Synthesis, Isolation, and Characterization of the Cis and Trans Isomers of Steroidal 20-Hydroxy-17(20)-en-21-aldehydes

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The *cis*- and *trans*-17(20)-ene-20-hydroxy-21-aldehydes (enol aldehydes) along with their acetate derivatives were prepared from the parent ketols, cortisol, cortisone, 11-deoxycortisol, prednisolone, and prednisone by reaction with zinc acetate in glacial acetic acid. Separation and isolation of the pure isomers was accomplished for the first time by reversed-phase high-performance liquid chromatography. Stereochemical assignments were based on unequivocal partial syntheses. Significant differences in the ultraviolet spectra, optical rotatory properties, and nuclear magnetic spectra of the cis and trans isomers were found. The availability of pure enol aldehydes will make possible studies centering on their possible role as intermediates in the metabolism of the ketol side chain.

Introduction

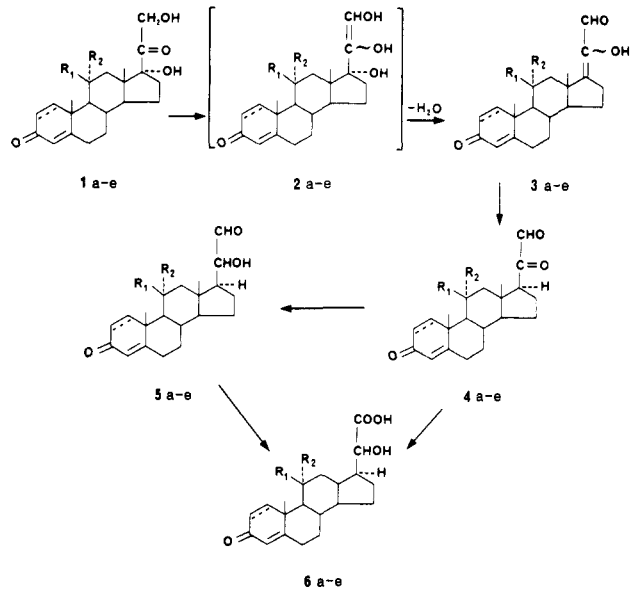
In 1976, Weiss et al.[1] isolated and characterized radioactive 17-deoxy-20-hydroxy-21-oic acid metabolites from the urine of a patient given a radiotracer dose of cortisol. The authors proposed that the enol aldehyde **3** (Scheme I) derived from the α-ketol **1** through the transient enetriol **2** rearranges via the dioxo intermediate **4** to the 17-deoxy acids **6**, either directly by internal dismutation or through reduction at C-20, generating **5** followed by oxidation at C-21 to give **6**. This reaction sequence is the biological equivalent of the Mattox rearrangement.[2] The syntheses of the cis and trans enol aldehydes **3** from a number of α-ketols were undertaken in order to determine whether these compounds can function as metabolic intermediates.

Results and Discussion

We found that previously published methods for the chemical synthesis of steroidal enol aldehydes were unsatisfactory because they are time-consuming and difficult to reproduce and gave low yields. Our modification of the procedure described by Smith[3] and Herzog[4] afforded enol aldehydes in acceptable yields. However, analyses of the crude reaction products by NMR indicated that they were mixtures of cis and trans isomers. We now report the first successful isolation in crystalline form of the isomeric enol aldehydes derived from cortisol (**1a**), cortisone (**1b**), 11-deoxycortisol (**1c**), prednisolone (**1d**), and prednisone (**1e**) by the use of reversed-phase high-performance liquid chromatography. In every case the yield of isolated cis enol aldehyde (16.6–43.3%) exceeded that of the trans isomer (4.6–7.8%).

Although the NMR spectra of the isolated enol aldehydes suggested the correct structures, unequivocal proof of the stereochemistry was established by independent synthesis (Scheme II). The cis and trans enol aldehydes **3d** obtained by refluxing prednisolone **1d** with zinc acetate in glacial acetic acid were converted to the corresponding enol aldehyde 20-acetate **7d** with pyridine–acetic anhydride (1:1). Subsequent reaction of **7d** with Jones reagent and diazomethane afforded the 11-oxo enol acetate methyl esters **8**. The C-20 epimeric acetoxy methyl glycolates **9a** and **9b** derived from cortisone (**1b**)[5] were utilized to establish the exact stereochemistry of 8-***cis*** and 8-***trans***. Reaction of **9a** and **9b** with dichlorodicyanobenzoquinone

Scheme I



a. 4-ene ; R_1 = OH, R_2 = H
b. 4-ene ; R_1, R_2 = O
c. 4-ene ; R_1 = R_2 = H
d. 1,4-diene ; R_1 = OH, R_2 = H
e. 1,4-diene ; R_1, R_2 = O

(DDQ) in refluxing benzene furnished the corresponding 1,2-dehydro products **10a** and **10b**. These same intermediates were obtained by the oxidation at C-11 of the methyl acetoxy glycolates **11a** and **11b** from prednisolone **1d**.[6] Treatment of **10a** and **10b** with thionyl chloride in pyridine gave in each case two dehydration products. Those possessing side-chain unsaturation (as evidenced by the presence of an additional UV chromophore and enol acetate bands in the IR) were identical with 8-***trans*** and 8-***cis***, respectively. Dehydration of 17-hydroxy-20-acetates with thionyl chloride proceeds stereospecifically (M. L.

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(1) Weiss, G.; Monder, C.; Bradlow, H. L. *J. Clin. Endocrinol.* **1976**, *37*, 811.
(2) Mattox, V. R. *J. Am. Chem. Soc.* **1952**, *74*, 4340.
(3) Smith, L. L. *Steroids* **1967**, *9*, 289.
(4) Herzog, H. L.; Gentles, M. J.; Marshall, H.; Hershberg, E. B. *J. Am. Chem. Soc.* **1961**, *83*, 4073.
(5) Lewbart, M. L.; Mattox, V. R. *J. Org. Chem.* **1963**, *28*, 1779.
(6) Lewbart, M. L. U.S. Patent No. 4, 511,511, April 6, 1985.

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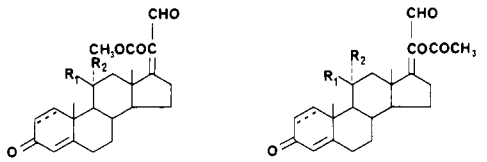
Chart I



7 cis a–e 7 trans a–e

a. 4-ene; R_1=OH, R_2=H
b. 4-ene; R_1=R_2=O
c. 4-ene; R_1=R_2=H
d. 1,4-diene; R_1=OH, R_2=H
e. 1,4-diene; R_1=R_2=O

Table I. Physical Properties of Enol Aldehydes and Their 20-Acetates Reported in the Literature

parent steroid	melting range, °C	λ_{max}, nm	α_{max}	citation
		20-Alcohol		
cortisol	203–208	242, 285	17 000, 14 200	4
cortisone	197–203	240, 285	16 000, 12 500	9
	189–191	238, 282	15 600, 13 100	10
	a	238, 279	*a*	9
11-deoxycortisol	175–180	242, 285	17 500, 11 500	11
11-deoxy-prednisolone	231–238	246, 270	16 200, 14 000	9
prednisolone	225–229	246, 270	15 500, 14 900	4
		20-Acetate		
cortisol	243–247	245	28 600	4
	213–217	239	26 500	11
cortisone	210–212	243	23 000	9
	232–234	241	23 500	10
	226–232	241	23 700	11
11-deoxycortisol	165–168	244	21 500	9
11-deoxy-prednisolone	186–188	248	34 400	4
prednisolone	246–250	248	30 600	4

[a] Not reported.

Lewbart, unpublished observations); the true isomeric identities of the original enol aldehydes **3d** were thus rigorously established. The second pair of dehydration products from **10a** and **10b** were presumed to be the 16-ene-20-acetates **12a** and **12b**. These structural assignments were confirmed by their deacetylation in methanolic sodium hydroxide to the allylic alcohols **13a** and **13b**. Oxidation of these epimers with chromic anhydride–pyridine generated a common product, namely the 16-en-20-one **14**, thereby establishing the presence of D ring unsaturation in the dehydration products **12a** and **12b**.

All enol aldehydes **3** exhibited two absorption maxima in the ultraviolet region. The absorbance at 237–245 nm reflects the chromophore in ring A; that ranging from 278 to 286 nm is due to the α,β-conjugated carbonyl system in the side chain. On the other hand, their acetylation products **7** (Chart I) show a single more intense (ϵ 26 700–30 500) chromophore ranging from 242 to 246 nm. Our results are consistent with UV constants of the steroidal enol aldehydes reported in the literature (Table I).

Melting ranges of the enol aldehydes listed in Table I were broad. This was in part due to the complexity of the mixtures, which were composed of undetermined proportions of cis and trans isomers, and unspecified degree of hydration. These conclusions were based on our findings that for each enol aldehyde pair, the free 20-trans alcohol retained water of hydration, while the cis isomer did not. Since water of hydration was not retained in stoichiometric amount, broad melting points were observed in each case; in contrast the cis isomers had much sharper melting points.

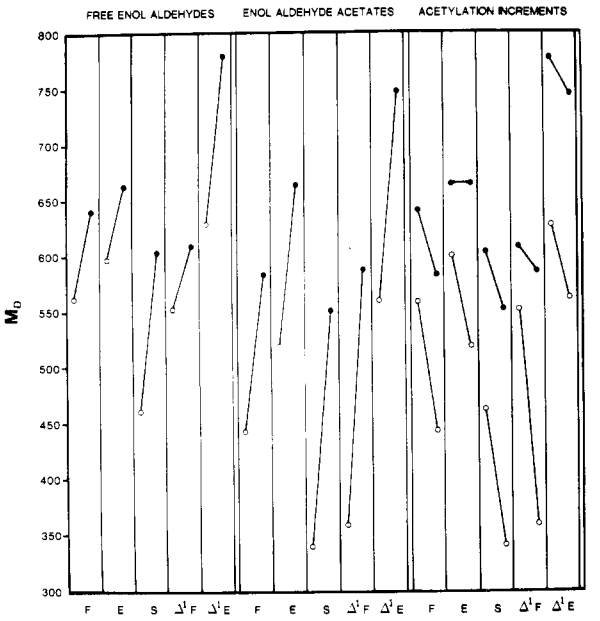


Figure 1.

Proton NMR served to confirm the structural assignments for the free and acetylated enol aldehydes suggested by other physicochemical measurements. Certain trends in chemical shifts were noted for the key functional groups in the cis–trans isomeric pairs. We note that on going from cis to trans isomer there was a consistent downfield (high frequency) shift of the C18 methyl and aldehyde C–H resonances. In addition, there was a small but consistent opposite change exhibited by the enol acetate methyl protons. For the 11β-hydroxy steroids there was also a small downfield shift for the 11α-proton resonance on going from the cis to trans isomer. A detailed paper extending and elaborating on these observations is in preparation.

When the molecular rotations (M_D) of the five isomeric pairs of enol acetate aldehydes (Figure 1) were compared, we observed that in every instance the cis isomer was more dextrorotatory than the corresponding trans isomer. The magnitude of this difference ($M_D^{cis} - M_D^{trans}$) ranged from +139 to +226 units. This finding is understandable if one regards the enol acetates as dehydration products of the hypothetical 17α-hydroxy-20-acetoxypregnanes. The Fieser–Sarett Rule[7] states that 20β-acetates are more dextrorotatory than their 20α-epimers. It is not surprising, therefore, that the cis isomers, which, by Fischer projections, have the acetoxy group in the same position on the side chain as a 20β-acetate, should exhibit optical activity comparable to that of their saturated counterparts. Indeed, the ($M_D^{cis} - M_D^{trans}$) values noted above are in almost exact agreement with M_D differences ($M_D^{20\beta} - M_D^{20\alpha}$) found earlier by Fieser[7] (+140 to +220 units) and by Lewbart and Schneider[8] (+142 to +245 units) for a number of C-20 epimeric acetates with a variety of substituents at C-17 and C-21. These data would suggest that the preferred conformations of the 20-acetoxypregnanes, where free rotation of the C-17–C-20 bond is possible, are virtually superimposable on the 17(20)-en-20-acetoxy-21-aldehydes in which the position of the acetoxyl group is fixed.

(7) Fieser, L. F.; Fieser, M. In *Steroids*; Reinhold: New York, 1959; pp 612–622.
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(10) Lewbart, M.; Mattox, V. R. *J. Org. Chem.* **1964**, *29*, 513.
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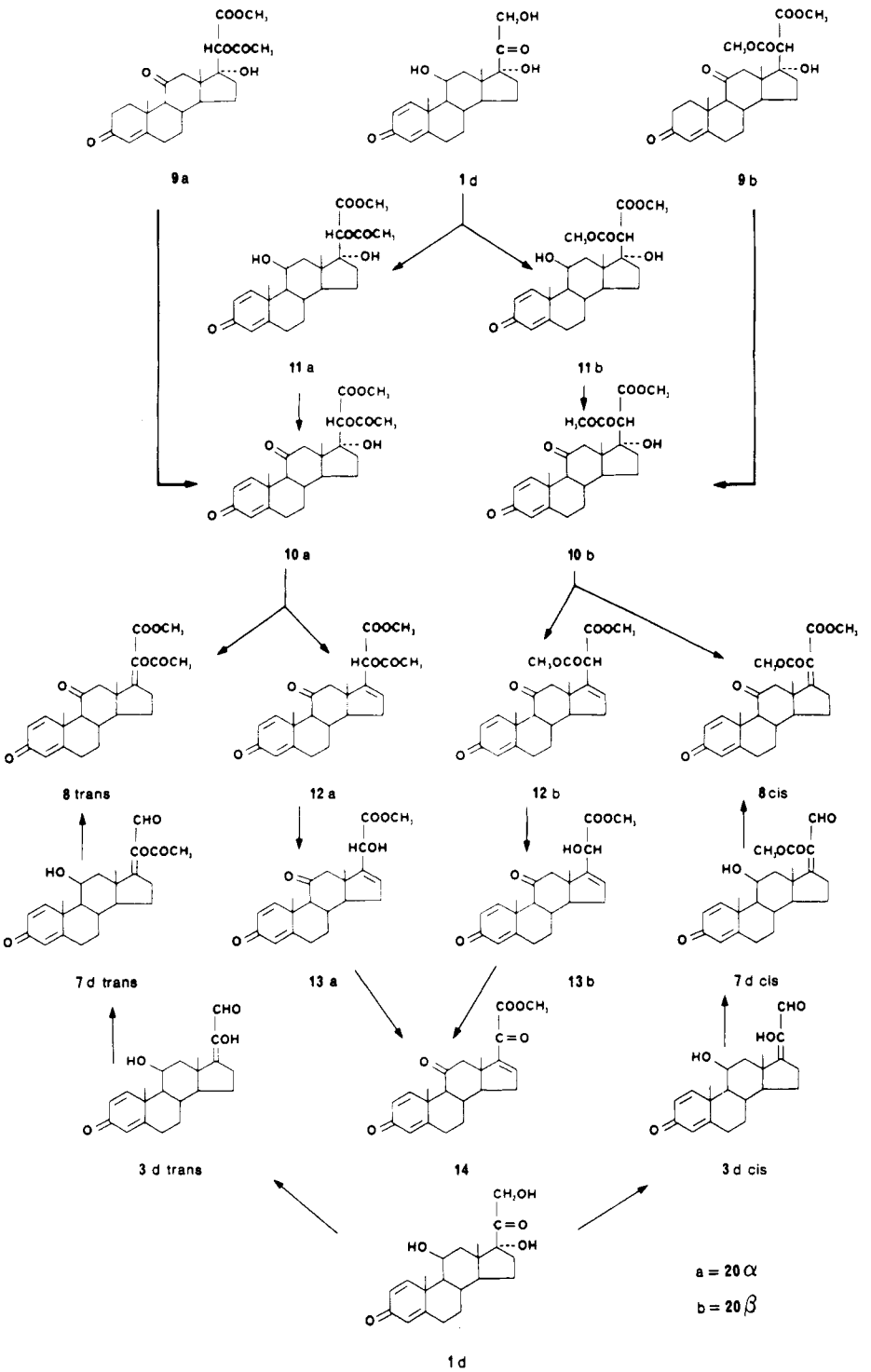
Scheme II



Inspection of the M_D values of the five pairs of cis and trans enol aldehydes (**3a–e**) showed consistently more positive dextrorotation for the cis isomers ($M_D^{cis} - M_D^{trans}$ = +58 to +150 units). Acetylation increments were determined by comparing M_D values of free enol aldehydes with the corresponding acetates. It was noted that acetylation of the trans isomers resulted in a greater levorotatory shift ($M_D^{free} - M_D^{acetate}$ = −68 to −190 units) than did similar derivatization of the cis isomers ($M_D^{free} - M_D^{acetate}$ = +1 to −57 units).

The Fieser–Sarett rule also states that 17,20β-dihydroxypregnanes are more dextrorotatory than 17,20α-dihydroxypregnanes and that acetylation of the 20β-epimers results in a strongly positive shift in M_D, whereas acetylation of a 20α-hydroxypregnanes brings about a weakly positive or negative shift in M_D. Although our data obtained with the free enol aldehydes and acetylation increments are less striking than those obtained by comparing M_D values of the isomeric enol acetates, they nevertheless show consistent trends that conform to the Fieser–Sarett rules.

Experimental Section

Melting points were obtained on a Fisher-Johns apparatus and are uncorrected. Optical activity was determined in chloroform with a Zeiss 0.005° photoelectric polarimeter at 589 nm (D line of sodium). Ultraviolet spectra were obtained in methanol with either a Zeiss RPQ 20A recording spectrophotometer or a Gilford

Model 240 spectrophotometer. Infrared spectra were obtained on zinc selenide multiple internal reflectance crystals in a Perkin-Elmer Model 681 spectrophotometer. Preparative HPLC was carried out with either a Perkin-Elmer Series 3B liquid chromatograph in series with a LC-75 detector or a Du Pont Model 850 liquid chromatograph and a Model 860 absorbance detector. HPLC was performed either at room temperature (free enol aldehydes) or at 40 °C (all other mixtures) with either 9.4 mm i.d. × 25 cm (8 mL/min) or 22.1 mm i.d. × 25 cm columns (22.5 mL/min) containing either 5 μm silica gel (normal phase) or octadecylsilane (ODS)-coated 5 μm silica gel (reversed phase). Proton NMR spectra were obtained in deuteriochloroform on either a Varian HR-300 spectrometer in the Fourier mode with a Nicolet 1080 accessory or a General Electric QE-500 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from internal tetramethylsilane (TMS). Mass spectra were generated with a VG 70-250 double-focusing magnetic sector mass spectrometer with a VG 11-250 data system (VG Analytical, Manchester, GB). Sample insertion was via the desorption chemical ionization probe. Isobutane was used as the reactant gas for positive chemical ionization. The source temperature was 220 °C. Scan speed was 0.2 s per decade in the mass range 600–60. Scan cycle time was 0.6 s.

Microanalyses were performed by either Galbraith Laboratories, Inc., Knoxville, TN, or Schwartzkopf Microanalytical Laboratory, Woodside, NY.

General Procedure for Preparation and Isolation of Enol Aldehydes. Method A. A solution of α-ketol (250 mg) in glacial acetic acid (5 mL) is refluxed with zinc acetate dihydrate (27.5 mg) for 2 h. The reaction mixture is concentrated to dryness in vacuo at 40 °C with several additions of toluene. The residue is partitioned between methylene chloride and water. The organic layer is filtered through anhydrous sodium sulfate and concentrated to dryness in vacuo. Reverse-phase HPLC in acetonitrile–water is performed with a suitable linear gradient (e.g., 40–70% acetonitrile in 30 min). Both the more mobile, minor trans isomer and the less mobile, major cis isomer are collected into flasks containing methylene chloride during multiple runs. The organic layers are concentrated directly in vacuo at a water bath temperature not exceeding 35 °C. The residues are dissolved in methylene chloride, transferred to small Erlenmeyer flasks, and crystallized from suitable organic solvents. Enol aldehydes are stored at −20 °C.

Method B. A solution of the α-ketol (200 mg) in glacial acetic acid (8.3 mL) is refluxed with zinc acetate dihydrate (25 mg) for 40 min and cooled to room temperature. Crystallization is initiated by the slow addition of aqueous sodium carbonate (4 g of Na_2CO_3 in 10 mL of water). Crystals are collected by filtration and washed with water. The cis and trans isomers are separated on a reverse-phase (ODS) column with a gradient of acetonitrile–methanol, 1:1 (I), and water (II). The gradient initial value, 50% I, is changed linearly to 70% I at a rate of 1% min. The flow rate is 3.5 mL/min. Methanol is evaporated from the eluate in vacuo, and the steroid is extracted from the aqueous phase with ethyl acetate. The ethyl acetate is evaporated under nitrogen.

20-Acetoxy-11β-hydroxy-3-oxo-1,4,*trans*-17(20)-pregnatrien-21-al (7d-*trans*) and 20-Acetoxy-11β-hydroxy-3-oxo-1,4,*cis*-17(20)-pregnatrien-21-al (7d-*cis*) from Prednisolone (1d). A solution of prednisolone (1.0 g) in glacial acetic acid (20 mL) was refluxed with zinc acetate (110 mg) for 2 h (method A). The more mobile, minor product (**3d-*trans***) was recovered and treated with excess pyridine/acetic anhydride overnight at room temperature. Crystallization of the product (**7d-*trans***) from methanol–acetonitrile gave 107 mg (10.0%) of needles, mp 221–223 °C. Recrystallization from methanol furnished the analytical sample: mp 230–233 °C; $[\alpha]_D$ +94.0°; λ_{max} 244 nm, ε 29 900; IR 3400 (hydroxyl), 1755, and 1190 cm^{-1} (enol acetate); ^1H NMR (500 MHz) δ 9.77 (s, CHO) 7.25 (dd, J = 10.1 Hz, H-1), 6.29 (dd, J = 10.1, 1.8 Hz, H-2), 6.04 (m, H-4), 4.50 (m, H-11α), 2.21 (s, $OCOCH_3$), 1.48 (s, 19-CH_3), 1.41 (s, 18-CH_3); CI-MS m/z 385 (M + 1, 100), 367 (M + 1 − H_2O, 60), 343 (M + 1 − CH − CHO, 9), 325 (M + 1 − CH_2OH − CHO, 22), 307 (M + 1 − H_2O − CH_2OH − CHO, 24), 238 (M + 1 − CHO − CH_2OCOCH_3, 11). Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.95; H, 7.66.

The original less mobile major product (**3d-*cis***) was acetylated as above, affording 289 mg (27.1%) of **7d-*cis*** as platelets for ethyl acetate, mp 233–235 °C. For the analytical sample: mp 234–237 °C; $[\alpha]_D$ + +153°; λ_{max} 246 nm, ε 30 800; IR 3460 (hydroxyl), 1760, and 1210 cm^{-1} (enol acetate); ^1H NMR (500 MHz) δ 9.57 (s, CHO), 7.22 (d, J = 10.0 Hz, H-1), 6.27 (dd, J = 10.0, 2.0 Hz, H-2), 6.03 (m, H-4), 4.46 (m, H-11α), 2.25 (s, $OCOCH_3$), 1.47 (s, 19-CH_3), 1.26 (s, 18-CH_3). CI-MS m/z 385 (M + 1, 100), 367 (M + 1 − H_2O, 58), 343 (M + 1 − CH − CHO, 10), 325 (M + 1 − CH_2OH − CHO, 32), 307 (M + 1 − H_2O − CH_2OH − CHO, 30), 283 (M + 1 − CHO − CH_2OCOCH_3, 14). Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 72.19; H, 7.64.

Methyl 20-Acetoxy-3,11-dioxo-1,4,*trans*-17(20)-pregnatrien-21-oate (8-*trans*) from 7d-*trans*. A solution of 20-acetoxy-11β-hydroxy-3-oxo-1,4,*trans*-17(20)-pregnatrien-21-al (40 mg) in acetone (10 mL) was treated with 0.4 mL of 8 N Jones oxidant for 2 h at room temperature. The reaction mixture was partitioned between ethyl acetate and brine. The organic layer was filtered through anhydrous sodium sulfate and taken to dryness. The acidic fraction, recovered by reversed-phase HPLC, was treated in methanol with excess diazomethane in ether. Rechromatography gave 1.7 mg of prisms from aqueous methanol, mp 230–232 °C.

Methyl 20-Acetoxy-3,11-dioxo-1,4,*cis*-17(20)-pregnatrien-21-oate (8-*cis*) from 7d-*cis*. Jones oxidation of 20-acetoxy-11β-hydroxy-3-oxo-1,4,*cis*-17(20)-pregnatrien-21-al (50 mg) as in the preparation of **8-*trans*** from **7d-*trans*** followed by treatment of the acidic fraction with diazomethane and rechromatography gave 4.8 mg of **8-*cis*** as prismatic needles from aqueous methanol, mp 138–140 °C.

Methyl 20α-Acetoxy-11β,17-dihydroxy-3-oxo-1,4-pregnadien-21-oate (11a). Treatment of methyl 11β,17,20α-trihydroxy-3-oxo-1,4-pregnadien-21-oate[6] (250 mg) with pyridine/acetic anhydride gave 230 mg of hairy needles from acetone–isooctane, mp 235–236 °C. For the analytical sample: mp 236–237 °C; $[\alpha]_D$ +64.8°; λ_{max} 245 nm, ε 16 900; IR 3460 (hydroxyl), 1742, and 1230 cm^{-1} (acetate); ^1H NMR (300 MHz) δ 7.3 (d, J = 10 Hz, H-1), 6.24 (dd, J = 10, 2 Hz, H-2), 6.00 (s, H-4), 5.10 (s, H-11α), 4.40 (m, H-20β), 3.76 (s, OCH_3), 2.13 (s, $OCOCH_3$), 1.45 (s, 19-CH_3), 1.20 (s, 18-CH_3); CI-MS m/z 433 (M + 1, 100), 415 (M + 1 − H_2O, 93), 397 (M + 1 − $2H_2O$, 46), 373 (M − $COOCH_3$, 9), 337 (M − $COOCH_3$ − $2H_2O$, 30), 355 (M − $COOCH_3$ − H_2O, 17). Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.48; H, 7.60.

Methyl 20β-Acetoxy-11β,17-dihydroxy-3-oxo-1,4-pregnadien-21-oate (11b). Acetylation of methyl 11β,17,20β-trihydroxy-3-oxo-1,4-pregnadien-21-oate[6] (100 mg) afforded 117 mg of platelets from acetone, mp 220–222 °C. For the analytical sample: mp 224–225 °C; $[\alpha]_D$ +49.9°, λ_{max} 244 nm, ε 15 100; IR 3470 (hydroxyl), 1742, 1730, 1230 cm^{-1} (acetate); ^1H NMR (300 MHz) δ 7.3 (d, J = 10 Hz, H-1), 6.24 (dd, J = 10, 2 Hz, H-2), 6.02 (s, H-4), 3.15 (s, OCH_3), 2.16 (s, $OCOCH_3$), 1.46 (s, 19-CH_3), 1.04 (s, 18-CH_3); CI-MS m/z 433 (M + 1, 40), 415 (M + 1 − H_2O, 44), 397 (M + 1 − $2H_2O$, 25), 373 (M − $COOCH_3$, 8), 355 (M − $COOCH_3$ − H_2O, 13), 337 (M − $COOCH_3$ − $2H_2O$, 23). Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.44; H, 7.52.

Methyl 20α-Acetoxy-17-hydroxy-3,11-dioxo-1,4-pregnadien-21-oate (10a) from 11a. Treatment of methyl 20α-acetoxy-11β,17-dihydroxy-3-oxo-1,4-pregnadien-21-oate (1.0 g) in 90% acetic acid (10 mL) with chromic anhydride (300 mg) for 1 h at room temperature followed by dilution of the reaction mixture with methylene chloride and successive washing of the organic phase with cold dilute NaOH and water gave 868 mg of prisms from ethyl acetate–isooctane: mp 158.5–159.5 °C; $[\alpha]_D$ +122°; λ_{max} 238 nm; ε 15 700; IR 3470 (hydroxyl), 1745 and 1230 (acetate), 1705 cm^{-1} (11-one); ^1H NMR (500 MHz) δ 7.64 (d, J = 10.2 Hz, H-1), 6.21 (dd, J = 10.2, 1.9 Hz, H-2), 6.09 (m, H-4), 5.04 (s, H-20β), 3.78 (s, OCH_3), 2.67 (d, J = 12.4 Hz, H-12β), 2.18 (s, $OCOCH_3$), 1.44 (s, 19-CH_3), 0.95 (s, 18-CH_3); CI-MS m/z 431 (M + 1, 30), 413 (M + 1 − H_2O, 10), 371 (M + 1 − $HCOOCH_3$, 15) 299 (M + 1 − $CH_3COOCHOCOCH_3$, 100), 281 (M + 1 − H_2O − $CH_3COOCHOCOCH_3$, 12). Anal. Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02. Found: C, 66.34; H, 7.12.

Methyl 20β-Acetoxy-17-hydroxy-3,11-dioxo-1,4-pregnadien-21-oate (10b) from 11b. Oxidation of methyl 20β-acetoxy-11β,17-dihydroxy-3-oxo-1,4-pregnadien-21-oate (500 mg) in pyridine (5 mL) with chromic anhydride (500 mg) overnight at room temperature afforded 432 mg of platelets from aqueous

ethanol: mp 218–221 °C; $[\alpha]_D$ +119°; λ_{max} 238 nm, ϵ 15 600; IR 3460 (hydroxyl), 1750 and 1230 (acetate), 1703 cm^{-1} (11-one); ^1H NMR (500 MHz) δ 7.64 (d, J = 10.2 Hz, H-1), 6.20 (dd, J = 10.2, 1.9 Hz, H-2), 6.08 (m, H-4), 5.04 (s, H-20α), 3.80 (s, OCH_3), 2.16 (s, $OCOCH_3$), 1.45 (s, 19-CH_3), 0.78 (s, 18-CH_3); CI-MS m/z 430 (M^+, 20), 412 ($M^+ - H_2O$, 8), 370 ($M^+ - COOCH_3 - H$, 7), 298 ($M^+ - CH_3COOCH - COOCH_3$, 100), 280 ($M^+ - H_2O - CH_3COOCH - COOCH_3$, 9). Anal. Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02. Found: C, 66.88; H, 7.09.

Methyl 20α-Acetoxy-17-hydroxy-3,11-dioxo-1,4-pregnadien-21-oate (10a) from 9a. A solution of methyl 20α-acetoxy-17-hydroxy-3,11-dioxo-4-pregnen-21-oate[5] (500 mg) in benzene (15 mL) was refluxed with DDQ (438 mg) for 18 h. The reaction mixture was diluted with an equal volume of ethyl acetate and washed successively with alkaline and neutral brine. Normal-phase HPLC in isopropyl alcohol–hexane followed by crystallization from ethanol supplied 230 mg of prisms, mp 164–165.5 °C. The infrared spectrum was identical with that of **10a** prepared by oxidation at C-11 of **11a**.

Methyl 20β-Acetoxy-17-hydroxy-3,11-dioxo-1,4-pregnadien-21-oate (10b) from 9b. Reaction of methyl 20β-acetoxy-17-hydroxy-3,11-dioxo-4-pregnen-21-oate[5] (500 mg) with DDQ in benzene as in the preparation of **10a** from **9a** followed by normal-phase HPLC gave 270 mg of prisms from ethanol, mp 209–212 °C. The infrared spectrum was identical with that of **10b** prepared by oxidation of **11b** at C-11.

Reaction of Methyl 20α-Acetoxy-17-hydroxy-3,11-dioxo-1,4-pregnadien-21-oate (10a) with Thionyl Chloride in Pyridine. A solution of the 20α-acetoxy methyl ester (250 mg) in cold pyridine (4.25 mL) was treated with 0.25 mL of thionyl chloride for 15 min at 3 °C. Addition of ice gave rise to a transient greenish-blue color and solution of the precipitated pyridinium chloride. The reaction mixture was extracted with methylene chloride. Successive washes with cold, dilute hydrochloric acid, sodium bicarbonate, and with ice water were followed by filtration of the organic layer through anhydrous sodium sulfate and concentration to dryness. Two crystallizations from ethyl acetate furnished **methyl 20α-acetoxy-3,11-dioxo-1,4,16-pregnatrien-21-oate (12a)** as prisms (69 mg): mp 196–197 °C; $[\alpha]_D$ +98.4°; λ_{max} 238 nm, ϵ 15 400; IR 1750 and 1230 (acetate), 1705 cm^{-1} (11-one); ^1H NMR (500 MHz) δ 7.74 (d, J = 10.3 Hz, H-1), 6.22 (dd, J = 10.3, 1.9 Hz, H-2), 6.10 (m, H-4), 5.98 (d, J = 3.0 Hz, H-16), 5.48 (s, H-20β), 3.75 (s, OCH_3), 2.64 (d, J = 12.6 Hz, H-12β), 2.14 (s, $OCOCH_3$), 1.46 (s, 19-CH_3), 0.85 (s, 18-CH_3); CI-MS m/z 412 (M^+, 100), 352 ($M^+ - COOCH_3 - H$, 50). Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 70.00; H, 6.84.

Reversed-phase HPLC of the mother liquor in methanol–water afforded an additional 34.5 mg of **12a**, raising the yield of 103.5 mg (43.2%). Crystallization of the less mobile, minor product from aqueous methanol supplied 5 mg (2.1%) of the **methyl 20-acetoxy-3,11-dioxo-1,4,*trans*-17(20)-pregnatrien-21-oate (8-*trans*)** as prisms, mp 226–229 °C. For the analytical sample: mp 228–232 °C; $[\alpha]_D$ +145°; λ_{max} 232 nm, ϵ 23 900; IR 1758 and 1220 (enol acetate), 1730 (carbomethoxyl), 1708 cm^{-1} (11-one); ^1H NMR (500 MHz) δ 7.72 (d, J = 10.2 Hz, H-1), 6.21 (dd, J = 10.2, 1.9 Hz, H-2), 6.09 (m, H-4), 3.75 (s, OCH_3), 3.34 (d, J = 12.7 Hz, H-12β), 2.18 (s, OCH_3), 1.45 (s, 19-CH_3), 1.11 (s, 18-CH_3); CI-MS m/z 413 (M + 1, 100), 381 (M – CH_3O, 28), 371 (M + 1 – CHCO, 28), 353 (M + 1 – $HCOOCH_3$, 10). Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 70.08; H, 6.95.

The infrared spectrum was identical with that of **8-*trans*** prepared by sequential Jones oxidation and diazomethane esterification of **7d-*trans***.

Reaction of Methyl 20β-Acetoxy-17-hydroxy-3,11-dioxo-1,4-pregnadien-21-oate (10b) with Thionyl Chloride in Pyridine. Dehydration of the 20β-acetoxy methyl ester (250 mg) was carried out as with **10a**. Two crystallizations from acetone–isooctane gave 30 mg of **methyl 20β-acetoxy-3,11-dioxo-1,4,16-pregnatrien-21-oate (12b)** as prismatic needles, mp 195–197 °C. For the analytical sample: mp 199–201 °C; $[\alpha]_D$ +187°; λ_{max} 238 nm, ϵ 15 500; IR 1750 and 1230 (acetate), 1708 cm^{-1} (11-one); ^1H NMR (500 MHz) δ 7.72 (d, J = 10.3 Hz, H-1), 6.27 (dd, J = 10.3, 1.9 Hz, H - 2), 6.10 (m, H-4), 5.78 (d, J = 3.5 Hz, H-16), 5.51 (s, H-20α), 3.76 (s, OCH_3), 2.52 (d, J = 12.6 Hz, H-12β), 2.13 (s, $OCOCH_3$), 1.46 (s, 19-CH_3), 0.91 (s, 18-CH_3); CI-MS m/z 412 (M^+, 100), 352 ($M^+ - COOCH_3 - H$, 50). Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 70.03; H, 6.89.

Preparative HPLC in methanol–water of the mother liquor afforded an additional 29 mg of **12b**, mp 195–197 °C, raising the yield to 59 mg (24.6%). The less mobile product, **methyl 20-acetoxy-3,11-dioxo-1,4,*cis*-17(20)-pregnatrien-21-oate (8-*cis*)**, was obtained as a filterable solid (54 mg, 22.5%) from aqueous methanol. The analytical sample crystallized as long needles from aqueous methanol: mp 116–118 °C; $[\alpha]_D$ +138°; λ_{max} 230 nm, ϵ 27 700; IR 1758, 1230, 1205 (enol acetate), 1725 (carbomethoxyl), 1705 cm^{-1} (11-one); ^1H NMR (500 MHz) δ 7.66 (d, J = 10.3 Hz, H-1), 6.21 (dd, J = 10.3, 1.9 Hz, H-2), 6.09 (m, H-4), 3.74 (s, OCH_3), 2.79 (d, J = 12.5 Hz, H-12β), 2.23 (s, $OCOCH_3$), 1.44 (s, 19-CH_3), 0.94 (s, 18-CH_3); CI-MS m/z 413 (M + 1, 100), 381 (M + 1 – OCH_3, 27), 371 (M + 1 – $COCH_2$, 28), 353 (M + 1 – $COOCH_3$, 5). Anal. Calcd for $C_{24}H_{28}O_6 \cdot {}^1/_2H_2O$: C, 68.39; H, 6.94. Found: C, 68.32; H, 7.26.

The product **8-*cis*** was identical in all respects with oxidation/esterification product obtained from **7d-*cis***.

Methyl 20α-Hydroxy-3,11-dioxo-1,4,16-pregnatrien-21-oate (13a) from 12a. To a solution of methyl 20α-acetoxy-3,11-dioxo-1,4,16-pregnatrien-21-oate (19 mg) in methanol (1 mL) was added 0.025 mL of 1 N methanolic sodium hydroxide. After 30 min at room temperature the solution was diluted with 10 mL of methylene chloride. The mixture was washed with water, dried over anhydrous sodium sulfate, and subjected to reverse-phase HPLC in acetonitrile–water. Crystallization from ethyl acetate gave 10.5 mg (61.4%) of prismatic needles: mp 190–191 °C; $[\alpha]_D$ +106°; λ_{max} 238 nm, ϵ 17 500; IR 3400 (hydroxyl), 3060 (16-ene), 1750 (carbomethoxyl), 1705 cm^{-1} (11-one); ^1H NMR (500 MHz) δ 7.74 (d, J = 10.3 Hz, H-1), 6.21 (dd, J = 10.3, 1.9 Hz, H-2), 6.09 (m, H-4), 5.85 (d, J = 3.1 Hz, H-16), 4.67 (d, J = 5.8 Hz, H-20β), 3.79 (s, OCH_3), 2.61 (d, J = 12.4 Hz, H-12β), 1.46 (s, 19-CH_3), 0.86 (s, 18-CH_3); CI-MS m/z 370 (M^+, 100), 352 ($M^+ - H_2O$, 21), 310 ($M^+ - COOCH_3 - H$, 10). Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.34, H, 7.19.

Methyl 20β-Hydroxy-3,11-dioxo-1,4,16-pregnatrien-21-oate (13b) from 12b. Deacetylation of methyl 20β-acetoxy-3,11-dioxo-1,4,16-pregnatrien-21-oate (25 mg) in methanol (2.5 mL) with 1 N methanolic sodium hydroxide for 30 min as in the preparation of **13a** from **12a** followed by HPLC afforded 14 mg (70.7%) of multifaceted prisms from ethyl acetate, mp 179–180 °C. For the analytical sample: mp 179.5–180 °C; $[\alpha]_D$ +195°; λ_{max} 238 nm, ϵ 16 600; IR 3400 (hydroxyl), 3050 (16-ene), 1740 (carbomethoxyl), 1700 cm^{-1} (11-one); ^1H NMR (500 MHz) δ 7.74 (d, J = 10.3 Hz, H-1), 6.21 (dd, J = 10.3, 1.8 Hz, H-2), 6.09 (m, H-4), 5.77 (d, J = 3.0 Hz, H-16), 4.72 (s, H-20α), 3.80 (s, OCH_3), 2.58 (d, J = 12.4 Hz, H-12β), 1.46 (s, 19-CH_3), 0.94 (s, 18-CH_3); CI-MS m/z 370 (M^+, 100), 352 ($M^+ - H_2O$, 22), 310 ($M^+ - COOCH_3 - H$, 10). Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.23; H, 7.30.

Methyl 3,11,20-Trioxo-1,4,16-pregnatrien-21-oate (14) from 13a. Treatment of methyl 20α-hydroxy-3,11-dioxo-1,4,16-pregnatrien-21-oate (49.5 mg) in pyridine (4 mL) with chromic anhydride (50 mg) overnight at room temperature afforded prisms from methanol (23 mg, mp 219–221 °C; 5 mg, mp 215–218 °C) in a yield of 56.9%. Recrystallization from ethyl acetate–isooctane furnished the analytical sample: mp 217–219 °C; $[\alpha]_D$ +202°; λ_{max} 242 nm, ϵ 24 300; IR 1740 (carbomethoxyl), 1705 (11-one), 1665, 1620, 1601 (1,4-dien-3-one), 1581 cm^{-1} (16-ene); ^1H NMR (500 MHz) δ 7.76 (d, J = 10.2 Hz, H-1), 7.26 (m, H-16), 6.22 (dd, J = 10.2, 2.0 Hz, H-2), 6.10 (m, H-4), 3.88 (s, OCH_3), 3.15 (d, J = 12.8 Hz, H-12β), 1.46 (s, 19-CH_3), 0.96 (s, 18-CH_3); CI-MS m/z 368 (M^+, 100), 308 ($M^+ - CHCOOCH_3$, 20), 88 ($HCOCOOCH_3$, 4). Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.52; H, 6.57. Found: C, 71.57; H, 6.59.

From 13b. Oxidation at C-20 of methyl 20β-hydroxy-3,11-dioxo-1,4,16-pregnatrien-21-oate (7.1 mg) with pyridine–chromic anhydride as in the preparation of **14** from **13a** gave 4.5 mg (63.7%) of prismatic needles from ethyl acetate–isooctane, mp 219–222 °C. The infrared spectrum was identical with that of **14** obtained from **13a**, and a mixed melting point showed no depression.

11β,20-Dihydroxy-3-oxo-4,*cis*-17(20)-pregnadien-21-al (3a-*cis*): small prisms from acetone (18.1% yield); mp 157–160 °C; $[\alpha]_D$ +186°; λ_{max_1}, 287 nm, ϵ 13 800, λ_{max_2}, 243 nm, ϵ 17 400; IR 3430 (hydroxyl), 1660, 1640 cm^{-1} (conjugated carbonyls); ^1H NMR (300 MHz) δ 9.57 (s, CHO)), 5.69 (s, H-4), 4.45 (m, H-11α),

1.47 (s, 19-CH_3), 1.26 (s, 18-CH_3); CI-MS m/z 345 ($M^+ + 1$, 100), 327 ($M^+ + 1 - H_2O$, 27), 273 ($M^+ + 1$ - HOCCOH - CH_2, 11). Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 72.82; H, 8.04.

20-Acetoxy-11β-hydroxy-3-oxo-4,*cis*-17(20)-pregnadien-21-al (7a-*cis*): platelets from methanol; mp 227–229 °C; $[\alpha]_D$ +151°; λ_{max} 247 nm, ϵ 28 900; IR 3500 (hydroxyl), 1755, 1205 (enol acetate), 1690–1610 cm^{-1} (multiple peaks, conjugated carbonyls); ^1H NMR (500 MHz) δ 9.58 (s, CHO), 5.70 (s, H-4), 4.43 (m, H-11α), 2.28 (s, $OCOCH_3$), 1.46 (s, 19-CH_3), 1.24 (s, 18-CH_3); CI-MS m/z 386 (M^+, 100), 368 ($M^+ - H_2O$, 8), 328 ($M^+ + 1 - CH_3COO$, 18) 308 ($M^+ - H_2O - CH_3COO$, 10), 284 ($M^+ + 1 - CH_3CO_2CCO$, 12). Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.47; H, 7.82. Found: C, 71.24; H, 8.06.

11β,20-Dihydroxy-3-oxo-4,*trans*-17(20)-pregnadien-21-al (3a-*trans*): needles from acetone (7.8% yield); mp 178–188 °C; $[\alpha]_D$ +163°; λ_{max_1} 282 nm, ϵ 13 100, λ_{max_2} 244 nm, ϵ 16 400; IR 3440 (hydroxyl), 1660, 1640 cm^{-1} (conjugated carbonyls); ^1H NMR (300 MHz) δ 9.74 (s, CHO), 5.71 (s, H-4), 4.46 (m, H-11α), 1.47 (s, 19-CH_3), 1.34 (s, 18-CH_3); CI-MS m/z 345 ($M^+ + 1$, 100), 327 ($M^+ + 1 - H_2O$, 27), 273 ($M^+ + 1$ - HOCCOH - CH_2,17). Anal. Calcd for $C_{21}H_{28}O_4 \cdot 2H_2O$: C, 66.29; H, 8.48. Found: C, 66.63; H, 7.76.

20-Acetoxy-11β-hydroxy-3-oxo-4,*trans*-17(20)-pregnadien-21-al (7a-*trans*): needles from methanol; mp 209–210 °C; $[\alpha]_D$ +115°; λ_{max} 245 nm, ϵ 31 000; IR 3490 (hydroxyl), 1752, 1195 (enol acetate), 1680–1610 cm^{-1} (multiple peaks, conjugated carbonyls); ^1H NMR (500 MHz) δ 9.72 (s, CHO), 5.70 (s, H-4), 4.48 (m, H-11α), 2.22 (s, $OCOCH_3$), 1.47 (s, 19-CH_3), 1.39 (s, 18-CH_3); CI-MS m/z 387 ($M^+ + 1$, 100), 368 ($M^+ - H_2O$, 8), 328 ($M^+ + 1 - H_2O - CH_3COO$, 42), 308 ($M^+ - H_2O - CH_3COO$, 8), 284 ($M^+ + 1 - CH_3CO_2CCO$, 10). Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.47; H, 7.82. Found: C, 71.19; H, 8.00.

20-Hydroxy-3,11-dioxo-4,*cis*-17(20)-pregnadien-21-al (3b-*cis*): needles from acetone–isooctane (21.0% yield); mp 203–204 °C; $[\alpha]_D$ +194 °C; λ_{max_1} 282 nm, ϵ 12 800, λ_{max_2} 237 nm, ϵ 16 100; IR 3440 (hydroxyl), 1700 (11-ketone), 1665, 1640 cm^{-1} (conjugated carbonyls); ^1H NMR (300 MHz) δ 9.59 (s, CHO), 5.75 (s, H-4), 3.25 (d, J = 13.2 Hz, H-12β), 1.43 (s, 19-CH_3), 0.98 (s, 18-CH_3); CI-MS m/z 343 ($M^+ + 1$, 100), 331 ($M^+ + 1 + H_2O$ - HCHO, 31), 301 ($M^+ + 1 + H_2O$ - HCOCOH - 2H, 69). Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.56; H, 7.77.

20-Acetoxy-3,11-dioxo-4,*cis*-17(20)-pregnadien-21-al (7b-*cis*): needles from methanol; mp 225–227 °C; $[\alpha]_D$ +173°; λ_{max} 244 nm, ϵ 29 000; IR 1760, 1205 (enol acetate), 1705 (11-ketone), 1665, 1620 cm^{-1} (conjugated carbonyls); ^1H NMR (500 MHz) δ 9.58 (s, CHO), 5.75 (s, H-4), 2.79 (d, J = 12.8 Hz, H-12β), 2.26 (s, $OCOCH_3$), 1.42 (s, 19-CH_3), 0.96 (s, 18-CH_3); CI-MS m/z 385 ($M^+ + 1$, 100), 343 ($M^+ + 1 + H_2O - CH_3COOH$, 20), 325 ($M^+ + 1 - CH_3COOH$, 20), 299 ($M^+ + 1 + H_2O - CH_3CO_2CCHO$, 34). Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.60; H, 7.69.

20-Hydroxy-3,11-dioxo-4,*trans*-17(20)-pregnadien-21-al (3b-*trans*): prismatic needles from methylene chloride–isooctane (6.7% yield); mp 159–162 °C; $[\alpha]_D$ +175°; λ_{max_1} 278 nm, ϵ 11 400; λ_{max_2} 238 nm, ϵ 16 200; IR 3440 (hydroxyl), 1700 (11-ketone), 1670–1620 cm^{-1} (multiple peaks, conjugated carbonyls); NMR spectra were unsuccessful because compound decomposed in deuteriochloroform; CI-MS m/z 343 ($M^+ + 1$, 88), 331 ($M^+ + 1 + H_2O$ - HCHO, 100), 301 ($M^+ + 1 + H_2O$ - HCOCOH - 2H, 22). Anal. Calcd for $C_{21}H_{26}O_4 \cdot 1.25H_2O$: C, 69.11; H, 7.87. Found: C, 69.08; H, 7.77.

20-Acetoxy-3,11-dioxo-4,*trans*-17(20)-pregnadien-21-al (7b-*trans*): multifaceted prisms from methanol; mp 208–211 °C; $[\alpha]_D$ +135°; λ_{max} 244 nm, ϵ 26 400; IR 1755 and 1200 (enol acetate), 1705 (11-ketone), 1670, 1620 cm^{-1} (conjugated carbonyls); ^1H NMR (500 MHz) δ 9.69 (s, CHO), 5.75 (s, H-4), 2.98 (d, J = 12.5 Hz, H-12β), 2.23 (s, $OCOCH_3$), 1.43 (s, 19-CH_3), 1.14 (s, 18-CH_3); CI-MS m/z 385 ($M^+ + 1$, 100), 343 ($M^+ + 1 + H_2O - CH_3COOH$, 52), 325 ($M^+ + 1 - CH_3COOH$, 28), 299 ($M^+ + 1 + H_2O - CH_2CO_2C(OH)_2$, 23). Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.85; H, 7.57.

20-Hydroxy-3-oxo-4,*cis*-17(20)-pregnadien-21-al (3c-*cis*): needles from acetonitrile (16.6% yield); mp 180–185 °C; $[\alpha]_D$ +184°; λ_{max_1} 287 nm, ϵ 12 300, λ_{max_2} 242 nm, ϵ 15 200; IR 3410 (sharp, hydroxyl), 1660, 1640, 1610 cm^{-1} (conjugated carbonyls); ^1H NMR (300 MHz) δ 9.58 (s, CHO), 5.75 (s, H-4), 1.22 (s, 19-CH_3), 1.02 (s, 18-CH_3); CI-MS m/z 529 ($M^+ + 1$, 100), 317 ($M^+ + 1 + H_2O - CH_2O$, 18), 287 ($M^+ + 1 + H_2O - CH_2C(OH)_2$, 18). Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.90; H, 8.74.

20-Acetoxy-3-oxo-4,*cis*-17(20)-pregnadien-21-al (7c-*cis*): fine needles from acetone–isooctane; mp 171–173 °C; $[\alpha]_D$ +149°; λ_{max} 246 nm, ϵ 28 300; IR 1760 and 1200 (enol acetate), 1675 and 1615 cm^{-1} (conjugated carbonyls); ^1H NMR (500 MHz) δ 9.72 (s, CHO), 5.82 (s, H-4), 2.26 (s, $OCOCH_3$), 1.22 (s, 19-CH_3), 1.02 (s, 18-CH_3); CI-MS m/z 371 ($M^+ + 1$, 100), 328 ($M^+ + 1 - CH_3CO$, 15), 311 ($M^+ + 1 - CH_2C(OH)_2$, 12), 269 ($M^+ + 1 - CH_3CO - CH_2OHCO$, 8). Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H. 8.16. Found: C, 74.68; H, 8.42.

20-Hydroxy-3-oxo-4,*trans*-17(20)-pregnadien-21-al (3c-*trans*): needles from aqueous acetonitrile (6.0% yield); mp 108–110 °C; $[\alpha]_D$ +141°; λ_{max_1} 280 nm, ϵ 10 400, λ_{max_2} 242 nm, ϵ 15 700; IR 3440 (hydroxyl), 1665, 1635 cm^{-1} (conjugated carbonyls); ^1H NMR (300 MHz) δ 9.76 (s, CHO), 5.76 (s, H-4), 1.22 (s, 19-CH_3), 1.12 (s, 18-CH_3); CI-MS m/z 329 ($M^+ + 1$, 62), 317 ($M^+ + 1 + H_2O - CH_2O$, 100) 287 ($M^+ + 1 + H_2O - CH_2C(OH)_2$, 50). Anal. Calcd for $C_{21}H_{28}O_3 \cdot H_2O$: C, 72.80; H, 8.72. Found: C, 72.15; H, 8.69.

20-Acetoxy-3-oxo-4,*trans*-17(20)-pregnadien-21-al (7c-*trans*): needles from acetone–isooctane; mp 188.5–190.5 °C; $[\alpha]_D$ +92.0°; λ_{max} 244 nm, ϵ 29 800; IR 1758 and 1195 (enol acetate), 1670–1610 cm^{-1} (multiple peaks, conjugated carbonyls); ^1H NMR (500 MHz) δ 9.94 (s, CHO), 5.82 (s, H-4), 2.25 (s, $OCOCH_3$), 1.23 (s, 19-CH_3), 1.19 (s, 18-CH_3); CI-MS m/z 371 ($M^+ + 1$, 100), 328 ($M^+ + 1 - CH_3CO$, 13), 311 ($M^+ + 1 - CH_3COOH$, 9), 269 ($M^+ + 1 - CH_3CO - CH_2OHCO$, 7). Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.56; H, 8.32.

11β,20-Dihydroxy-3-oxo-1,4,*cis*-17(20)-pregnatrien-21-al (3d-*cis*): needles from methylene chloride–acetonitrile (43.4% yield); mp 194–196 °C; $[\alpha]_D$ +178°; λ_{max_1} 286 nm, ϵ 16 200, ω_{max_2} 245 nm, ϵ 18 200; IR 3450 (hydroxyl), 1660, 1620, 1600 cm^{-1} (conjugated carbonyls; ^1H NMR (500 MHz) δ 9.56 (s, CHO), 7.32 (d, J = 10.1 Hz, H-1), 6.31 (dd, J = 10.1, 1.7 Hz, H-2), 6.06 (m H-4), 4.45 (m, H-11α), 1.49 (s, 19-CH_3), 1.28 (s, 18-CH_3); CI-MS m/z 343 ($M^+ + 1$, 72), 325 ($M^+ + 1 - H_2O$, 100), 307 ($M^+ + 1 - 2H_2O$, 12), 279 ($M^+ + 1 - 2H_2O$ - CO, 5). Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.66; H, 7.49.

11β,20-Dihydroxy-3-oxo-1,4-*trans*-17(20)-pregnatrien-21-al (3d-*trans*): prisms from methylene chloride–acetonitrile (4.6% yield); mp 193–196 °C; $[\alpha]_D$ +161°; λ_{max_1} 282 nm, ϵ 12 400, λ_{max_2} 245 nm, ϵ 17 200; IR 3440 (hydroxyl), 1660, 1640 cm^{-1} (conjugated carbonyls); ^1H NMR (500 MHz) δ 9.72 (s, CHO), 7.27 (d, J = 10.0 Hz, H-1), 6.31 (m, H-2), 6.06 (m, H-4), 4.49 (m, H-11α), 1.49 (s, 19-CH_3), 1.34 (s, 18-CH_3); CI-MS m/z 343 ($M^+ + 1$, 75), 325 ($M^+ + 1 - H_2O$, 100), 307 ($M^+ + 1 - 2H_2O$, 15), 279 ($M^+ + 1 - 2H_2O$ - CO, 5). Anal. Calcd for $C_{21}H_{26}O_4 \cdot 0.75H_2O$: C, 70.86; H, 7.79. Found: C, 70.91; H, 7.64.

20-Hydroxy-3,11-dioxo-1,4,*cis*-17(20)-pregnatrien-21-al (3e-*cis*): needles from methylene chloride–isooctane (42.2% yield); mp 224–227 °C; $[\alpha]_D$ +229°; λ_{max_1} 285 nm, ϵ 14 700, λ_{max_2} 242 nm, ϵ 15 700; IR 3400 (hydroxyl), 1705 (11-ketone), 1665, 1620, 1605 cm^{-1} (conjugated carbonyls); ^1H NMR (500 MHz) δ 9.59 (s, CHO) 7.75 (d, J = 10.2 Hz, H-1), 6.23 (dd, J = 10.2, 1.5 Hz, H-2), 6.11 (m, H-4), 3.27 (d, J = 13.1 Hz, H-12β), 1.47 (s, 19-CH_3), 1.01 (s, 18-CH_3); CI-MS m/z 341 ($M^+ + 1$, 100), 323 ($M^+ + 1 - H_2O$, 22), 311 ($M^+ + 1 - CH_2O$, 18). Anal. Calcd for $C_{21}H_{24}O_4 \cdot 0.5H_2O$: C, 72.18; H, 7.21. Found: C, 72.56; H, 7.44.

20-Acetoxy-3,11-dioxo-1,4,*cis*-17(20)-pregnatrien-21-al (7e-*cis*): hairy needles from ethyl acetate–isooctane; mp 217–219 °C; $[\alpha]_D$ +195°; λ_{max} 244 nm, ϵ 29 600; IR 1765 and 1205 (enol acetate), 1708 (11-ketone), 1690–1610 cm^{-1} (multiple peaks, conjugated carbonyls); ^1H NMR (500 MHz) δ 9.69 (s, CHO), 7.75 (d, J = 10.5 Hz, H-1), 6.30 (dd, J = 10.5, 2.0 Hz, H-2), 6.18 (m, H-4) 2.85 (d, J = 12.8 Hz, H-12β), 2.29 (s, $OCOCH_3$), 1.47 (s, 19-CH_3), 0.99 (s, 18-CH_3); CI-MS m/z 383 ($M^+ + 1$, 100), 341 ($M^+ + 1 - CH_3COH$, 11). Anal. Calcd for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85. Found: C, 72.33; H. 7.16.

20-Hydroxy-3,11-dioxo-1,4,*trans*-17(20)-pregnatrien-21-al (3e-*trans*): small prisms from methylene chloride (5.1% yield; mp 213.5–214.5 °C; $[\alpha]_D$ +185°; λ_{max_1} 280 nm, ϵ 9500, λ_{max_2} 242 nm, ϵ 15 200; IR 3430 (hydroxyl), 1705 (11-ketone), 1660–1610 cm^{-1} (multiple peaks, conjugated carbonyls). NMR spectra were unsuccessful because compound decomposed in deuteriochloroform.

Anal. Calcd for $C_{21}H_{24}O_4 \cdot 2H_2O$: C, 67.00; H, 7.49. Found: C, 67.33; H, 6.78.

20-Acetoxy-3,11-dioxo-1,4-*trans*-17(20)-pregnatrien-21-al (7e-*trans*): small prisms from ethanol; mp 207-210 °C; $[\alpha]_D$ +147°; λ_{max} 244 nm; ϵ 30 500; IR 1768 and 1200 (enol acetate), 1710 (11-ketone), 1690-1610 cm^{-1} (multiple peaks, conjugated carbonyls); CI-MS m/z 383 ($M^+ + 1$, 100), 341 ($M^+ + 1 - CH_3COH$, 13). NMR spectra were unsuccessful because compound decomposed in deuteriochloroform. Anal. Calcd for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85. Found: C, 72.02; H, 7.11.

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Registry No. **1a**, 50-23-7; **1b**, 53-06-5; **1c**, 152-58-9; **1d**, 50-24-8; **1e**, 53-03-2; *cis*-**3a**, 105562-13-8; *trans*-**3a**, 105562-12-7; *cis*-**3b**, 118916-30-6; *trans*-**3b**, 118864-84-9; *cis*-**3c**, 118864-85-0; *trans*-**3c**, 118864-86-1; *cis*-**3d**, 118864-87-2; *trans*-**3b**, 118864-88-3; *cis*-**3e**, 118724-35-9; *trans*-**3e**, 118724-36-0; *cis*-**7a**, 118864-89-4; *trans*-**7a**, 118864-90-7; *cis*-**7b**, 118864-91-8; *trans*-**7b**, 118864-92-9; *cis*-**7c**, 118864-93-0; *trans*-**7c**, 118864-94-1; *cis*-**7d**, 118866-09-4; *trans*-**7d**, 118864-95-2; *cis*-**7e**, 118724-37-1; *trans*-**7e**, 118724-38-2; *cis*-**8**, 118724-39-3; *trans*-**8**, 118724-40-6; **9a**, 95811-04-4; **9b**, 95909-27-6; **10a**, 118724-41-7; **10b**, 118724-42-8; **11a**, 98039-97-5; **11b**, 98040-02-9; **12a**, 118724-43-9; **12b**, 118724-44-0; **13a**, 118724-45-1; **13b**, 118724-46-2; **14**, 118724-47-3; methyl 11β,17,20α-trihydroxy-3-oxo-1,4-pregnadien-21-oate, 97232-42-3; methyl 11β,17,20β-trihydroxy-3-oxo-1,4-pregnadien-21-oate, 97274-84-5.

A General Method for the Synthesis of Glycerophospholipids and Their Analogues via H-Phosphonate Intermediates†

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A general chemical method for the synthesis of glycerophospholipids and their analogues via H-phosphonate intermediates has been developed. It was found that 1,2-dipalmitoylglycero-3-H-phosphonate, prepared by the reaction of 1,2-dipalmitoylglycerol with PCl_3/imidazole, reacts with various hydroxylic components (choline tosylate, *N*-(*tert*-butoxycarbonyl)ethanolamine, *N*-(*tert*-butoxycarbonyl)-L-serine) in the presence of condensing agents to produce in high yield the corresponding glycero-3-H-phosphonate diesters. These can be converted into natural phospholipids via oxidation with iodine or into thio or seleno analogues by using sulfur or selenium as oxidant, respectively.

The vital role played by phospholipids in many biological processes has in the last decade stimulated a numbers of studies concerning their chemistry, biochemistry, and physical properties.[1,2] Interactions of phospholipids with biopolymers such as peptides,[3] DNA,[4] and polysaccharides of cell structures[5,6] have been extensively investigated. Phospholipid analogues were found to be a valuable tool in studies concerning elucidation of the mechanism of some enzymatic reactions,[7] in probing biomembranes structures,[8] and in the preparation of liposomes with the desired properties.[9] Also therapeutical applications of phospholipids have been investigated that use these molecules as drug carriers[10] or as drugs per se.[9,11] Such studies caused high demand for phospholipids and their analogues of unequivocal structure and have resulted in an extensive expansion in the field of chemical synthesis of phospholipids.[12,13]

The most important stage in the chemical synthesis of phospholipids is phosphorylation, which leads to formation of a phosphodiester bond, the major structural element of these compounds. Due to considerable achievements during the past years, the synthetic chemistry of phospholipids has now at its disposal a variety of phosphorylation methods which make use of phosphodiester,[12-14] phosphotriester,[13,15] and phosphite[16] chemistries. Some other methods have also been developed.[16,17]

The most straightforward one, the phosphodiester method for phospholipids synthesis, consisting of condensation of glycerol phosphate with a suitable hydroxylic component, is inefficient in terms of both yield and la-

† The H is being used to emphasize that the phosphonic acid is unsubstituted.

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