped of solvent to give the hydroxy dienol ether **22b** as 27 g of extremely viscous yellow resin.

To a solution of the hydroxy dienol ether **22b** in 400 ml of tetrahydrofuran (filtered through Woelm neutral alumina I) was added 1.5 g of 5% palladium on carbon catalyst[23] and the resulting suspension was hydrogenated at atmospheric pressure and room temperature. After 7.0 hr, the uptake of H_2 (1650 ml) had virtually ceased. The catalyst was removed by filtration and washed with fresh tetrahydrofuran. Solvent removal from the filtrates gave the enol ether **23b** as a greenish resin.

To a solution of this material in 400 ml of acetone was added 100 ml of 1 *N* H_2SO_4 and the resulting solution was stirred at room temperature under nitrogen overnight. The solution of the hemiketal **24b** was cooled in an ice bath as 75 ml of cold, freshly prepared Jones reagent[24] was added dropwise over 30 min (more slowly at first until a brown color persisted). The mixture was stirred for another 15 min with cooling and then at room temperature for an additional 3.5 hr. Sufficient saturated $NaHSO_3$ solution was added to destroy the remaining oxidizing agent and the resulting green mixture was diluted with H_2O and extracted with benzene. The benzene solutions were washed with saturated brine, saturated $NaHCO_3$ solution, and saturated brine and dried (Na_2SO_4). Solvent removal at reduced pressure gave the trione **25b** as an orange oil.

To a solution of the crude trione **25b** in 300 ml of methanol was added 2.0 g of NaOH and the resulting dark solution was degassed, placed under nitrogen, and heated at reflux for 2.0 hr. The mixture was cooled, diluted with H_2O, and extracted with benzene. The benzene solutions were washed with H_2O and dried (Na_2SO_4). Solvent removal gave the crude tricyclic enedione **26b** as 18.0 g of reddish-orange resin. This material was taken up in benzene, treated with decolorizing carbon, filtered, concentrated, and finally crystallized from 100 ml of benzene–ether to give 11.35 g of the enedione **26b** as an off-white powder, mp 110–113°.

To a solution of the crystallized tricyclic enedione **26b** prepared above in 300 ml of ethanol and 100 ml of triethylamine was added 500 mg of 5% palladium on carbon catalyst and the resulting suspension was hydrogenated at atmospheric pressure and room temperature. After 2.0 hr, the uptake of hydrogen (895 ml) had ceased. The catalyst was removed by filtration and washed with

(31) Part VI: J. W. Scott, R. Borer, and G. Saucy, *J. Org. Chem.*, **37**, 1659 (1972).

fresh ethanol. The solvent was removed at reduced pressure (finally at 50° and 0.01 mm to remove the last traces of triethylamine) to give the isoxazole dione **27b** as a cream-white solid.

A solution of the isoxazole dione **27b** and 5.0 g of *p*-toluenesulfonic acid monohydrate in 50 ml of ethylene glycol and 500 ml of benzene was degassed, placed under nitrogen, and heated at reflux, with azeotropic removal of H_2O (water-jacketed Dean–Stark trap), for 20 hr. The solution was cooled, washed twice with saturated $NaHCO_3$ solution, twice with H_2O, and saturated brine, and dried (Na_2SO_4). Solvent removal gave the diketal **29b** as a pale yellow resin, the infrared spectrum of which indicated that ketalization was complete.

The isoxazole diketal **29b** was dissolved in a solution of 16.0 g of sodium hydroxide in 400 ml of ethanol. To this mixture was added 1.5 g of 5% palladium on carbon catalyst and the resulting suspension was hydrogenated at atmospheric pressure and room temperature. After 2.5 hr, the uptake of hydrogen (880 ml) had ceased. The catalyst was removed by filtration and washed with fresh ethanol. The solvent was removed from the filtrates until a residue of approximately 100 ml remained. To this solution of the vinylogous amide **30b** was added 400 ml of 20% aqueous NaOH solution and the resulting mixture was degassed, placed under nitrogen, and heated at reflux for 18 hr. The solution was cooled and extracted with benzene. The benzene solutions were washed with saturated brine and dried (Na_2SO_4). Solvent removal at reduced pressure gave the keto diketal **31b** as a yellowish-orange resin.

To a solution of the ketal diketal **31b** in 250 ml of methanol was added 25 ml of 3 *N* HCl and the resulting solution was heated at reflux under nitrogen for 3.0 hr. The solution was cooled, poured into H_2O–brine, and extracted with benzene. The benzene solutions were washed with saturated brine, saturated $NaHCO_3$ solution, and saturated brine and dried (Na_2SO_4). The solvent was removed until a residue of approximately 300 ml remained. This solution was treated with decolorizing carbon, filtered, and stripped of solvent to give 9.6 g of yellow solid. Crystallization from acetone gave 6.10 g of pale yellow prisms, mp 156–160°. A second crystallization from acetone gave 5.86 g (23% from the lactone **11**) of (±)-13β-ethylgon-4-ene-3,17-dione (**5b**) as large white prisms: mp 158–161° (lit.[10] mp 159–161°); uv max (C_2H_5OH) 240 nm (ε 17,000); ir 1734 (cyclopentanone), 1668 (cyclohexenone), and 1619 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.81 (t, 3, J = 7 Hz, CH_2CH_3) and 5.87 ppm (s, 1, C=CH). The compound was found to be identical with the product obtained[1] by another route.

The following intermediates were isolated from a similar preparation.

Trans dienol ether 20b was obtained as yellow-orange prisms from isopropyl ether: mp 101–104°; uv max (C_2H_5OH) 222 nm (sh, ε 9500) and 253 (19,600); ir ($CHCl_3$) 1737 (cyclopentanone) and 1640 cm^{-1} (dienol ether and isoxazole); nmr ($CDCl_3$) δ 0.85 (t, 3, J = 7 Hz, CH_2CH_3), 2.25 (s, 3), and 2.33 (s, 3, 2 isoxazole-CH_3), 2.97 (m, 2, CH_2C=O), 3.70 (s, 1, >CHO–), and 5.55 ppm (t, 1, C=CHCH$_2$).

Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.91; H, 7.95; N, 4.11.

Trans hydroxy dienol ether 22b was obtained as pale orange prisms from ether: mp 105–109.5°; uv max (C_2H_5OH) 224 nm (sh, ε 11,000) and 251 (18,800); ir ($CHCl_3$) 3625 and 3445 (OH) and 1647 cm^{-1} (dienol ether and isoxazole); nmr ($CDCl_3$) δ 0.95 (t, 3, J = 7 Hz, CH_2CH_3), 2.22 (s, 3), and 2.31 (s, 3, 2 isoxazole-CH_3), 3.65 (m, 1 >CHO), 4.10 (t, 1, CHOH), and 5.15 ppm (t, 1, C=CHCH$_2$).

Anal. Calcd for $C_{21}H_{29}NO_3$: C, 73.43; H, 8.51; N, 4.08. Found: C, 73.65; H, 8.50; N, 3.74.

Hydroxy enol ether 23b was obtained as a clear, colorless glass: ir ($CHCl_3$) 3618 and 3442 (OH), 1680 (enol ether), and 1639 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 1.05 (t, 3, J = 7 Hz, CH_2CH_3), 2.19 (s, 3) and 2.29 (s, 3, 2 isoxazole-CH_3) and 3.5 ppm (m, 1, >CHO–).

Isoxazole enedione 26b was obtained as fine, white needles from benzene–ether: mp 111–115.5°; uv max (C_2H_5OH) 228 nm (ε 12,350) and 242 (13,900); ir ($CHCl_3$) 1739 (cyclopentanone), 1669 (cyclohexenone), 1635 (isoxazole), and 1605 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.85 (t, 3, J = 7 Hz, CH_2CH_3), 2.15 (s, 3) and 2.28 (s, 3, 2 isoxazole-CH_3), and 3.39 ppm (s, 2, isoxazole-CH_2).

Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.71; H, 7.85; N, 4.02.

Isoxazole dione 27b was obtained as small, white needles from methylene chloride–ether: mp 143.5–146°; uv max (C_2H_5OH) 224 nm (ε 4650); ir ($CHCl_3$) 1735 (cyclopentanone), 1715 (cyclohexanone), and 1640 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 0.84 (t, 3, J = 7 Hz, CH_2CH_3), 2.25 (s, 3), and 2.40 ppm (s, 3, 2 isoxazole-CH_3).

Anal. Calcd for $C_{21}H_{29}NO_3$: C, 73.43; H, 8.51; N, 4.08. Found: C, 73.77; H, 8.74; N, 4.17.

Isoxazole diketal 29b was obtained as white prisms from ether: mp 140–143° (clear melt at 170°); uv max (C_2H_5OH) 225 nm (ε 4600); ir ($CHCl_3$) 1639 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 0.90 (t, 3, J = 7 Hz, CH_2CH_3), 2.24 (s, 3) and 2.31 (s, 3, 2 isoxazole-CH_3), and 3.92 ppm (m, 8, 2 –OCH$_2$CH$_2$O–).

Anal. Calcd for $C_{25}H_{37}NO_5$: C, 69.57; H, 8.64; N, 3.25. Found: C, 69.41; H, 8.70; N, 3.11.

Keto diketal 31b was obtained as fine, white needles from ether: mp 117.5–119.5°; no uv max; ir ($CHCl_3$) 1711 cm^{-1} (CH_3C=O); nmr ($CDCl_3$) δ 0.95 (t, 3, J = 7 Hz, CH_2CH_3), 2.11 (s, 3, CH_3-C=O), 2.56 (t, 2, J = 6 Hz, $-CH_2C$=O), and 3.90 ppm (d, 8, 2 –OCH$_2$CH$_2$O–).

Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.10; H, 9.30.

Registry No.—**5a**, 5972-59-8; **5b**, 23477-67-0; **9**, 31612-44-9; **10**, 34769-88-5; **11**, 33587-68-7; **13**, 28241-32-0; **15**, 34769-91-0; **17**, 34769-92-1; **18**, 33282-03-0; **20a**, 34769-94-3; **20b**, 34769-95-4; **22a**, 34769-96-5; **22b**, 34769-97-6; **23a**, 34769-98-7; **23b**, 34769-99-8; **26a**, 27510-08-3; **26b**, 29282-22-2; **27a**, 34770-02-0; **27b**, 34770-03-1; **29a**, 29371-34-4; **29b**, 34770-05-3; **31a**, 29371-35-5; **31b**, 34770-07-5.

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