A Stereoselective Total Synthesis of 11-Oxoprogesterone, a Precursor to the Corticosteroids, *via* an Intramolecular Cycloaddition Reaction†

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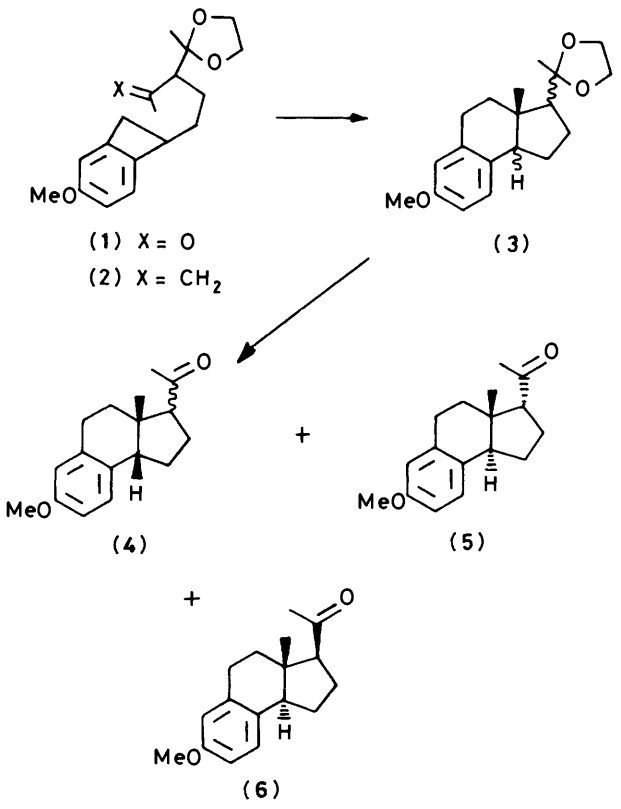
A stereoselective synthesis of 11-oxoprogesterone (pregn-4-ene-3,11,20-trione) (**21**) has been achieved *via* 19-norpregna-4,9(10)-diene-3,20-dione (**14**) and pregna-4,9(10)-diene-3,20-dione (**18**). The compound (**14**) was derived from the des-A,B-aromatic steroid (**6**), which was, in turn, constructed in a stereoselective manner *via* (**3**) by the thermolysis of the olefinic benzocyclobutene (**2**).

Corticosteroids which have an oxygen functionality at C-11 are important regulatory hormones.[1] Because of this physiological importance, there has been much effort[2] devoted to solving the problems presented by this class of steroids, with a recent resurgence of interest in the total synthesis of 11-oxosteroids.[3] During our studies of the synthesis of steroids *via* intramolecular cycloadditions,[4] our attention has recently focussed on the stereoselective construction of des-A,B-aromatic steroids[5] because of their potential importance as intermediates in the synthesis of C-11-functionalized compounds. Here, we report an efficient synthesis of the des-A,B-aromatic steroids (**6**), and its conversion into (±)-11-oxoprogesterone (**21**)[3e,3g,6] which is a known precursor of corticoids[7] (*i.e.* cortisone,[7a] cortisone acetate,[7b] hydrocortisone acetate,[7b] and 9α-fluoro-1-dehydrohydrocortisone acetate[7c]).

Although the synthesis of the des-A,B-aromatic steroid (**6**) has been achieved previously,[5a] Wittig reaction of the monoacetal (**1**) to give the isopropenyl derivative (**2**) followed by the intramolecular cycloaddition of this to form compound (**3**) have not been achieved in satisfactory yield. Thus, the monoacetal (**1**) was subjected to Nozaki's olefination procedure[8] (Zn, $TiCl_4$, CH_2Br_2, THF, CH_2Cl_2) to give the acetal (**2**) (81% yield) which was then thermolysed in *o*-dichlorobenzene under reflux to afford the cyclized compound (**3**) (99% yield) as a stereoisomeric mixture; this was then hydrolysed (10% HCl, MeOH) to give the ketones (**4**), (**5**), and (**6**) in a ratio of 1:1:10. The structures of these products were assigned tentatively at this point by comparison with previously obtained compounds.[5a]

Since effective procedures for producing the ketone (**6**) selectively were known, its conversion into 19-norpregna-4,9(10)-diene-3,20-dione (**14**) was investigated as follows.

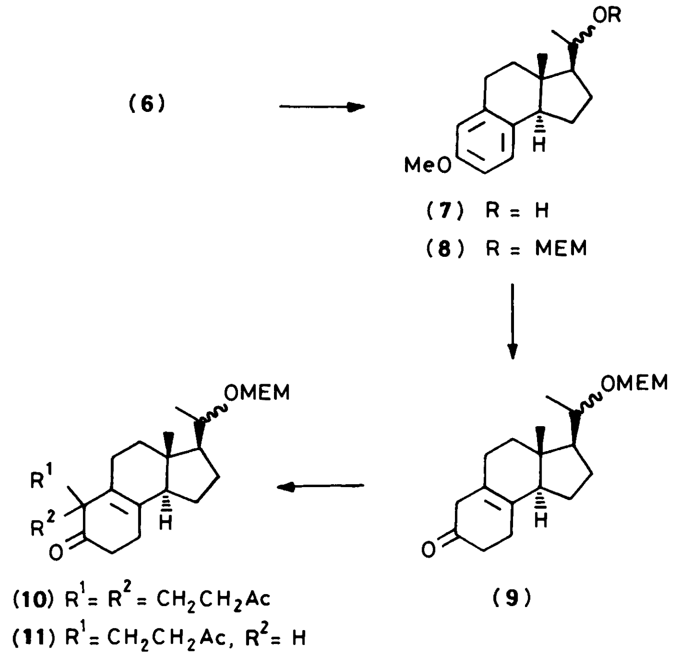
First, the hydroxy compound (**7**) obtained ($NaBH_4$, MeOH) from compound (**6**) in 99% yield was converted (MEMCl, Hünig base, CH_2Cl_2) into the ether (**8**) (99%) which was then subjected successively to Birch reduction (Li, EtOH, liq. NH_3, THF) and acid hydrolysis [$(CO_2H)_2$, EtOH, H_2O] to give the β,γ-unsaturated ketone (**9**) [*m/z* 336 (M^+)] in 82% overall yield. Next, the alkylation of (**9**) was conducted under two different sets of conditions: (i) LDA, methyl α-trimethylsilylvinyl ketone,[9] HMPA, THF; Bu_4NF, THF and (ii) [$KN(SiMe_3)_2$, Et_3B, methyl α-trimethylsilylvinyl ketone, THF; Bu_4NF, THF].[10] These afforded a mixture of compounds (**10**) [*m/z* 476 (M^+)] and (**11**) [*m/z* 406 (M^+)] in a ratio of 3:2 (50% yield) and 1:1 (63% yield), respectively. The monoalkylated compound (**11**) was then successively cyclized (4% KOH, MeOH) and hydrolysed (10% HCl, MeOH) to give, *via* (**12**) the tetracyclic compound (**13**) (38%) [*m/z* 300 (M^+)], which was finally oxidized (Jones reagent, acetone) to furnish 19-norpregna-4,9(10)-diene-3,20-dione (**14**), identified by i.r. ($CHCl_3$) and ^1H n.m.r. ($CDCl_3$; 100 MHz) spectral comparison with an authentic sample.[11] Thus, we determined unambiguously the structure of compound (**6**), the structure of which had previously been assigned only tentatively.[5a]



Scheme 1.

The transformation of (**14**) into 11-oxoprogesterone (**21**) was then investigated as follows. First, the diacetal (**15**) [*m/z* 386 (M^+)], obtained (93% yield) by acetalization [$HO(CH_2)_2OH$, CSA, benzene] of compound (**14**), was oxidized (MCPBA, satd. $NaHCO_3$, CH_2Cl_2) to give the monoepoxide (**16**) [*m/z* 402 (M^+)] (40%) and the diepoxide (**17**) [*m/z* 418 (M^+)] (37%), the

† A part of this work has been published in preliminary form. H. Nemoto, M. Nagai, K. Fukumoto, and T. Kametani, *Tetrahedron Lett.*, 1985, **26**, 4613.



Scheme 2.

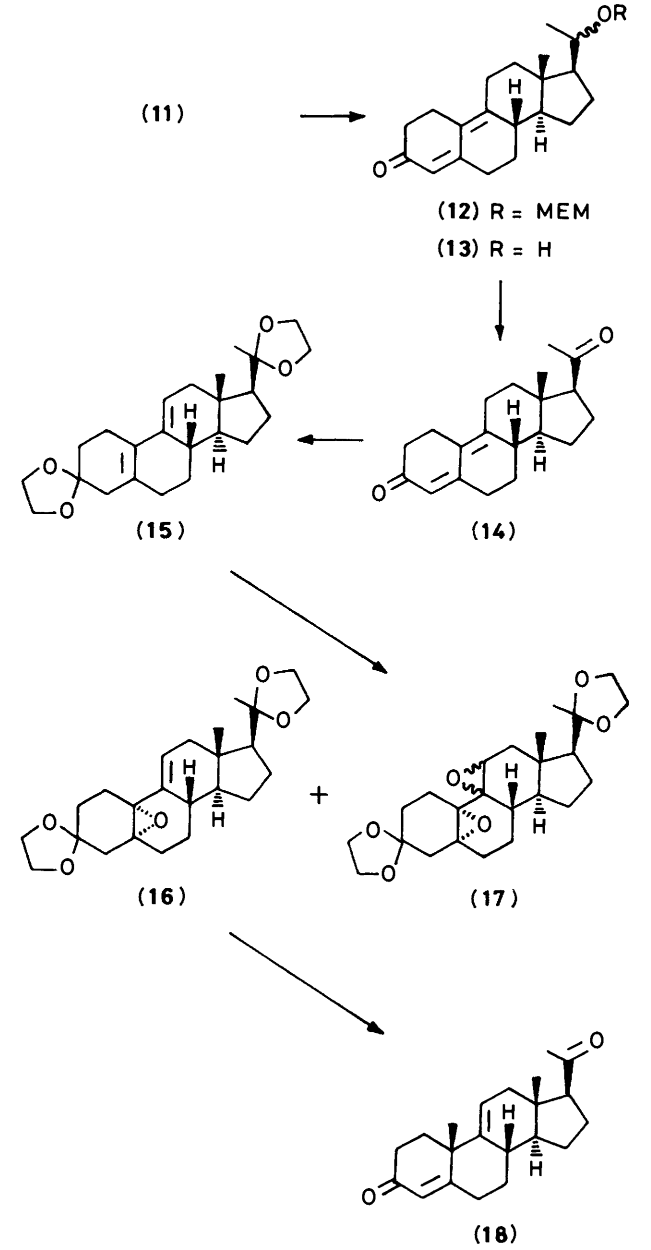
former of which was then successively treated with a Grignard reagent (MeMgBr, Et_2O) and acid (10% HCl, MeOH) to furnish pregna-4,9(10)-diene-3,20-dione (**18**)[12] (46%). Compound (**18**) was then converted (NBA, dioxane, H_2O) into the bromohydrin (**19**) (96%) [*m*/*z* 328 (M^+ − Br)]. Finally, oxidation [PDC, CH_2Cl_2] followed by reductive debromination (Zn, AcOH) of (**19**) afforded the initial target compound, (±)-11-oxoprogesterone* (**21**) (70%) [*m*/*z* 328 (M^+)] *via* the oxo bromide (**20**) [*m*/*z* 326 (M^+ − Br)].

Experimental

General Methods.—M.p.s were determined on a Yanagimoto MP-22 apparatus and are uncorrected. I.r. spectra were recorded on a Hitachi 260-10 spectrophotometer. N.m.r. spectra were obtained on JEOL PS-100 and JEOL JNM-PMX-60 spectrometers. Chemical shifts are reported as δ values relative to internal $SiMe_4$. Mass spectra were taken on a Hitachi M-52G and JEOL-TMS-01SG-2 spectrometers. All reactions were carried out under dry nitrogen. Column chromatography was carried out with silica gel (Wako gel C-200). The phrase 'residue upon work-up' refers to the residue obtained when the organic layer was separated, dried over anhydrous Na_2SO_4, and the solvent evaporated under reduced pressure. All new compounds described in this Experimental section were homogeneous on t.l.c.

3-*Isopropenyl*-5-(4-*methoxy*-1,2-*dihydrobenzocyclobuten*-1-*yl*)*pentan*-2-*one Ethylene Acetal* (**2**).—To a suspension of zinc (5.9 g, 90.2 mmol) and dibromomethane (5.6 g, 32.2 mmol) in anhydrous tetrahydrofuran (THF) (150 ml) was added titanium tetrachloride (1.0M dichloromethane solution; 24 ml, 24 mmol) at room temperature, and the mixture was stirred for 15 min at the same temperature. A solution of the monoacetal (**1**) (3.3 g, 10.9 mmol) in anhydrous THF (30 ml) was then added dropwise

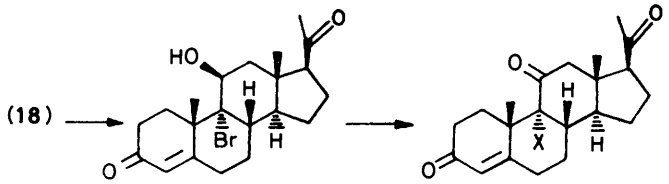
* Commercially available (**18**) and (**21**) were purified by crystallization (benzene–CH_2Cl_2 and ether, respectively) and used as authentic samples.



Scheme 3.

and the reaction mixture was stirred for 15 h. The mixture was filtered through Celite. The filtrate was diluted with water and extracted with ether, and the extract was washed with aqueous ammonium chloride and saturated aqueous sodium chloride. The residue upon work-up was chromatographed with hexane–ethyl acetate (19:1, v/v) to afford the *isopropenyl derivative* (**2**) (2.65 g, 81%) as an oil; $\delta_H(CCl_4)$ 1.16 (3 H, s, Me), 1.69 (3 H, s, C=CMe), 3.69 (3 H, s, OMe), 3.88 (4 H, s, OCH_2CH_2O), 4.74 (2 H, s, CH_2=C), and 6.48—6.99 (3 H, m, ArH) [Found: *m*/*z* 302.1860 (M^+). $C_{19}H_{26}O_3$ requires *M*, 302.1880].

Thermolysis of (**2**) *and Synthesis of* trans-3β-*Acetyl*-7-*methoxy*-3aβ-*methyl*-2,3,3a,4,5,9b-*hexahydro*-1H-*benz*[e]*indene* (**6**).—A solution of the benzocyclobutene (**2**) (3.5 g, 11.5 mmol) in *o*-dichlorobenzene (180 ml) was heated at 180 °C for 13 h. After removal of the solvent, the residue was chromatographed with hexane–ethyl acetate (19:1, v/v) to give an inseparable



(19) (20) X = Br (21) X = H

Scheme 4.

stereoisomeric mixture of (**3**) (3.45 g, 99%) as an oil, $\delta_H(CDCl_3)$ 0.63 (2.5 H, s, Me), 1.06 (0.25 H, s, Me), 1.16 (0.25 H, s, Me), 1.32 (3 H, s, Me), 3.74 (3 H, s, OMe), 3.92 (4 H, s, OCH_2CH_2O), and 6.52—7.10 (3 H, m, ArH). A solution of (**3**) (3 g, 9.9 mmol) in 10% aqueous hydrochloric acid (7 ml) and methanol (100 ml) was stirred at room temperature for 3 h. The mixture was basified with sodium hydrogen carbonate and the solvent was then evaporated. The residue was diluted with water (50 ml) and extracted with ether, and the extract was washed with saturated aqueous sodium chloride. The residue upon work-up gave a crude mixture of the ketones (**4**), (**5**), and (**6**), $\delta_H(CDCl_3)$ 0.52 (2.5 H, s, Me), 0.76 (0.25 H, s, Me), 0.95 (0.25 H, s, Me), 2.19 (3 H, s, COMe), 3.74 (3 H, s, OMe), and 6.54—7.04 (3 H, m, ArH). The mixture was chromatographed using hexane–ethyl acetate (19:1, v/v) to afford a mixture of (**4**), (**5**), and (**6**) (0.6 g, 24%) as an oil. From the later fractions, the pure compound (**6**) (1.9 g, 74%), identical with an authentic sample,[5a] was obtained as needles after recrystallization from methanol.

trans-3-(1-*Hydroxyethyl*)-7-*methoxy*-3aβ-*methyl*-2,3,3a,4,5,9a-*hexahydro*-1H-*benz*[e]*indene* (**7**).—To a stirred solution of the ketone (**6**) (2.59 g, 10.0 mmol) in methanol (250 ml) was added portionwise sodium borohydride (600 mg, 15.9 mmol) at 0 °C, and the mixture was stirred for 4 h. After removal of the solvent, the residue was diluted with water (50 ml) and extracted with ether, and the extract was washed with saturated aqueous sodium chloride. The residue upon work-up was chromatographed using hexane–ethyl acetate (9:1, v/v) to yield the *alcohol* (**7**) (2.58 g, 99%) as plates after recrystallization from methanol, m.p. 117—118 °C (Found: C, 78.25; H, 9.05. $C_{17}H_{24}O_2$ requires C, 78.4; H, 9.3%); $\nu_{max.}(CHCl_3)$ 3 450 cm^{-1} (OH); $\delta_H(CCl_4)$ 0.56 (3 H, s, Me), 1.25 (3 H, d, *J* 6 Hz, Me), 3.70 (3 H, s, OMe), and 6.48—6.92 (3 H, m, ArH); *m/z* 260 (M^+).

trans-7-*Methoxy*-3aβ-*methyl*-3-(1-*methoxyethoxymethoxyethyl*)-2,3,3a,4,5,9a-*hexahydro*-1H-*benz*[e]*indene* (**8**).—To a stirred solution of the alcohol (**7**) (317 mg, 1.22 mmol) in dichloromethane (20 ml) was added di-isopropylethylamine (787 mg, 6.09 mmol) and methoxyethoxymethyl chloride (455 mg, 3.65 mmol) at room temperature. After being stirred for 4 h at the same temperature, the reaction mixture was diluted with water (30 ml) and extracted with dichloromethane, and the extract was washed with saturated aqueous sodium chloride. The residue upon work-up was chromatographed using hexane–ethyl acetate (9:1, v/v) to give the *ether* (**8**) (421 mg, 99%) as needles after recrystallization from methanol, m.p. 53—54 °C (Found: C, 72.05; H, 9.05. $C_{21}H_{32}O_4$ requires C, 72.4; H, 9.25); $\delta_H(CCl_4)$ 0.56 (3 H, s, Me), 1.15 (3 H, d, *J* 6 Hz, Me), 3.30 (3 H, s, OMe), 3.68 (3 H, s, OMe), 4.66 (2 H, d, *J* 3 Hz, OCH_2O), and 6.43—6.96 (3 H, m, ArH); *m/z* 348 (M^+).

trans-3aβ-*Methyl*-3-(1-*methoxyethoxymethoxyethyl*)-2,3,3a,4,5,6,9,9b-*octahydro*-1H-*benz*[e]*inden*-7(6H)-*one* (**9**).—A solution of the ether (**8**) (942 mg, 2.71 mmol) in anhydrous THF (25 ml) and ethanol (4 ml) was added cautiously to liquid ammonia (65 ml). To this solution was added lithium (128 mg, 18.3 mmol) at −78 °C. The mixture was stirred for 20 min at −78 °C, ethanol (10 ml) was added dropwise, and the solvent was then evaporated. The residue was diluted with water (30 ml), the mixture was extracted with ether, and the extract was washed with saturated aqueous sodium chloride and evaporated to give the residue which was then dissolved in ethanol (29 ml) and water (3 ml). This solution was treated with oxalic acid (328 mg, 3.64 mmol) for 3 h at room temperature. The mixture was neutralized with 10% aqueous sodium hydroxide and the solvent was then evaporated. The residue was diluted with water (30 ml) and extracted with ether, and the extract was washed with saturated aqueous sodium chloride. The residue upon work-up was chromatographed using hexane–ethyl acetate (4:1, v/v) to afford the β,γ-*unsaturated enone* (**9**) (838 mg, 92%) as an oil; $\nu_{max.}(CHCl_3)$ 1 718 cm^{-1} (C=O); $\delta_H(CCl_4)$ 0.70 (3 H, s, Me), 1.13 (3 H, d, *J* 6 Hz, Me), 3.29 (3 H, s, OMe), 3.40—3.73 (4 H, m, OCH_2CH_2O), and 4.63 (2 H, d, *J* 3 Hz, OCH_2O) [Found: *m/z* 336.2302 (M^+). $C_{20}H_{32}O_4$ requires *M*, 336.2300].

Alkylation of Compound (**9**).—*Method A.* To a solution of lithium di-isopropylamide [0.59 mmol, prepared from di-isopropylamine (62.9 mg, 0.62 mmol) and butyl-lithium (1.27M hexane solution; 0.46 ml, 0.59 mmol)] in anhydrous THF (8 ml) was added a solution of the β,γ-unsaturated ketone (**9**) (190 mg, 0.56 mmol) in anhydrous THF (1 ml) at −78 °C. After the mixture had been stirred for 40 min at the same temperature, hexamethylphosphoramide (101 mg, 0.56 mmol) and methyl α-trimethylsilylvinyl ketone (104 mg, 0.73 mmol) in anhydrous THF (2 ml) was added to it at −78 °C and the whole stirred for a further 1 h at the same temperature. After being quenched with saturated aqueous ammonium chloride (5 ml), the mixture was extracted with ether and the extract washed with saturated aqueous sodium chloride, and evaporated to give the residue which was dissolved in THF (8 ml). This solution was treated with tetrabutylammonium fluoride (1.0M THF solution; 1.7 ml, 1.7 mmol) for 1 h at room temperature. The mixture was diluted with water (20 ml) and extracted with ethyl acetate, and the extract was washed with saturated aqueous sodium chloride. The residue upon work-up was chromatographed using benzene–ethyl acetate (5:1, v/v) to give the monoalkylated compound (**11**) (45 mg, 20%) as a pale yellow oil; $\nu_{max.}(CHCl_3)$ 1 710 cm^{-1} (C=O); $\delta_H(CCl_4)$ 0.66 (3 H, s, Me), 1.20 (3 H, d, *J* 6 Hz, Me), 2.08 (3 H, s, COMe), 3.30 (3 H, s, OMe), 3.35—3.70 (4 H, m, OCH_2CH_2O), and 4.63 (2 H, d, *J* 3 Hz, OCH_2O); *m/z* 406 (M^+). From the later fractions the dialkylated compound (**10**) (67 mg, 30%) was obtained as a pale yellow oil; $\nu_{max.}(CHCl_3)$ 1 710 cm^{-1} (C=O); $\delta_H(CCl_4)$ 0.65 (3 H, s, Me), 1.18 (3 H, d, *J* 6 Hz, Me), 2.05 (6 H, br s, COMe), 3.30 (3 H, s, OMe), 3.36—3.72 (4 H, m, OCH_2CH_2O), and 4.64 (2 H, d, *J* 3 Hz, OCH_2O); *m/z* 476 (M^+).

Method B. To a stirred suspension of potassium hydride (17 mg, 0.42 mmol) in anhydrous THF (2.5 ml) was added bis-(trimethylsilyl)amine (74 mg, 0.46 mmol) at room temperature. After the evolution of hydrogen was complete (30 min), the reaction mixture was cooled to −78 °C, and the β,γ-unsaturated ketone (**9**) (129 mg, 0.38 mmol) in anhydrous THF (1.5 ml) was added dropwise, followed by addition of triethylborane (1.0M THF solution; 0.54 ml. 0.54 mmol). The resultant mixture was warmed to room temperature, after which it was added to a stirred solution of methyl α-trimethylsilylvinyl ketone (71 mg, 0.49 mmol) in anhydrous THF (3 ml). The reaction mixture was stirred for 1 h at the same temperature after which it was quenched with saturated aqueous ammonium chloride (5 ml) and extracted with ether; the extract was washed with saturated aqueous sodium chloride and evaporated to leave a residue which was dissolved in THF (3.5 ml). This solution was treated

with tetrabutylammonium fluoride (1.0M THF solution; 1.4 ml, 1.4 mmol) for 14 h at room temperature. The mixture was diluted with water (20 ml) and extracted with ethyl acetate, and the extract was washed with saturated aqueous sodium chloride. The residue upon work-up was chromatographed using benzene–ethyl acetate (5:1, v/v) to afford the monoalkylated compound (**11**) (43 mg, 33%) as a pale yellow oil. From the later fractions the dialkylated compound (**10**) (39 mg, 30%) was obtained as a pale yellow oil.

20-*Hydroxy*-19-*norpregna*-4,9(10)-*dien*-3-*one* (**13**).—To a stirred suspension of potassium hydride (62 mg, 1.55 mmol) in anhydrous THF (8 ml) was added bis(trimethylsilyl)amine (275 mg, 1.71 mmol) at room temperature. After the evolution of hydrogen was complete (30 min), the reaction mixture was cooled to −78 °C, and the β,γ-unsaturated ketone (**9**) (480 mg, 1.43 mmol) in anhydrous THF (5 ml) was added dropwise, followed by addition of triethylborane (1.0M THF solution; 1.85 ml, 1.85 mmol). The resultant mixture was warmed to room temperature, after which it was added to a stirred solution of methyl α-trimethylsilylvinyl ketone (243 mg, 1.71 mmol) in anhydrous THF (9 ml). The reaction mixture was stirred for 1 h at the same temperature and was then quenched with saturated aqueous ammonium chloride (15 ml). The mixture was extracted with ether and the extract washed with saturated aqueous sodium chloride and evaporated to give a residue which was dissolved in methanol (10 ml). To this solution was added 4% aqueous potassium hydroxide (0.9 ml). The reaction mixture was refluxed for 4 h, after which it was evaporated and water (20 ml) added to the residue; this was then extracted with ethyl acetate, and the extract was washed with saturated aqueous ammonium chloride and saturated aqueous sodium chloride. The extract was evaporated to give a residue which was dissolved in methanol (7 ml) and to this solution was added 10% aqueous hydrochloric acid (1 ml). The reaction mixture was refluxed for 7 h before being basified with sodium hydrogen carbonate and then evaporated. The residue was diluted with water (20 ml) and extracted with ethyl acetate, and the extract was washed with saturated aqueous sodium chloride. The residue upon work-up was chromatographed using benzene–ethyl acetate (5:1, v/v) to yield the *alcohol* (**13**) [162 mg, 38% from (**9**)] as an oil; $\nu_{max.}(CHCl_3)$ 1 650 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 0.90 (3 H, s, Me), 1.15 (3 H, d, *J* 6 Hz, Me), 3.75 (1 H, br s, C*H*OH), and 5.83 (1 H, br s, C*H*CO) [Found: *m/z* 300.2075 (M^+). $C_{20}H_{28}O_2$ requires *M*, 300.2088].

19-*Norpregna*-4,9(10)-*diene*-3,20-*dione* (**14**).—To a stirred solution of the alcohol (**13**) (92 mg, 0.31 mmol) in acetone (10 ml) was added Jones reagent (7 drops) at 0 °C and the mixture was stirred for 5 min. After removal of the solvent, water (10 ml) was added to the residue which was then extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride and the residue upon work-up was chromatographed using hexane–ethyl acetate (5:1, v/v) to afford the title compound (**14**) (63 mg, 69%) as needles after recrystallization from di-isopropyl ether, m.p. 104—105 °C; $\nu_{max.}(CHCl_3)$ 1 650 and 1 700 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 0.78 (3 H, s, Me), 2.13 (3 H, s, MeCO), and 5.66 (1 H, br s, CHCO); *m/z* 298 (M^+); the spectral data of this compound were superposable upon those of the authentic sample provided by Mr. V. Torelli.

19-*Norpregna*-5(10),9(11)-*diene*-3,20-*dione Ethylene Acetal* (**15**).—To a solution of compound (**14**) (378 mg, 1.26 mmol) in benzene (10 ml) was added D-camphor-10-sulphonic acid (catalytic amount) and ethylene glycol (314 mg, 5.06 mmol). The reaction mixture was refluxed in a flask fitted with a Dean-Stark trap for 6 h. The reaction mixture was diluted with benzene (50 ml), and the benzene solution was washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride. The residue upon work-up was chromatographed using hexane–ethyl acetate (9:1, v/v) to give the *diacetal* (**15**) (453 mg, 93%) as plates after recrystallization from methanol, m.p. 94—95.5 °C; $\delta_H(CDCl_3)$ 0.72 (3 H, s, Me), 1.26 (3 H, s, Me), 3.85 (8 H, s, 2 × OCH_2CH_2O), and 5.42 (1 H, br s, olef. H) [Found: *m/z* 386.2470 (M^+). $C_{24}H_{34}O_4$ requires *M*, 386.2458].

9(10)-*Pregna*-4,9(10)-*diene*-3,20-*dione* (**18**).—To a stirred solution of the diacetal (**15**) (396 mg, 1.03 mmol) in dichloromethane (9 ml) and aqueous sodium hydrogen carbonate (0.5M; 3 ml) was added *m*-chloroperbenzoic acid (202 mg, 0.82 mmol) at 0 °C. After being stirred for 10 min at the same temperature, the mixture was diluted with water (5 ml) and extracted with dichloromethane.

The extract was washed with 10% aqueous sodium hydroxide and saturated aqueous sodium chloride and the residue upon work-up was chromatographed using hexane–ethyl acetate (9:1, v/v) to afford the monoepoxide (**16**) (166 mg, 40%) as a pale yellow oil; $\delta_H(CDCl_3)$ 0.74 (3 H, s, Me), 1.29 (3 H, s, Me), 3.88 (8 H, br s, 2 × OCH_2CH_2O), and 5.94 (1 H, br s, olef. H); *m/z* 406 (M^+). The later fractions gave the diepoxide (**17**) (155 mg, 37%) as a pale yellow oil; $\delta_H(CDCl_3)$ 0.75 (1.5 H, s, Me), 0.80 (1.5 H, s, Me), 1.25 (1.5 H, s, Me), 1.30 (1.5 H, s, Me), and 3.86 (8 H, br s, 2 × OCH_2CH_2O); *m/z* 418 (M^+).

To a stirred solution of the monoepoxide (**16**) (117 mg, 0.29 mmol) in anhydrous ether (10 ml) was added methylmagnesium bromide (1.0M ether solution; 2.6 ml, 2.6 mmol) at 0 °C and the reaction mixture was stirred for 5 min at the same temperature. After being quenched with saturated aqueous ammonium chloride (5 ml), the mixture was extracted with ether and the extract was washed with saturated aqueous sodium chloride. The extract was evaporated to give the residue which was dissolved in methanol (20 ml) and 10% aqueous hydrochloric acid (1 ml). This solution was refluxed for 1 h. The mixture was basified with sodium hydrogen carbonate and the solvent was then evaporated. The residue was diluted with water (10 ml) and extracted with ether, and the extract was washed with saturated aqueous sodium chloride. The residue upon work-up was chromatographed using hexane–ethyl acetate (5:1, v/v) to give the title compound (**18**) (42 mg, 46%) as prisms after recrystallization from benzene–dichloromethane, m.p. 183—185 °C; $\nu_{max.}(CHCl_3)$ 1 665 and 1 700 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 0.61 (3 H, s, Me), 1.33 (3 H, s, Me), 2.12 (3 H, s, MeCO), 5.50 (1 H, br s, olef. H), and 5.73 (1 H, br s, olef. H); *m/z* 312 (M^+), the spectral data for which were identical with those of the authentic sample.[12]

9α-*Bromo*-11β-*hydroxypregn*-4-*ene*-3,20-*dione* (**19**).—To a solution of compound (**18**) (46 mg, 0.17 mmol) in dioxane (3 ml) and water (0.5 ml) was added *N*-bromoacetamide (52 mg, 0.38 mmol) and 71% perchloric acid (1 drop) at room temperature. After being stirred for 1 h at the same temperature, the mixture was diluted with water (5 ml), extracted with chloroform, and the extract was washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride. The residue upon work-up was chromatographed using dichloromethane–chloroform (3:2, v/v) to yield the *bromohydrin* (**19**) (57 mg, 96%) as needles after recrystallization from ethanol, m.p. 166—168 °C (Found: C, 60.7; H, 7.3; Br, 19.45. $C_{21}H_{29}O_3Br$·0.25 H_2O requires C, 60.95; H, 7.2; Br, 19.3%); $\nu_{max.}(CHCl_3)$ 1 660, 1 700 (C=O), and 3 400 cm^{-1} (OH); $\delta_H(CDCl_3)$ 0.91 (3 H, s, Me), 1.74 (3 H, s, Me), 2.12 (3 H, s, COMe), 4.60 (1 H, br s, HOC*H*), and 5.72 (1 H, br s, olef. H); *m/z* 329 (M^+ − Br).

9α-*Bromopregn*-4-*ene*-3,11,20-*trione* (**20**).—To a stirred solution of pyridinium dichromate (93 mg, 0.25 mmol) in

anhydrous dichloromethane (3 ml) was added a solution of the bromohydrin (**19**) (51 mg, 0.13 mmol) in anhydrous dichloromethane (2 ml) at room temperature, and the mixture was stirred for 5 h. The mixture was diluted with ether (30 ml) and filtered through Celite. The filtrate was washed with water. The residue upon work-up was chromatographed using dichloromethane–chloroform (7:3, v/v) to give the *oxo bromide* (**20**) (39 mg, 76%) as needles after recrystallization from ethanol, m.p. 167—168 °C (Found: C, 61.45; H, 6.6; Br, 19.45. $C_{21}H_{27}BrO_3$ requires C, 61.9; H, 6.7; Br, 19.6%); $\nu_{max.}(CHCl_3)$ 1 665 and 1 705 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 0.64 (3 H, s, Me), 1.56 (3 H, s, Me), 2.11 (3 H, s, COMe), and 5.80 (1 H, br s, olef. H); *m/z* 327 (M^+ − Br).

Pregn-4-ene-3,11,20-trione (**21**).—To a suspension of zinc (47 mg, 0.72 mmol) in acetic acid (0.2 ml) was added a solution of the oxo bromide (**20**) (9.9 mg, 0.24 mol) in acetic acid (0.1 ml) at room temperature, and the mixture was stirred for 30 min at the same temperature. The mixture was diluted with chloroform (20 ml) and filtered through Celite. The filtrate was washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride. The residue upon work-up was chromatographed using dichloromethane–chloroform (1:1, v/v) to afford 11-oxoprogesterone (**21**) (7.4 mg, 93%) as needles after recrystallization from ether, m.p. 174—175 °C; $\nu_{max.}(CDCl_3)$ 1 665 and 1 705 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 0.64 (3 H, s, Me), 1.40 (3 H, s, Me), 2.10 (3 H, s, COMe), 5.70 (1 H, br s, olef. H); *m/z* 328 (M^+), the spectral data for which were superposable upon those of the authentic sample.[12]

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