[Chem. Pharm. Bull. 21(10)2195—2201(1973)]

UDC 547.92.057

Total Synthesis of 13β-Allylgonanes. I. Synthesis of *dl*-17α-Ethynyl-17β-hydroxy-13β-allylgon-4-en-3-one[1,2]

Kouichi Yoshioka, Tsunehiko Asako, Giichi Goto, Kentaro Hiraga, and Takuichi Miki

Chemical Research Laboratories, Central Research Division, Takeda Chemical Industries, Ltd.[3]

(Received February 7, 1973)

dl-17α-Ethynyl-17β-hydroxy-13β-allylgon-4-en-3-one (XXIV) was synthesized *via* 17β,2′-epoxy pentaene (X). The double bonds at C-14 and -8 of X was hydrogenated sequentially by conventional methods. 17β,2′-Epoxy triene (XIII) was treated with *p*-toluenesulfonic acid in acetic anhydride to give 13β-allylgonane (XIV) as a major product. Birch reduction of the tetrahydropyranyl ether (XIX) followed by acid treatment yielded the 4-en-3-one compound (XXI), which was oxidized with chromium trioxide-pyridine complex to the 17-ketone (XXII). The enol ether (XXIII) was treated with lithium acetylide in ethylenediamine, and then with acid to yield XXIV. The progestational activity of XXIV is as potent as norgestrel.

Many attempts have been made to prepare steroids having novel skeletons not occurring in nature.[4] In particular, ethyl[5] and *n*-propyl[5,6] gonanes substituted at the C-13 angular position are known to have potent biological activities.[7] This prompted us to synthesize 13-allylgonanes because the allyl group plays an important role in medicinal chemistry.

In this paper we report the preparation of *dl*-17α-ethynyl-17β-hydroxy-13β-allylgon-4-en-3-one (XXIV) by a sequence of reactions shown in Charts 1 and 2. The starting material, 4-allyl-2,3,5-trioxo-cyclopentyl glyoxylic acid (I) was prepared by treatment of allylacetone with diethyl oxalate in the presence of sodium ethoxide in ethanol[8] in 25% yield. Treatment of I with hydrochloric acid gave 3-allylcyclopentane-1,2,4-trione (II) in 70% yield, which was reduced with sodium borohydride in alkaline solution to give 2-allyl-4-hydroxycyclopentane-1,3-dione (III) as a colorless oil in good yield. Acetylation of III with acetic anhydride and pyridine yielded the crystalline acetate (IV).

Condensation of IV with the isothiuronium salt (V)[9] in methanol gave 3-methoxy-13-allyl-8,14-secogona-1,3,5(10),9,15-pentaene-14,17-dione (VI) in 50% yield, calculated on the basis of IV. An alternative procedure involving condensation of III with V in methanol followed by alkaline dehydration, gave VI in 45% yield. The structure VI was determined by spectral data: ν_{max} cm^{-1} 1710 (C=O), λ_{max} nm (ε) 267 (17800), δ 7.2 (2H, singlet, C_{15}–H and C_{16}–H).

1) This work was presented at the 90th Annual Meeting of Pharmaceutical Society of Japan, Sapporo, July, 1970.
2) Preliminary communication of this work appeared in K. Yoshioka, G. Goto, T. Asako, K. Hiraga, and T. Miki, *Chem. Commun.*, **1971**, 336.
3) Location: *Juso-Nishino-cho, Higashiyodogawa-ku, Osaka.*
4) *a*) H.O. Huisman, *Angew. Chem. Intern. Ed. Engl.*, **10**, 450 (1971); *b*) P. Morand and J. Lyall, *Chem. Rev.*, **68**, 85 (1968); *c*) A.A. Akhrem and Yu. A. Titov, "Total Synthesis of Steroids," Isreal Prsgram for Scientific Translation, Jerusalem, 1969. p. 1.
5) H. Smith, G.A. Hughes, G.H. Douglas, G.R. Wendt, G.C. Buzby, R.A. Edren, 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.*, **1964**, 4472.
6) L. Velluz, G. Nominé, R. Bucourt, A. Pierdet, and Ph. Dufay, *Tetrahedron Letters*, **1961**, 127.
7) R.A. Edgren, H. Smith, D.L. Peterson, and D.L. Carter, *Steroids*, **2**, 319 (1963).
8) J.J. Panouse and C. Sannié, *Bull. Soc. Chim. France*, **1955**, 1036.
9) C.H. Kuo, D. Taub, and N.L. Wendler, *Angew. Chem.*, **77**, 1142 (1965).

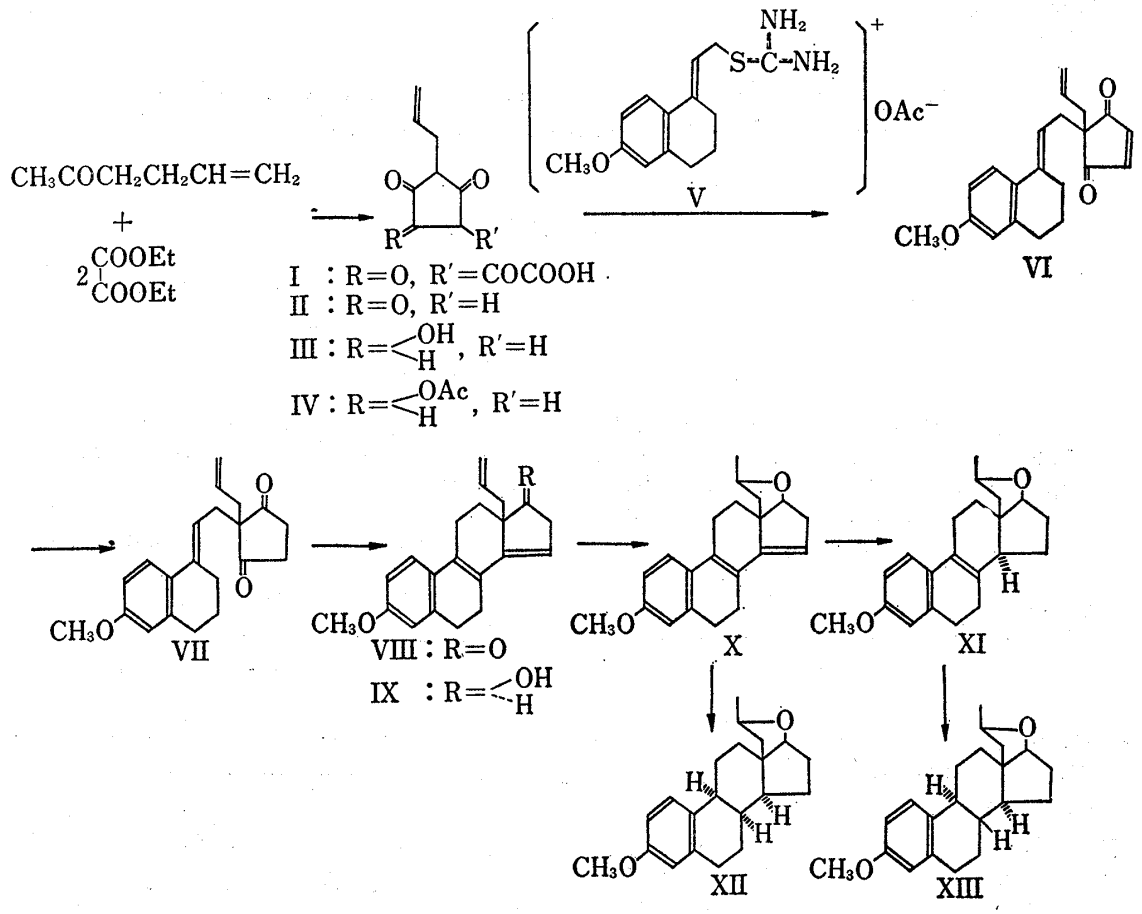

Chart 1

Reduction of the double bond at C-15 of VI with zinc dust and acetic acid at room temperature yielded the secogonadione (VII) in 67% yield. This structure was confirmed by nuclear magnetic resonance (NMR) spectrum; two methylenic protons at C-15 and C-16 gave a singlet at δ 2.54.

Treatment of VII with hydrochloric acid in methanol gave *dl*-3-methoxy-13β-allylgona-1,3,5(10),8,14-pentaen-17-one (VIII) in quantitative yield, λ_{max} nm (ε) 314 (30900). Reduction of VIII with sodium borohydride in tetrahydrofuran and methanol at 0° yielded the 17β-hydroxy compound (IX) as a colorless oil in high yield, ν_{max} cm^{-1} 3350—3500. The configuration of the hydroxy group at C-17 was confirmed by NMR spectrum exhibiting a triplet for the 17α proton at δ 4.09 (J=8 Hz),[10] and also by the ready formation of an epoxide (X) on treatment of IX with hydrochloric acid in methanol. The structure X was supported by the absence of hydroxy and terminal double bond absorptions in the infrared (IR) spectrum and by the secondary methyl signal which appeared at δ 1.19 (doublet, J=6.0 Hz) in the NMR spectrum.

This epoxide (X) proved to be a key intermediate leading to the objective compound. Since the C-13 allyl group in X was protected from reduction, the double bonds at C-14 and C-8 of X were hydrogenated sequentially by conventional methods. Partial hydrogenation of X in the presence of Raney nickel in dioxane yeilded the gonatetraene (XI) (70%), λ_{max} nm (ε) 278 (12200), which was reduced with potassium in liq. ammonia and tetrahydrofuran to give the gonatriene (XIII) in 92% yield, λ_{max} nm (ε) 278 (1890), 286 (1780). Complete catalytic hydrogenation of X in the presence of Raney nickel gave the 8-iso-gonatriene (XII).

10) N.S. Bhacca and D.H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day Inc., San Francisco, 1964, p. 78.

We tried to cleave the ether ring of XIII and regenerate the allyl group. The ether ring was successfully cleaved by treatment of XIII with a large amount of *p*-toluenesulfonic acid in acetic anhydride at 80° for 1.5 hours, which resulted in the desired product, *dl*-17β-acetoxy-3-methoxy-13β-allylgona-1,3,5(10)-triene (XIV) in 26% yield. Presence of the allyl group in XIV was confirmed by NMR spectrum; the terminal olefinic protons gave a multiplet at δ 4.70—5.15 and the other olefinic proton at C-2′ gave a multiplet at δ 5.70—6.30.

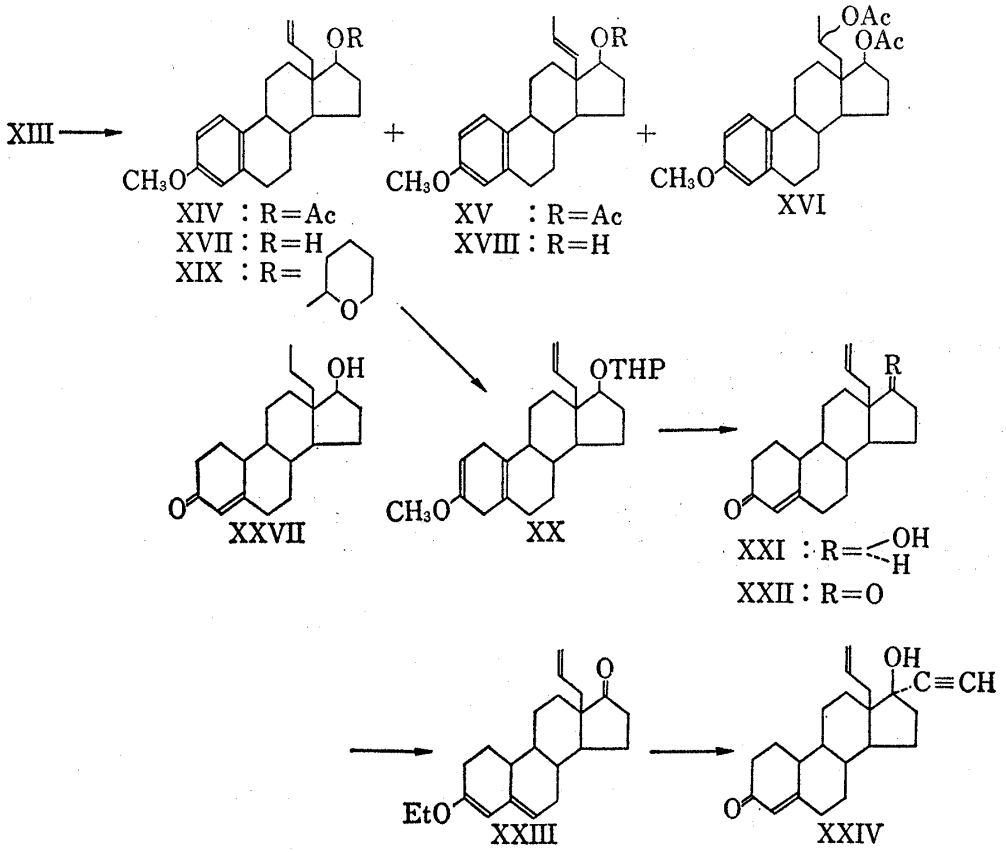

Chart 2

In this reaction two other products were obtained; 13β-propenylgonatriene (XV) (15%) and the 13β-(2′-acetoxy)propyl compound (XVI) (16%). The ratio of the products varied slightly according to the reaction conditions. The double bond isomers XIV and XV were successfully separated by column chromatography over silica gel containing 5% silver nitrate, or by first changing the mixture to the 17β-hydroxy compounds (XVII and XVIII) by hydrolysis with alkaline methanol, then using conventional chromatography over silica gel.

Birch reduction of XIV or XVII with lithium in liq. ammonia, ethanol and tetrahydrofuran, followed by acid treatment yielded 13β-propylgon-4-en-3-one (XXVII) having a saturated angular substituent. Windholz, *et al.*[11] described the phenyl group at C-13 of 17β-tetrahydropyranyl ether derivatives as not susceptible to Birch reduction. Thus, the 17β-tetrahydropyranyl ether (XIX) was subjected to Birch reduction followed by acid treatment to yield the desired 4-en-3-one compound (XXI) in 85% yield. The structure of XXI was supported by spectral data: ν_{max} cm^{-1} 3400 (OH), 3100, 1635, 910 (allyl), 1660, 1615 (C=C–C=O), λ_{max} nm (ε) 240 (16000), δ 5.81 (1H, singlet, C_4–H), 5.00—5.30 (2H, multiplet, $C=CH_2$), 5.90—6.30 (1H, multiplet, CH=C).

11) T.B. Windholz, R.D. Brown, and A.A. Patchett, *Steroids*, **6**, 409 (1965).

Oxidation of XXI with chromium trioxide–pyridine complex gave the 17-ketone (XXII) in 96% yield, ν_{max} cm^{-1} 1740. Treatment of XXII with ethyl orthoformate in dioxane in the presence of *p*-toluenesulfonic acid as a catalyst, gave the enol ether (XXIII) in high yield, ν_{max} cm^{-1} 1740, 1655, 1630. XXIII was subsequently reacted with lithium acetylide in ethylenediamine, and the following hydrolysis with acid yielded *dl*-17α-ethynyl-17β-hydroxy-13β-allylgon-4-en-3-one (XXIV) (76%). This structure was confirmed by spectral data: ν_{max} cm^{-1} 3400 (OH), 3300, 2100 (C≡C), 3100, 1620, 910 (allyl), 1670, 1630 (C=C–C=O), λ_{max} nm (ε) 240 (15900), δ 2.40 (1H, singlet, C≡CH), 4.80—5.10 (2H, multiplet, C=CH$_2$), 5.66 (1H, singlet, C$_4$–H), 5.80—6.20 (1H, multiplet, CH=C), *m/e* 324 (M$^+$), 306 (M$^+$—H$_2$O), 283 (M$^+$—allyl).

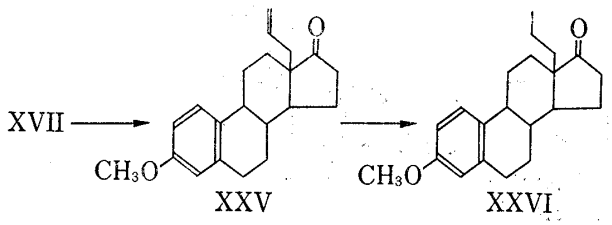

Chart 3

To examine the stereochemistry of the skeleton of 13-allylgonane, we did the following experiment. Oxidation of XVII with chromium trioxide complex gave the 17-ketone (XXV), ν_{max} cm^{-1} 1725. Catalytic hydrogenation of XXV over 5% palladium-carbon yielded *dl*-3-methoxy-13β-propylgona-1,3,5(10)-trien-17-one (XXVI), which was identical with the authentic sample[5] in all respects. Therefore, the stereochemistry of the ring juncture of the 13β-allylgonatrienes was established as *trans* anti *trans*.

The progestational activity of XXIV was estimated by McPhail test in rabbit. This compound shows stronger activity than norethisterone[12] and is as potent as norgestrel, which has been reported to have extremely strong activity.[7] The estrogenicity of XXIV is about one-five hundredth that of estrone.

Experimental[13]

2,3,5-Trioxo-4-allylcyclopentyl Glyoxylic Acid (I)——To an EtONa solution (prepared from 71 g of Na and 760 ml of abs. EtOH), a mixture of allylacetone (133 g) and diethyl oxalate (400 g) was added dropwise with stirring for 30 min nuder ice-cooling. The resulting mixture was refluxed for 45 min, cooled, then acidified with 50% H_2SO_4. The resulting Na_2SO_4 was filtered off and washed with AcOEt. The filtrate and the AcOEt solution were combined and concentrated under reduced pressure to give crude crystals. Recrystallization from acetone–benzene gave pale yellow scales. Yield 75 g (25%), mp 165—167°. *Anal.* Calcd. for $C_{10}H_8O_6$: C, 53.58; H, 3.30. Found: C, 53.85; H, 3.46. IR ν_{max}^{KBr} cm^{-1}: 3700, 3400 (OH), 1740, 1640 (C=O). NMR (d_6-DMSO) δ: 2.96 (2H, doublet, J=6 Hz, CH$_2$), 4.8—5.1 (2H, multiplet, -CH$_2$=C), 5.5—5.8 (1H, multiplet, -C=CH-), 10.1—10.6 (3H, multiplet, OH). UV $\lambda_{max}^{H_2O}$ nm (ε): 256 (13500), 327 (10600).

3-Allylcyclopentane-1,2,4-trione (II)——A solution of I (70 g) in conc. HCl (140 ml) and H_2O (280 ml) was refluxed for 30 min. The reaction mixture was extracted with AcOEt. The AcOEt layer was washed with H_2O and dried. After evaporation of the solvent, the residue was crystallized from benzene. Yield 33 g (70%), mp 43—45°. *Anal.* Calcd. for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 63.12; H, 5.08. IR ν_{max}^{Nujol} cm^{-1}: 3000—3400, 2500—2700 (OH), 1750, 1650—1700 (C=O). NMR ($CDCl_3$) δ: 2.93 (2H, singlet, C$_5$-H), 3.15 (2H, doublet, J=6 Hz, -CH$_2$), 4.9—5.2 (2H, multiplet, CH$_2$=C), 5.65—6.10 (1H, multiplet, C=CH), 6.4—7.2 (1H, broad singlet, OH). UV λ_{max}^{EtOH} mn (ε): 276 (12000).

2-Allyl-4-hydroxycyclopentane-1,3-dione (III)——The pH of a solution of II (30 g) in H_2O (100 ml) was adjusted to 10 with 10% NaOH soln. Next, $NaBH_4$ (40 g) in H_2O (300 ml) was added and the resulting mixture was refluxed for 2 hr. After adjusting the pH of the mixture to 3 with dilute H_2SO_4, the H_2O was concentrated under reduced pressure and the precipitated Na_2SO_4 was filtered off then washed with acetone. The filtrate and acetone solution were combined and concentrated to give a pale brown oil (28 g). IR ν_{max}^{liq} cm^{-1}: 2900—3500 (OH), 1710 (C=O).

12) G. Pincus, M.C. Chang, E.S.E. Hafez, M.X. Zarrow, and A. Merrill, *Science*, **124**, 890 (1956).

13) All melting points are uncorrected. Ultraviolet (UV) spectra were taken with a Hitachi EPS-3T recording spectrophotometer and NMR spectra with a Varian HA-100 high resolution spectrometer operated at 100 Mc with tetramethylsilane as an internal standard. Infrared (IR) spectra were taken with a Hitachi EPI-S2 spectrophotometer and mass spectra were taken with a Hitachi RMU-6D.

4-Acetoxy-2-allylcyclopentane-1,3-dione (IV)——A solution of III (2.6 g) in Ac_2O (50 ml) and pyridine (50 ml) was allowed to stand overnight at room temperature. The reaction mixture was poured into ice-water and extracted with AcOEt. The AcOEt layer was successively washed with dilute HCl and H_2O then dried. Evaporation of AcOEt gave crude crystals (1.5 g). Recrystallization from ether gave colorless crystals, mp 124—126.5°. *Anal.* Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 60.95; H, 6.26. IR ν_{max}^{KBr} cm^{-1}: 2500—2700 (OH), 1760 (C=O). NMR ($CDCl_3$) δ: 2.15 (3H, singlet, OAc), 2.45 (1H, quartet, $J_{AB}=18$ Hz, $J_{AX}=2.5$ Hz, C_5-H), 2.96 (1H, quartet, $J_{AB}=18$ Hz, $J_{BX}=6.5$ Hz, C_5-H), 2.94 (2H, doublet, $J=6$ Hz, CH_2-C=), 4.8—5.3 (2H, multiplet, CH_2=C), 5.6—6.3 (1H, multiplet, -C=CH), 5.63 (1H, quartet, $J_{AX}=2.5$ Hz, $J_{BX}=6.5$ Hz, C_4-H). UV λ_{max}^{EtOH} nm (ε): 250 (14300).

3-Methoxy-13-allyl-8,14-secogona-1,3,5(10),9,15-pentaene-14,17-dione (VI)——Preparation from III: A mixture of III (45 g) and isothiuronium salt[9] (65 g) in MeOH (1000 ml) was refluxed for 1 hr. The reaction mixture was poured into H_2O and extracted with ether. The ether layer was shaken with 5% aqueous NaOH solution and allowed to stand for 20 min. The ether layer was washed with H_2O, dried and concentrated to yield VI (40 g, 44.7%, calculated based on III). Recrystallization from ether–*n*-hexane gave slightly yellow crystals, mp 81—83°. *Anal.* Calcd. for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.07; H, 6.75. IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O). NMR ($CDCl_3$) δ: 3.73 (3H, singlet, OCH_3), 4.9—5.1 (2H, multiplet, CH_2=C), 5.3—5.7 (2H,multiplet, C=CH and C_{11}-H), 6.5—6.7 (2H, multiplet, arom. H), 7.2 (2H, singlet, C_{15} and C_{16}-H), 7.2—7.3 (1H, doublet, arom.H). UV λ_{max}^{EtOH} nm (ε): 267 (17800).

Preparation from IV: A solution of IV (1.5 g) in MeOH (50 ml) was refluxed with the isothiuronium salt (2.4 g) for 1 hr. The mixture was poured into H_2O and extracted with ether. The organic layer was successively washed with aqueous $NaHCO_3$ solution and H_2O, then dried and evaporated to give crystals. Yield 1.1 g (47%).

3-Methoxy-13-allyl-8,14-secogona-1,3,5(10),9-tetraene-14,17-dione (VII)——VI (18 g) in AcOH (900 ml) was stirred vigorously at room temperature with Zn powder (150 g) for 30 min. The solution was filtered, poured into H_2O (2 liters), and extracted with ether. The extract was successively washed with aqueous $NaHCO_3$ solution and H_2O, then dried and evaporated to give a pale yellow oil (16 g). Chromatography of this oil over silica gel with benzene–ether (10: 1) gave 12 g (66.5%) of VII as crystals. Recrystallization from ether–*n*-hexane gave colorless columns, mp 68—69°. *Anal.* Calcd. for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.99; H, 7.48. IR ν_{max}^{KBr} cm^{-1}: 1730 (C=O). NMR ($CDCl_3$) δ: 2.54 (4H, singlet, C_{15} and C_{16}-H), 3.72 (3H, singlet, OCH_3), 4.9—5.1 (2H, multiplet, CH_2=C), 5.3—5.8 (2H, multiplet, C=CH, C_{11}-H), 6.5—7.4 (3H, multiplet, arom.H). UV λ_{max}^{EtOH} nm (ε): 267 (22100).

***dl*-3-Methoxy-13β-allylgona-1,3,5(10),8,14-pentaen-17-one (VIII)**——To a solution of VII (5.7 g) in MeOH (100 ml), conc. HCl (2 ml) was added. The mixture was heated under reflux for 10 min, poured into H_2O and extracted with ether. The ether layer was successively washed with aqueous $NaHCO_3$ solution and H_2O. Evaporation of the dried extract gave VIII (5.4 g), mp 73—76°. *Anal.* Calcd. for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24. Found: C, 82.35; H, 7.29. IR ν_{max}^{KBr} cm^{-1}: 1750 (C=O). NMR ($CDCl_3$) δ: 3.79 (3H, singlet, OCH_3), 4.83—5.30 (2H, multiplet, CH_2=C), 5.4—5.8 (1H, multiplet, C=CH), 5.89 (1H, multiplet, C_{15}-H), 6.6—7.3 (3H, multiplet, arom.H). UV λ_{max}^{EtOH} nm (ε): 314 (30900).

***dl*-17β-Hydroxy-3-methoxy-13β-allylgona-1,3,5(10),8,14-pentaene (IX)**——To a solution of VIII (5.4 g) in MeOH (300 ml) and tetrahydrofuran (150 ml), $NaBH_4$ was added at 0° with stirring and the reaction was monitored by thin-layer chromatography (TLC). When the spot of VIII on TLC disappeared, H_2O was added to the reaction mixture. The resulting mixture was extracted with ether. The ether layer was washed with H_2O, dried and concentrated to yield 4.9 g (91%) of IX as an oil. IR ν_{max}^{liq} cm^{-1}: 3350—3500 (OH). NMR ($CDCl_3$) δ: 3.76 (3H, singlet, OCH_3), 4.09 (1H, triplet, $J=8$ Hz, 17α-H), 4.9—5.2 (2H, multiplet, CH_2=C), 5.52 (1H, multiplet, C_{15}-H), 5.8—6.3 (1H, multiplet, C=CH), 6.6—7.3 (3H, multiplet, arom.H). UV λ_{max}^{EtOH} nm: 312 (25800).

***dl*-17β,2′-Epoxy-3-methoxy-13β-propylgona-1,3,5(10),8,14-pentaene (X)**——A solution of IX (5.4 g) in MeOH (100 ml) was refluxed with conc. HCl (15 ml) for 6 hr. The mixture was poured into H_2O and extracted with ether. The ether layer was successively washed with aqueous $NaHCO_3$ solution and H_2O, then dried and evaporated to give 2.9 g of X (53.5%), mp 129—132° (from MeOH). *Anal.* Calcd. for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.62; H, 7.79. IR ν_{max}^{KBr} cm^{-1}: no OH. NMR ($CDCl_3$) δ: 1.19 (3H, doublet, $J=6$ Hz, $CHC\underline{H}_3$), 3.72 (1H, singlet, OCH_3), 3.85—4.15 (1H, multiplet, CH-O), 4.21 (1H, quartet, $J_1=8$ Hz, $J_2=4$ Hz, 17α-H), 5.30 (1H, multiplet, C_{15}-H), 6.5—7.1 (3H, multiplet, arom.H). UV λ_{max}^{EtOH} nm (ε): 310 (30300).

***dl*-17β,2′-Epoxy-3-methoxy-13β-propylgona-1,3,5(10),8-tetraene (XI)**——A suspension of X (5.0 g) and Raney Ni (2.5 g, wet) in dioxane (300 ml) was shaken under a stream of hydrogen. After absorption of *ca.* 370 ml of hydrogen, the catalyst was filtered off and the filtrate concentrated to yield crystals. Yield 3.5 g (70%). Recrystallization from *n*-hexane gave colorless columns, mp 117—123°. *Anal.* Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.18; H, 8.23. UV λ_{max}^{EtOH} nm (ε): 228 (30500), 278 (12200).

***dl*-17β,2′-Epoxy-3-methoxy-13β-propyl-8-isogona-1,3,5(10)-triene (XII)**——A suspension of X (1.0 g) and Raney Ni (0.5 g, wet) in dioxane (50 ml) was shaken under a stream of hydrogen until absorption of hydrogen stopped. The catalyst was filtered off and the filtrate was evaporated to give crystals (0.95 g). Recrystallization from *n*-hexane gave columns, mp 123—125°. *Anal.* Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.59; H, 8.90. UV λ_{max}^{EtOH} nm (ε): 278 (2640), 286 (2420).

***dl*-17β,2′-Epoxy-3-methoxy-13β-propylgona-1,3,5(10)-triene (XIII)**——To a solution of XI (1.4 g) in tetrahydrofuran (300 ml) and liq. NH_3 (300 ml), potassium (8 g) was added at −50°. The mixture was stirred for 1.5 hr between −40 and −50°. After addition of NH_4Cl (1 g), NH_3 was allowed to evaporate. The residue was extracted with ether. The ether layer was washed with H_2O, dried and evaporated to give crystals. Yield 1.3 g (92%). Recrystallization from EtOH gave columns, mp 125—128°. *Anal.* Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H. 9.03. Found: C, 80.72; H, 8.95. UV λ_{max}^{EtOH} nm (ε): 278 (1890), 286 (1780).

***dl*-17β-Acetoxy-3-methoxy-13β-allylgona-1,3,5(10)-triene (XIV), *dl*-17β-Acetoxy-3-methoxy-13β-propenylgona-1,3,5(10)-triene (XV), *dl*-17β,2′-Diacetoxy-3-methoxy-13β-propylgona-1,3,5(10)-triene (XVI)**——XIII (1.2 g) was treated with *p*-TsOH (0.7 g) and Ac_2O (60 ml) at 80° for 1.5 hr. The reaction mixture was poured into ice-water and extracted with ether. The ether layer was successively washed with aqueous $NaHCO_3$ solution and H_2O, then dried. The solvent was evaporated under reduced pressure to give a pale yellow oil (1.1 g), which was chromatographed on silica gel (containing 5% $AgNO_3$) using benzene–ether (10:1) as eluent, to give 0.2 g of XIV (15%), 0.35 g of XIII (26%) and 0.25 g of XV (16%).

XIII: mp 113—117°. *Anal.* Calcd. for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.82; H, 8.24. NMR ($CDCl_3$) δ: 2.04 (3H, singlet, $COCH_3$), 4.75 (1H, triplet, J=8 Hz, 17α-H), 4.70—5.15 (2H, multiplet, CH_2=C), 5.7—6.3 (1H, multiplet, C=CH), 6.55—7.20 (3H, multiplet, arom.H).

XIV: mp 138.5—140°. NMR ($CDCl_3$) δ: 1.71 (3H, doublet, J=6 Hz, $CHCH_3$), 2.02 (3H, singlet, $COCH_3$), 4.77 (1H, triplet, J=7 Hz, 17α-H), 5.28 (1H, doublet, J=18 Hz, C<u>H</u>=CHCH$_3$), 5.38—5.80 (1H, multiplet, C=C<u>H</u>-CH$_3$), 6.55—7.20 (3H, multiplet, arom.H).

XV: mp 185—186°. *Anal.* Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.55; H, 8.21. NMR ($CDCl_3$) δ: 1.23 (3H, doublet, J=6 Hz, $CHCH_3$), 1.96, 2.08 (6H, singlet, $COCH_3$), 4.76 (1H, triplet, 17α-H), 6.4—7.1 (3H, multiplet, arom.H).

***dl*-17β-Hydroxy-3-methoxy-13β-allylgona-1,3,5(10)-triene (XVII), *dl*-17β-Hydroxy-3-methoxy-13β-propenylgona-1,3,5(10)-triene (XVIII)**——A mixture of XIV and XV (1.9 g) was treated with 0.1% KOH–MeOH (50 ml) at 60° for 30 min. The reaction mixture was poured into H_2O and extracted with ether. The organic layer was washed with H_2O, dried and evaporated to give a colorless oil (1.75 g), which was chromatographed on silica gel (30 g). The $CHCl_3$ eluate gave 430 mg of XVIII (18%) and then 631 mg of XVII (26%).

XVII: Colorless needles (from MeOH), mp 140—142°. *Anal.* Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.37; H, 8.99. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 3150, 1635, 910 (allyl). NMR ($CDCl_3$) δ: 3.68 (3H, singlet, OCH_3), 4.8—5.2 (2H, multiplet, C=CH_2), 6.3—7.2 (3H, multiplet, arom.H). Mass Spectrum *m/e*: 312 (M^+).

XVIII: Colorless needles (from MeOH), mp 79—80°. *Anal.* Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 79.99; H, 9.20. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 975 (C=C). NMR ($CDCl_3$) δ: 3.66 (3H, singlet, OCH_3), 5.1—5.8 (2H, multiplet, CH=CH), 6.3—7.2 (3H, multiplet, arom.H). Mass Spectrum *m/e*: 312 (M^+).

***dl*-17β-Tetrahydropyranyloxy-13β-allylgona-1,3,5(10)-triene (XIX)**——A mixture of XVII (1.54 g), dihydropyran (2.5 g) and *p*-TsOH (40 mg) in benzene (40 ml) was stirred at room temperature for 30 min. The reaction mixture was poured into water and extracted with ether. The ether layer was washed with H_2O and dried. The solvent was evaporated under reduced pressure and the residue was crystallized from ether to give colorless needles. Yield 1.7 g (87.3%), mp 97—98°. *Anal.* Calcd. for $C_{26}H_{36}O_3$: C, 78.74; H, 9.15. Found: C, 78.81; H, 9.18. IR ν_{max}^{KBr} cm^{-1}: 3100, 1635, 910 (allyl), no OH. NMR (CCl_4) δ: 3.67 (3H, singlet, OCH_3), 4.60 (1H, multiplet, pyran-C_2′-H), 4.7—5.0 (2H, multiplet, C=CH_2), 5.8—6.2 (1H, multiplet, CH=C), 6.4—7.2 (3H, multiplet, arom.H).

***dl*-17β-Hydroxy-13β-allylgon-4-en-3-one (XXI)**——To a solution of XIX (1.5 g) in EtOH (40 ml), tetrahydrofuran (140 ml) and liq. NH_3 (200 ml), Li (2.8 g) was added portionwise at −50° and stirred for 30 min. NH_3 was allowed to evaporate and the residue was extracted with ether. The ether layer was washed with H_2O, dried and evaporated to give XX as colorless crystals (1.48 g), mp 115—116°. IR ν_{max}^{KBr} cm^{-1}: 1670, 1690 (enol ether), 3100, 1635, 910 (allyl). A solution of XX in MeOH (30 ml) was treated with conc. HCl (3 ml) at room temperature for 10 min. The reaction mixture was poured into ice-water and extracted with ether. The organic layer was washed with H_2O, dried and evaporated to give a pale yellow oil (1.41 g). This oil was chromatographed on silica gel to give crystals. Recrystallization from ether gave colorless needles. Yield 970 mg (85%), mp 150—151°. *Anal.* Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.73; H, 9.46. IR ν_{max}^{KBr} cm^{-1}: 3100, 1635, 910 (allyl), 3400 (OH), 1660, 1615 (C=C–C=O). UV λ_{max}^{EtOH} nm: 240. NMR ($CDCl_3$) δ: 3.72 (1H, triplet, J=8 Hz, 17α-H), 5.0—5.3 (2H, multiplet, C=CH_2), 5.81 (1H, singlet, C_4-H), 5.9—6.3 (1H, multiplet, CH=C). Mass Spectrum *m/e*: 300 (M^+), 282 (M^+-H_2O), 259 (M^+—allyl).

***dl*-13β-Allylgon-4-ene-3,17-dione (XXII)**——To a solution of XXI (1.1 g) in pyridine (50 ml), CrO_3–pyridine complex (prepared from 200 mg of CrO_3) was added at 0°. After stnading for 12 hr, the reaction mixture was poured into ice-water and extracted with ether. The organic layer was washed with H_2O and dried. Evaporation of solvent gave colorless crystal needles. Yield 1.05 g (96%). Recrystallization from ether gave colorless needles, mp 167—168°. *Anal.* Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.54; H, 9.02. IR ν_{max}^{KBr} cm^{-1}: 1740 (C=O). NMR ($CDCl_3$) δ: 5.0—5.2 (2H, multiplet, CH_2=C), 5.4—5.8 (1H, multiplet, C=CH), 5.88 (1H, singlet, C_4-H). Mass Spectrum *m/e*: 298 (M^+), 257 (M^+—allyl).

***dl*-13*β*-Allylgona-3-ethoxy-3,5-dien-17-one (XXIII)**——A mixture of XXII (900 mg), *p*-TsOH (40 mg), dioxane (40 ml) and freshly distilled ethyl orthoformate (3 ml) was stirred at room temperature for 20 min. Then pyridine (1 ml), ether (100 ml) and H_2O (130 ml) were added to the mixture. Next, the organic layer was separated and washed with H_2O, then dried and evaporated to give a slightly yellow oil. Yield 910 mg (92.5%). IR ν_{max}^{Nujol} cm^{-1}: 1665, 1630 (enol ether), 1740 (C=O).

***dl*-17*α*-Ethynyl-17*β*-hydroxy-13*β*-allylgon-4-en-3-one (XXIV)**——To a solution of lithium acetylide (prepared from 1.3 g of Li and acetylene) in ethylenediamine (50 ml), 900 mg of XXIII in tetrahydrofuran (2 ml) was added. After being stirred at room temperature for 3 hr, the reaction mixture was poured into ice-water and extracted with ether. The extract was washed with H_2O, dried and evaporated to give a slightly yellow oil (910 mg). This oil was dissolved in MeOH (30 ml) and treated with conc. HCl (3 ml) for 10 min. The reaction mixture was extracted with ether. The ether layer was washed with H_2O, dried and evaporated to give a slightly yellow oil (905 mg). This oil was chromatographed over silica gel and gave crystals. Recrystallization from ether gave colorless needles. Yield 680 mg (76%), mp 144—145°. *Anal.* Calcd. for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70. Found: C, 81.38; H, 8.71. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 3300, 2100 (C≡CH), 3100, 1620, 910 (allyl), 1670, 1630 (C=C-C=O). UV λ_{max}^{EtOH} nm (ε): 240 (15900). NMR ($CDCl_3$) δ: 2.40 (1H, singlet, C≡CH), 4.8—5.1 (2H, multiplet, C=CH_2), 5.66 (1H, singlet, C_4-H), 5.8—6.2 (1H, multiplet, -CH=C). Mass Spectrum *m/e*: 324 (M^+), 306 (M^+-H_2O), 283 (M^+—allyl).

***dl*-17*β*-Hydroxy-13*β*-propylgon-4-en-3-one (XXVII)**——XIV (350 mg) was reduced with Li (0.23 g), EtOH (5 ml) and liq. NH_3 (75 ml) in tetrahydrofuran (30 ml) as described above for the preparation of XXI. Yield 210 mg, colorless crystals (from ether–petroleum ether), mp 154—155°. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1660, 1610 (C=C-C=O). NMR ($CDCl_3$) δ: 0.93 (3H, triplet, J=5 Hz, CH_2CH_3), 3.71 (1H, triplet, J=8 Hz, 17*α*-H), 5.81 (1H, singlet, C_4-H). UV λ_{max}^{EtOH} nm (ε): 240 (14700).

***dl*-3-Methoxy-13*β*-allylgona-1,3,5(10)-trien-17-one (XXV)**——XVII (158 mg) was oxidized with CrO_3–pyridine complex as described above for the preparation of XXII. Yield 100 mg, needles (from ether–*n*-hexane), mp 117—118°. *Anal.* Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.04; H, 8.50. IR ν_{max}^{KBr} cm^{-1}: 1725 (C=O). NMR ($CDCl_3$) δ: 3.75 (3H, singlet, OCH_3), 4.82—5.10 (2H, multiplet, CH_2=C), 5.40—5.85 (1H, multiplet, C=CH), 6.60—7.25 (3H, multiplet, arom.H).

***dl*-3-Methoxy-13*β*-propylgona-1,3,5(10)-trien-17-one (XXVI)**——XXV (55 mg) was hydrogenated over 5% Pd-C in AcOEt. Yield 53 mg, columns (from MeOH), mp 120—122°. *Anal.* Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.83; H, 8.92. IR ν_{max}^{KBr} cm^{-1}: 1730 (C=O). NMR ($CDCl_3$) δ: 3.75 (3H, singlet, OCH_3), 6.50—7.30 (3H, multiplet, arom.H). XXV was identical with the authentic sample[5] in all respects.