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SYNTHESIS OF DEHYDRO-OOGONIOL AND OOGONIOL: THE ADRENOSTERONE ROUTE

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Abstract: Dehydro-oogoniol (3β,11α,15β,29-tetrahydroxystigmasta-5,24(28)(E)-dien-7-one), a female-activating hormone of the water mold *Achlya*, has been synthesized from 4-androstene-3,11,17-trione by a series of highly stereoselective reactions. One of these involved 1,4-addition of the magnesium cyanocuprate derivative of 3-(1,3-dioxolan-2-yl)-4-methylpentyl bromide to 3β-hydroxy-15β,16β-epoxy-11-oxo-(17E)-pregna-5,17(20)-diene 3-*tert*-butyldimethylsilyl ether. The structure of an intermediate, 3β,11α,15β-triacetoxy-5-cholesten-24-one, was confirmed by X-ray crystallographic analysis. Oogoniol [(24R)-3β,11α,15β,29-tetrahydroxy-stigmast-5-en-7-one] was synthesized in a similar manner by reaction of the magnesium cyanocuprate of (S)-3-(1-methylethyl)-5-[(*tert*-butyldimethylsilyl)oxy]pentyl bromide with the above epoxy pregnadiene.

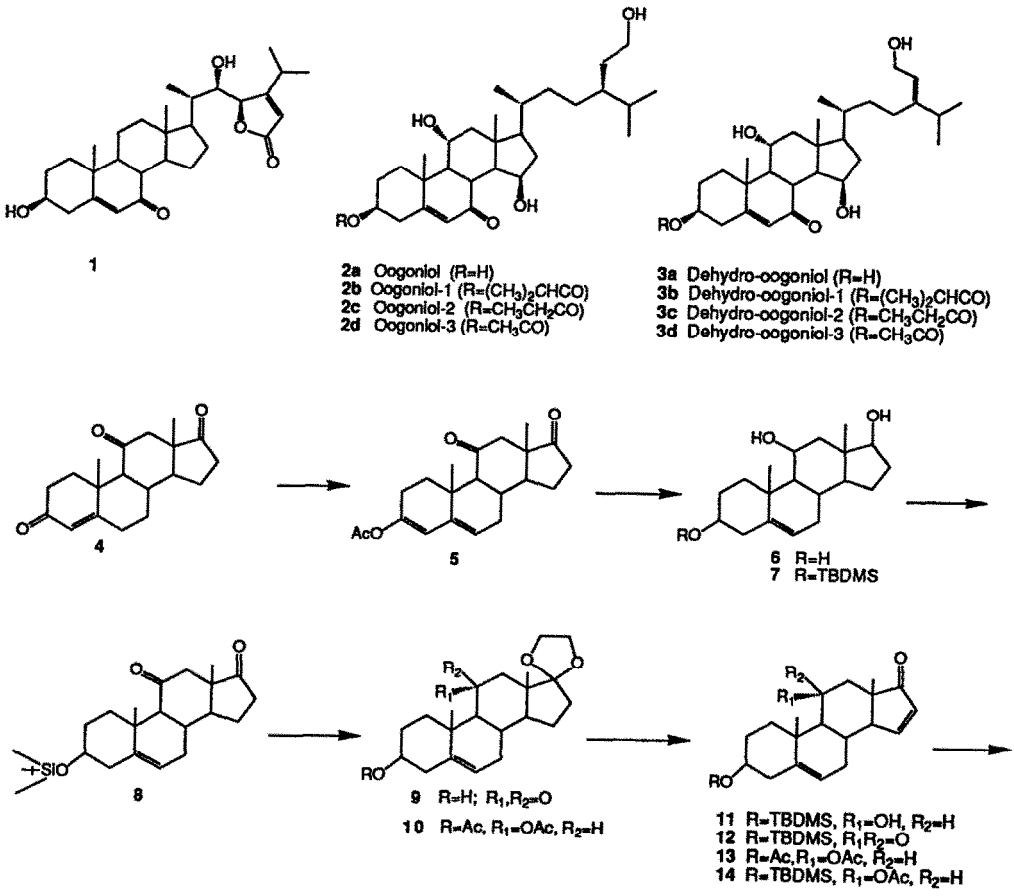
The water mold *Achlya* is a primitive eukaryote whose sexual reproduction is mediated by steroid hormones. Female strains secrete the steroid antheridiol (**1**) which induces formation of antheridia (male sex organs) in the male. Antheridiol also causes the male strains to secrete other steroids, oogoniols (**2a, 2b, 2c, 2d, 3a, 3b, 3c, 3d**) which induce formation of oogonia (female sex organs) in the female.[1]

The structure of dehydro-oogoniol, **3a**, (3β,11α,15β,29-tetrahydroxystigmasta-5,24(28)E-dien-7-one) has been confirmed by a synthesis starting from progesterone.[2] This was converted to the 11α,15β-dihydroxy derivative by fermentation with *Aspergillus giganteus*, and the sidechain was constructed by means of Wittig and Horner-Emmons reactions.

While this synthesis was important because it confirmed the structure proposed for dehydro-oogoniol, the yields were low. Therefore, we have carried out further extensive studies to develop a more practical route to the hormones. These compounds are produced only in minute amounts by the organism so that advances in our knowledge of sexual reproduction in *Achlya* will depend on the availability of the hormones through chemical synthesis.

In this paper we report details of an improved route to dehydro-oogoniol. The starting material for the synthesis was the commercially available 17-keto steroid adrenosterone (**4**), which was converted in reasonable yield to a 15β,16β-epoxy-17-ketone **15**. Wittig reaction with ethylidene triphenylphosphorane converted **15** to the $\Delta^{17(20)}$ vinyl oxirane **16** which, on reaction with an appropriate magnesium organocuprate, gave in good yield a product possessing a 15β-hydroxy substituent and a sidechain with the natural configuration at C-20. The reaction was patterned off one first reported by Marino and Abe, who used a lithium organocuprate rather than a magnesium organocuprate.[3] We have found the latter compound to be a much better reagent, and in two recent papers we described the use of this reaction in the synthesis of 15β-hydroxy-24-oxocholesterol and 15β,29-dihydroxy-7-oxofucosterol in good yield from 3β-acetoxyandrost-5-en-17-one[4] and of oogoniol

[(24R)-3β,11α,15β,29-tetrahydroxy-stigmast-5-en-7-one], from adrenosterone.[5] Improvements in the later steps of the synthesis of dehydro-oogoniol over those reported earlier[2] and details of the synthesis of oogoniol are also given in this report.



Adrenosterone was first converted to the 3β–hydroxy derivative **6** by forming the dienol acetate **5** which was reduced with $Ca(BH_4)_2$ in absolute ethanol at -15°C, giving **6** in 89% yield. Reduction of **5**, with $NaBH_4$ was not satisfactory since the reaction was very sluggish at low temperatures.[6] When the temperature was raised to 10°, reaction proceeded more quickly but appreciable amounts of the Δ^4 isomer of **6** were formed. This isomer (thermodynamic product) could not be separated from **6** by chromatography.

Selective protection of the 3β-hydroxyl of **6** was achieved by adding 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU)[7] to a solution of **6** in tetrahydrofuran (THF) followed by a solution of *t*-butyldimethylsilyl chloride (TBDMSCl) in THF to give the 3β-silyloxy derivative **7** in 85% yield. Other conditions, e.g. dimethylaminopyridine (DMAP) instead of DBU and dichloromethane or dimethylformamide instead of

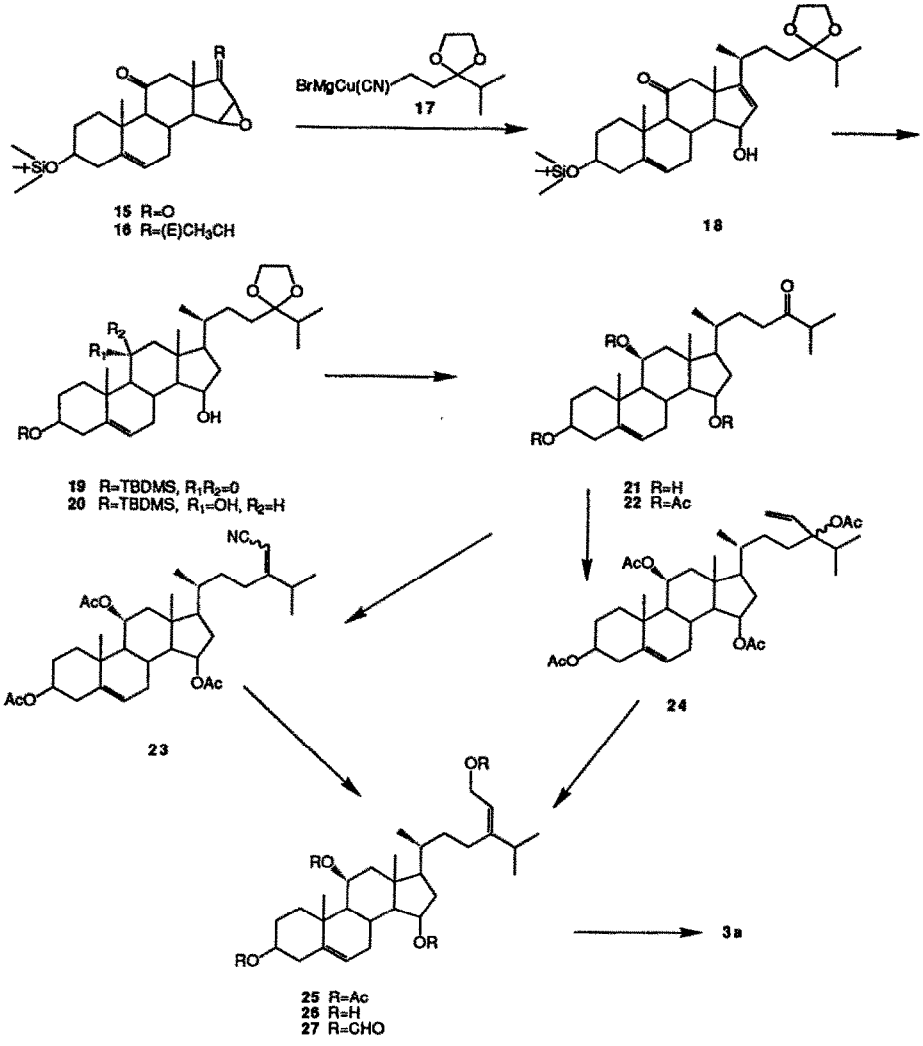
THF, gave mixtures of mono and disilylated products. The derivative **7** was then oxidized with pyridinium dichromate (PDC) in CH_2Cl_2, giving the diketone **8** (98%).

Our plan for introducing the hydroxyl in ring D required the preparation of αβ-unsaturated ketone (**12**), and we attempted to do this by silylation of the diketone (**8**) followed by treatment with palladium (II) acetate in acetonitrile.[8] The desired product (**12**) was obtained after selective desilylation of the 11-silyloxy intermediate, but only in 40% yield, and it was accompanied by starting material (40%) which was difficult to separate. Other closely related methods[9] employing palladium-catalyzed reactions of the allyl enol carbonate or enol acetate of the 17-ketone in **8** gave disappointing results. Attempts to introduce a double bond in ring D by selenoxide elimination were unsuccessful. Therefore, we reverted to the classical method of bromination-dehydrobromination of the 17-acetal.[10] The silyl protecting group in **8** was removed [p-toluene sulfonic acid (TsOH), water-acetone-methanol solution], and the product was treated with ethylene glycol and TsOH in refluxing benzene to give the 17-acetal **9** (96% for the two steps). Reduction of the 11-ketone with sodium in propanol gave the 3β,11α-diol (93%), which was converted to the diacetate **10** (97%). Bromination of **10** with pyridinium bromide perbromide gave the 16α-bromo derivative (94%), which was deacetylated (dilute KOH in DMSO-water) and subjected to dehydrobromination (potassium *t*-butoxide in DMSO at 50°) to give the corresponding diene in 84% yield. The diene was then converted to **12** (80%) by hydrolysis of the acetal (TsOH, acetone-water), selective silylation (TBDMSCl, DBU, THF) and oxidation (PDC, CH_2Cl_2).

The next step in the synthesis involved epoxidation of the newly formed double bond. Two problems were encountered: stereoselectivity in the epoxidation reaction, and instability of the desired β-epoxide. These problems were overcome by carrying out the epoxidation on the diketone **12** rather than on related compounds such as the hydroxyketone **11** or the diacetate **13**. Reaction of **12** with 30% hydrogen peroxide and 1M sodium hydroxide solution[11] in methanol, at temperatures ranging from –78 °C to 25 °C, gave poor yields of epoxide. However, when the epoxidation was carried out with 5.25% sodium hypochlorite (commercial bleach) in pyridine at room temperature,[12] a mixture of epoxides was obtained in good yield with the β-epoxide predominating (ratio of β to α, 7:3). The epoxides were readily distinguished by their ^1H NMR spectra, e.g. [δ 3.43 (d, J = 2.7 Hz, 15-H), 3.98 (d, J = 2.7 Hz, 16-H) for β-isomer and 3.40-3.75 (m, 15-H, 16-H), for α isomer] of epoxides from **13**.

Preference for formation of the β-epoxide can be explained by smaller steric 1,3 interaction between the approaching OCl^- and the angular methyl group (C-18) compared to the 1,2-interaction with the 14α–H when OCl^- approaches from the α side of ring D. Greater selectivity was obtained by carrying out the reaction at lower temperatures. Thus, epoxidation with NaOCl at –20 °C in pyridine-ethanol gave the β-epoxide (**15**) exclusively in an isolated yield of 87%. The compound (**15**) was relatively stable and could be stored for months in the refrigerator without decomposition. In contrast, when enones **11** or **13** were oxidized under the same conditions (–20 °C), a mixture of α- and β-epoxides was formed. The β-epoxide of **13** was formed exclusively at –78 °C. However, the compound decomposed on work-up of the reaction. Epoxidation of **14** gave only the β isomer, at –20 °C, and the compound was somewhat more stable than the product of **13**, though not suitable for subsequent operations. We had previously found that epoxidation of the enone unsubstituted at C-11 gave the β-epoxide in high yield at room temperature.[4]

The effect of remote polar substituents on the stereochemistry of epoxidation has been demonstrated with 3-oxo-Δ^4 steroids by Henbest and Jackson,[13] and was attributed to electrostatic interactions between the substituents and the anionic transition states. The situation with the epoxidations discussed above appears to be more complex since the stability of the epoxides is also dependent on the nature of the remote substituent.



Reaction of epoxide **15** with the ylid from ethyl triphenylphosphonium bromide and lithium diisopropylamide (LDA) gave the key intermediate **16** which, however, was quite unstable. Therefore **16** was not isolated but was added immediately to a solution of the magnesium cyanocuprate **17** of 2-(2-bromoethyl)-2-

isopropyl-1,3-dioxolane prepared from 4-methyl-3-oxopentanoate, as reported earlier.[4] It should be noted that the aforementioned bromide sometimes failed to form the Grignard reagent unless it was purified by chromatography on silica gel (or alumina) with freshly distilled solvents (diethyl ether and ethyl acetate). The pure bromide was smoothly converted to the Grignard reagent by heating at 50 °C for 1h. No byproducts from intramolecular reaction with the acetal group were observed.[14] The dark violet cuprate solution was cooled to -78°C and the Wittig product **16** was added *via* cannula. This reaction gave the crystalline 1,4-adduct **18** (63% from **15**). A trace of 1,2-adduct was detected by TLC and the amount of this product increased when the reaction was carried out at higher temperatures (-20 °C).[15] The stereochemistry at C-20 in **18** results from attack of the mixed cuprate on the α face of the E-17(20) alkene. As expected, the hindered 11-ketone in **15** was unreactive in both Wittig and Grignard reactions. Selective hydrogenation of the Δ^{16} double bond was achieved (90%) by using platinum on carbon as catalyst in ethyl acetate. Hydrogenolysis of the 15β-hydroxyl was avoided by addition of sodium carbonate to the reaction mixture. These three steps were highly stereoselective and gave a single product. None of the possible isomers of **19** (at C-15, C-17 or C-20) could be isolated.

Reduction of the 11-ketone of **19** with sodium in propanol furnished the 11α-hydroxy product **20** and removal of the protecting groups (TsOH, water) gave 3β,11α,15β-trihydroxy-5-cholesten-24-one **21** (95% for the two steps).

The triacetate (**22**) of this compound formed beautiful crystals from hexane-ethyl acetate. Therefore, an X-ray crystallographic analysis was carried out in order to confirm the structure of the intermediate, particularly in respect to the stereochemical assignments at C-15, C-17 and C-20. The crystals were triclinic with space group P1. The structure was solved by direct methods using SHELXTLPLUS software and a computer-generated drawing of the molecule is shown in Figure 1, while crystallographic data are given in Table 1.

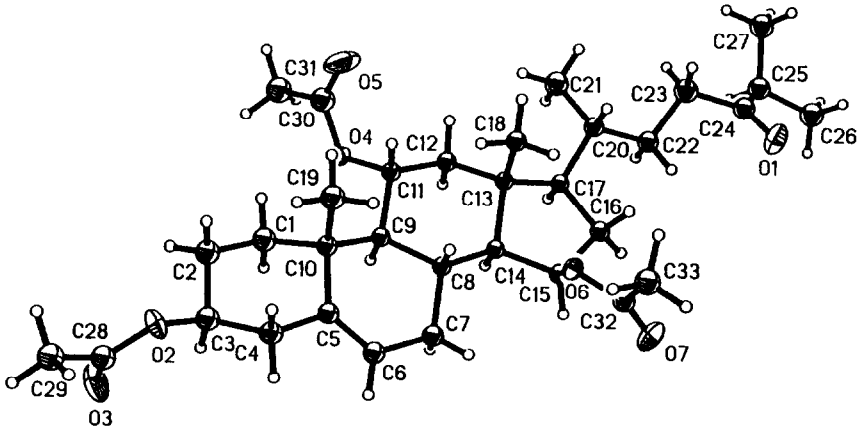


Figure 1. ORTEP view of X-ray molecular structure of 3β,11α,15β–triacetoxycholest–5–en–24–one (**22**).

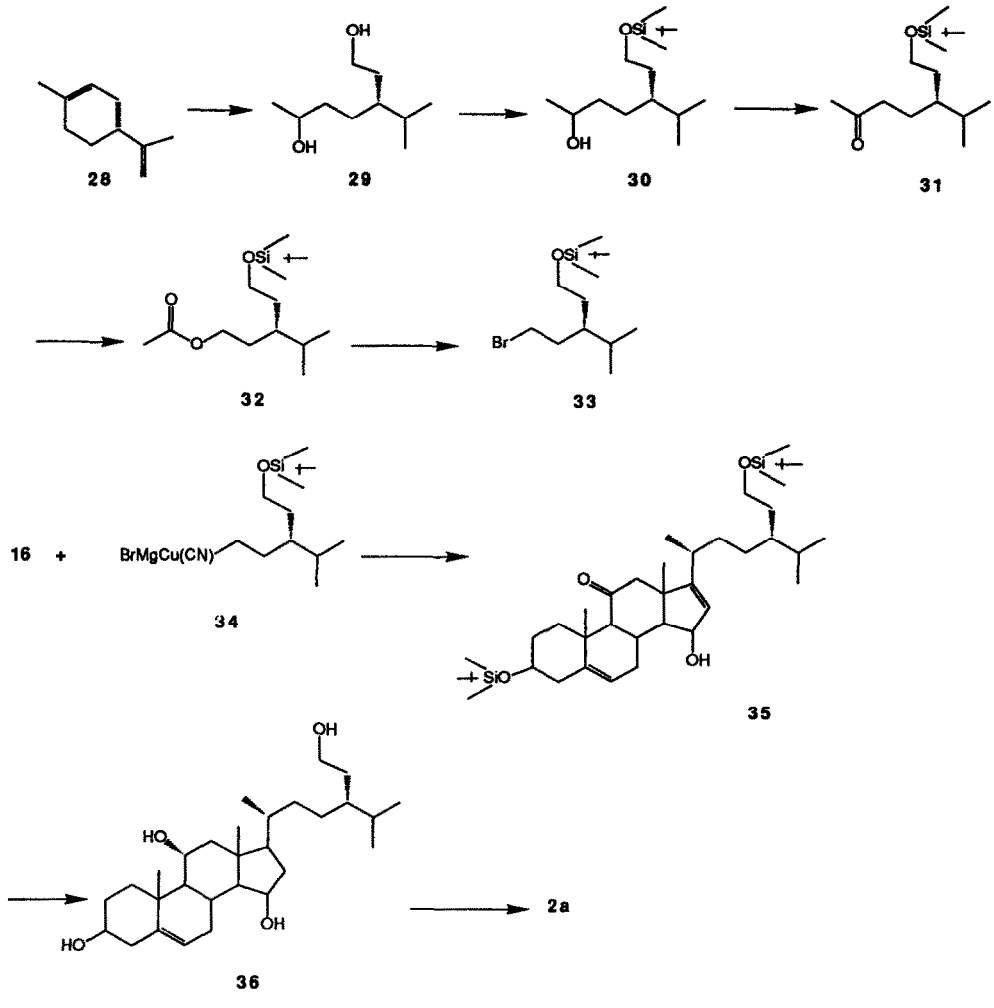
The synthesis of dehydro-oogoniol was completed by two routes. One, which was employed in our first synthesis[2] involved Horner-Emmons reaction of the triacetate (**22**) with diethyl cyanomethylphosphonate to give

the nitrile (**23**) as a mixture of isomers (E:Z, ~3:1). The nitrile was converted to the αβ-unsaturated aldehyde by reduction with diisobutyl aluminum hydride (DIBAL-H). Further reduction of the aldehyde with DIBAL-H furnished a 3:1 mixture of the tetraol **26** and its Z isomer.

A better way of getting to the tetraol was to react the triacetate **22** with vinylmagnesium bromide. The resulting Grignard product was acetylated and the tetraacetate (**24**) subjected to palladium (II)-catalyzed rearrangement of the allyl acetate[16] leading exclusively to the E isomer **25** in high yield (86% from **24**). Before introducing the 7-ketone the acetate groups were replaced by formate groups since hydrolysis of the 15β-acetate, after the 7-ketone was in place, led to extensive elimination of the 3β-hydroxy function.[2] Tetraformate **27** was obtained by treatment of tetraol **26** with acetic formic anhydride. Oxidation was effected with CrO_3-3,5-dimethylpyrazole in CH_2Cl_2 at –20°C to –15°C[17] and dehydro-oogoniol (**3a**) was obtained by subsequent mild reaction of the product with methanolic potassium carbonate at room temperature. The overall yield of **3a** from adrenosterone was 6%. Similar reactions on **26** (diastereomeric mixture) from the DIBAL-H reaction furnished a mixture of dehydro-oogoniol and its Z-isomer which were separated by reverse phase HPLC. Synthetic dehydro-oogoniol had spectral and chromatographic (HPLC) properties identical to those of the natural compound. Moreover, it displayed the same biological activity as the natural compound.

For the synthesis of oogoniol the vinyl oxirane intermediate **16** was also used, this time in a reaction with the magnesium cyanocuprate prepared from (R)-(+)-limonene (**28**) in the following way. Catalytic hydrogenation of the disubstituted double bond[18] followed by ozonolysis and reductive workup gave (3R, 6RS)-3-(1-methylethyl) heptan-1,6-diol **29**.[19] Protection of the primary alcohol as the *tert*–butyldimethylsilyl ether [TBDMSCl, DMAP, triethylamine in CH_2Cl_2, 92% yield] followed by oxidation with PDC afforded the corresponding ketone **31** (98%). Reaction of the latter with 3,5-dinitroperoxybenzoic acid in CH_2Cl_2[20] gave a single ester **32** (95%) which, on hydrolysis with methanolic potassium carbonate, gave (R)-5-[(*tert*-butyldimethylsilyl)oxy]-3-(1-methylethyl) pentanol (85%). (Oxidation with m-chloroperoxybenzoic acid was sluggish and this resulted in partial loss of the silyl protecting group.) Treatment with triphenylphosphine and carbon tetrabromide in THF gave the corresponding bromide **33** (65%), $[\alpha]_D$-1.2° ($CHCl_3$), which was converted to the Grignard reagent in THF and this was added to dry CuCN (1 mol) in THF. After stirring the mixture for 1h at room temperature, the dark violet solution of the cuprate **34** was cooled to –78°C and the solution of **16** was added giving exclusively the 1,4-addition product **35**. Selective hydrogenation of the Δ^{16} double bond as above followed by reduction of the 11-ketone with sodium in propanol and removal of the protecting groups gave the tetraol **36**. This compound was converted to the tetraformate and oxidized as above to give the corresponding 7-ketone. Finally removal of the protecting groups with methanolic potassium carbonate solution yielded oogoniol (**3a**) in an overall yield of 8% from adrenosterone.[21] Synthetic and natural oogoniol had identical spectral and chromatographic (HPLC) properties.

In summary, our investigations have resulted in the development of a highly stereoselective method for construction of steroidal sidechains from readily available 17-keto steroids. This is exemplified by syntheses of cholesterol derivatives and of oogoniol and dehydro-oogoniol. The latter compounds are now available for biological research, and we shall report in another paper the effect of dehydro-oogoniol, oogoniol and related compounds on the induction of sex organs in *Achlya*.



Experimental Section

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were taken in $CDCl_3$ on a Varian EM 390 spectrometer (90 MHz) or more frequently on a General Electric QE-300 NMR spectrometer (300 MHz for ^{1}H, 75.48 MHz for ^{13}C). Chemical shifts are reported in ppm relative to tetramethylsilane in ^{1}H NMR and relative to deuterated $CDCl_3$ (the middle peak of $CDCl_3$, 77.0) in ^{13}C NMR as the internal standard. The peak multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened. Infrared spectra (IR) were run on a Perkin-Elmer 1330 Infrared spectrometer. High resolution mass spectra were obtained on AEI MS-30 or VG 7070E-HF spectrometers from the Mass Spectrometry Service Laboratory of the University of Minnesota. Column chromatography was carried out on Merck silica gel 60 (70-230 mesh or finer ASTM). Analytical thin-layer chromatography was carried out on Merck silica gel 60 F-254 plastic sheets (0.2 mm thickness), the spots were detected either by UV (254 nm) lamp or by charring with a solution of sulfuric acid (5%) and p-anisaldehyde (3%) in ethanol.

Solvent mixtures were prepared by volume. All solvents and reagents were of commercial grade, unless otherwise indicated. Tetrahydrofuran (THF) was freshly distilled from lithium aluminum hydride under argon. Lithium diisopropylamide (LDA monotetrahydrofuran, 1.5 M in cyclohexane), DIBAL-H (1 M in dichloromethane), potassium t-butoxide, sodium hydride (60% dispersion in oil), copper(I) cyanide, palladium(II) acetate, bis(acetonitrile)palladium(II) chloride, vinylmagnesium bromide (1 M in THF), and anhydrous reagents such as dichloromethane, pyridine and dimethylsulfoxide were purchased from the Aldrich Chemical Company. Chromium trioxide was purchased from Mallinckrodt Inc. All reactions using moisture-sensitive reagents were carried out in flame-dried glassware under an atmosphere of dry argon. Work-up of reactions involved washing the solution of the product in ether with sodium bicarbonate solution, brine and drying with anhydrous magnesium sulfate followed by removal of solvent under reduced pressure.

3-Acetoxyandrosta-3,5-dien-11,17-dione (5)

A solution of adrenosterone **4** (androst-4-en-3,11,17-trione, 12 g, 40 mmol) (Steraloids Inc. Wilton NH) in acetyl chloride (5 mL, 70 mmol) and acetic anhydride (50 mL, 530 mmol) was heated to 130 °C in an oil bath for 4 h, and then cooled to room temperature. The white crystalline solid was filtered and washed with ether to give pure compound **5** (12.1 g) as plates: mp 180-185 °C (decomposed); ^{1}H NMR δ 0.88 (3, s, 18-H), 1.21 (3, s, 19-H), 2.14 (3, s, Ac), 5.38-5.41 (1, m, 6-H), 5.69 (1, d, J = 1.5 Hz, 4-H); IR (KBr) 2962, 1740, 1704, 1671, 1366, 1215, 1125, 1054 cm^{-1}. The filtrate was concentrated under vacuum, and then triturated with ethyl acetate. By filtration an additional amount of **5** (0.8 g) was obtained as a pale yellow solid which was pure enough for the next reaction. Total yield was 12.9 g (94%).

3β,11β,17β-Trihydroxyandrost-5-ene (6)

A calcium borohydride solution was prepared by addition of a solution of sodium borohydride (5.4 g, 143 mmol) in absolute ethanol (200 mL) to a solution of anhydrous calcium chloride (9.5 g, 86 mmol) in absolute ethanol (200 mL) at –15 °C under nitrogen. A solution of the enol acetate **5** (12.6 g, 36.8 mmol) in dichloromethane (80 mL) was added with vigorous stirring to the calcium borohydride solution at –15 °C. The mixture was stirred at that temperature for 12 h and then warmed up to room temperature and stirred for 6 h. The reaction mixture was concentrated under reduced pressure until it became a slurry, cooled in an ice-water bath, and then acidified with a cold aqueous HCl solution (0.5 M, 260 mL). The solution was stirred for 1 h and the precipitate was filtered and washed with water. The product was dried over P_2O_5 *in vacuo* to afford the triol **6** (10.0 g, 89%) as a white solid. An analytical sample was obtained by recrystallization from dimethylsulfoxide-water: mp 222-225 °C; ^{1}H NMR in $CDCl_3$ δ 1.01 (3, s, 18-H), 1.28 (3, s, 19-H), 3.47-3.57 (1, m, 3-H), 3.61 (1, t, J = 8.1 Hz, 17-H), 4.42 (1, br s, 11-H), 5.24 (1, br s, 6-H) and in DMSO-d_6 δ 0.88 (3, s, 18-H), 1.20 (3, s, 19-H), 3.20-3.43 (2, m, 3-H and 17-H), 3.88 (1, d, J = 3 Hz, OH), 4.17-4.25 (1, m, 11-H), 4.30 (1, d, J = 5.1 Hz, OH), 4.52 (1, d, J = 4.2 Hz, OH), 5.10 (1, br, 6-H).

3β-(t-Butyldimethylsilyloxy)-11β,17β-dihydroxyandrost-5-ene (7)

The triol **6** (9.6 g, 31 mmol) was dissolved in dry THF (300 mL) and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU, 7.0 mL, 47 mmol) was added under a nitrogen atmosphere. A solution of t-butyldimethylsilyl chloride (7.0 mL, 47 mmol) in THF (50 mL) was added and the mixture was stirred at room temperature for 20 h (monitored by TLC). The mixture was diluted with ether (200 mL) and successively washed with water (3 x 20 mL) and saturated ammonium chloride. Work-up gave a solid which was recrystallized from acetone-water and dried over P_2O_5 *in vacuo* to give pure compound **7** (11.2 g, 85%) as needles: mp 173-175 °C; ^{1}H NMR δ 0.06 (6, s, $SiMe_2$), 0.89 (9, s, $SiCMe_3$), 1.01 (3, s, 18-H), 1.27 (3, s, 19-H), 3.42-3.54 (1, m, 3-H), 3.57-3.65 (1, m, 17-H), 4.41 (1, br s, 11-H), 5.21 (1, br s, 6-H); IR (KBr) 3445, 2920, 1460, 1250, 1187, 832 cm^{-1}.

3β-(t-Butyldimethylsilyloxy)androst-5-en-11,17-dione (8)

The alcohol **7** (11.2 g, 26.6 mmol) was dissolved in dry dichloromethane (200 mL), and pyridinium dichromate (PDC, 27.0 g, 72.0 mmol) was added under an atmosphere of argon. The mixture was stirred at room temperature for 2 days; then it was diluted with ether (100 mL) and passed through a short column of silica gel which was eluted with ether. Evaporation gave a pale yellow solid, which was recrystallized from acetone-water to afford the ketone **8** (10.9 g, 98%) as needles: mp 205-208 °C; ^{1}H NMR, δ 0.06 (6, s, $SiMe_2$), 0.85 (3, s, 18-H), 0.89 (9, s, $SiCMe_3$), 1.20 (3, s, 19-H), 3.40-3.55 (1, m, 3-H), 5.30-5.35 (1, m, 6-H); ^{13}C

NMR δ 217.8, 208.6, 142.8, 119.0, 72.2, 61.5, 50.4, 49.9, 49.7, 42.5, 37.2, 36.22, 36.16, 32.8, 31.8, 31.6, 25.9, 21.8, 18.7, 18.2, 14.7, -4.6; IR (KBr) 2920, 1750, 1704, 1100 cm^{-1}; high resolution MS, m/z (relative intensity) 359.2031 (M^+–C_4H_9, 89), 285.1870 (5), 75.0270 (100) (Calcd for $C_{25}H_{40}O_3Si$-C_4H_9: 359.2043).

3β-Hydroxyandrost-5-en-11,17-dione

The ether **8** (3.0 g, 7.2 mmol) was dissolved in acetone (60 mL) and methanol (60 mL), p-toluenesulfonic acid (0.1 g) and water (9 mL) were added. The mixture was stirred at room temperature for 10 h, then neutralized with sodium bicarbonate (0.3 g). The solution was concentrated under reduced pressure at 30 °C until methanol and acetone were removed. The resulting solid was filtered and washed with water and then dried over P_2O_5 *in vacuo* to afford the alcohol (2.14 g, 98%) as plates: mp 219-220 °C; ^1H NMR, δ 0.86 (3, s, 18-H), 1.22 (3, s, 19-H), 3.45-3.57 (1, m, 3-H), 5.37-5.39 (1, m, 6-H); ^{13}C NMR δ 217.8, 208.6, 142.1, 119.5, 71.3, 61.4, 50.3, 49.8, 49.7, 41.8, 37.1, 36.12, 36.05, 32.8, 31.5, 31.4, 21.8, 18.7, 14.7; IR (KBr) 3500, 2924, 1743, 1705, 1225, 1043, 1030 cm^{-1}.

17-Ethylenedioxy-3β-hydroxyandrost-5-en-11-one (9)

A mixture of the above diketone (2.14 g, 7.08 mmol) and ethylene glycol (3 mL, 54 mmol) was refluxed in the presence of p-toluenesulfonic acid (0.2 g) in benzene (120 mL) for 2.5 h, during which time the water was trapped with a Dean-Stark apparatus. The reaction mixture was cooled to 10 °C and diluted with ether (100 mL). Work-up gave a white solid, which was recrystallized from ether-hexane to afford the ketal **9** (2.41 g, 98%) as plates: mp 145-147 °C; ^1H NMR δ 0.80 (3, s, 18-H), 1.18 (3, s, 19-H), 3.45-3.60 (1, m, 3-H), 3.78-3.98 (4, m, acetal), 5.32 (1, d, J = 4.8 Hz, 6-H); ^{13}C NMR δ 211.1, 141.8, 120.0, 117.9, 71.4, 65.3, 64.5, 60.7, 50.1, 48.8, 48.6, 41.92, 36.9, 36.1, 34.3, 33.8, 32.0, 31.4, 22.5, 18.6, 14.9; IR (KBr) 3390, 2920, 1700, 1175, 1055 cm^{-1}.

3β,11α-Dihydroxy-17-ethylenedioxyandrost-5-ene

Thirty spheres of sodium metal (1.5 g, 65 mmol) were added with vigorous stirring to a refluxing solution of the ketone **9** (2.41 g, 6.96 mmol) in n-propanol (70 mL) in 5 min. Stirring was continued for 60 min (monitored by TLC). After destruction of the excess sodium metal with methanol, the reaction mixture was concentrated under reduced pressure and ether (150 mL) was added. Work-up gave an amorphous solid, which was recrystallized from ether-hexane to give the pure alcohol (2.25 g, 93% yield) as a white solid: mp 120-123 °C; ^1H NMR δ 0.87 (3, s, 18-H), 1.16 (3, s, 19-H), 3.43-3.60 (1, m, 3-H), 3.80-3.98 (4, m, acetal), 3.98-4.13 (1, m, 11-H), 5.40 (1, d, J = 5.1 Hz, 6-H); ^{13}C NMR δ 141.2, 121.3, 118.8, 69.5, 68.9, 65.2, 64.6, 56.9, 49.6, 46.3, 42.7, 42.2, 39.1, 38.2, 34.4, 32.1, 31.8, 31.2, 22.6, 19.1, 15.2; IR (KBr) 3400, 2932, 1468, 1110, 1040 cm^{-1}.

3β,11α-Diacetoxy-17-ethylenedioxyandrost-5-ene (10)

The above alcohol (2.25 g, 6.46 mmol) was dissolved in acetic anhydride (5 mL) and pyridine (5 mL) was added. The mixture was stirred at room temperature for 12 h and diluted with ether (200 mL). After work-up, the residue was triturated with methanol. The white solid was filtered and recrystallized from methanol to afford the diacetate **10** (2.71 g, 97%) as needles: mp 177-178 °C; ^1H NMR δ 0.91 (3, s, 18-H), 1.09 (3, s, 19-H), 2.00 (3, s, Ac), 2.01 (3, s, Ac), 3.78-3.95 (4, m, acetal), 4.50-4.64 (1, m, 3-H), 5.20-5.30 (1, m, 11-H), 5.44 (1, d, J = 5.4 Hz, 6-H); IR (KBr) 2940, 2883, 1725, 1380, 1255, 1230, 1103, 1040, 1030 cm^{-1}.

16α-Bromo-3β,11α-diacetoxy-17-ethylenedioxyandrost-5-ene

To a solution of the acetal **10** (2.71 g, 6.27 mmol) in THF (20 mL) was added a solution of pyridinium bromide perbromide (90%, 5 g, 14 mmol) in THF (12 mL). The mixture was stirred at room temperature for 2 h. A mixture of pyridine (3 g, 38 mmol), sodium iodide (4.5 g, 30 mmol), sodium thiosulfate (6 g, 24 mmol), and water (10 mL) was added. The mixture was stirred for 3 h at room temperature and diluted with ether (100 mL), and saturated sodium bicarbonate solution (10 mL) was added. The organic layer was separated and the aqueous phase was extracted with ether (3 x 50 mL). Work-up gave an oily liquid, which crystallized from methanol to afford the bromide (3.0 g, 94%) as plates: mp 163-164 °C; ^1H NMR δ 0.96 (3, s, 18-H), 1.09 (3, s, 19-H), 2.01 (3, s, Ac), 2.02 (3, s, Ac), 3.85-3.96 (2, m, acetal), 4.07-4.27 (2, m, acetal), 4.50 (1, dd, J = 9.6 and 4.5 Hz, 16-H), 4.53-4.63 (1, m, 3-H), 5.18-5.30 (1, m, 11-H), 5.43 (1, d, J = 5.4 Hz, 6-H); ^{13}C

NMR δ 170.5, 170.2, 139.7, 122.2, 116.1, 73.5, 71.2, 66.5, 66.2, 54.8, 52.8, 47.3, 45.2, 38.5, 38.2, 38.1, 36.9, 35.3, 32.0, 31.0, 27.8, 21.9, 21.4, 19.2, 15.0; IR (KBr) 2970, 2890, 1727, 1379, 1367, 1250, 1035 cm^{-1}; high resolution MS, m/z (relative intensity) 510.1657 (M^+, 7), 450.1401 (53), 311.1972 (66), 248.1548 (67), 233.1328 (62), 99.0552 (100) (Calcd for $C_{25}H_{35}O_6Br$: 510.1618).

16α-Bromo-3β,11α-dihydroxy-17-ethylenedioxyandrost-5-ene

The above diacetoxy bromide (1.60 g, 3.13 mmol) was dissolved in dimethylsulfoxide (25 mL) and a solution of potassium hydroxide (2 g, 36 mmol) in water (6 mL) was added at 0 °C. The mixture was stirred at room temperature for 2 h and partitioned into water (20 mL) and ether (100 mL). The organic phase was separated and the aqueous layer was extracted with ether (5 x 20 mL) until no product was detected by TLC. Work-up gave a yellowish solid which was recrystallized from ether to give the dihydroxy bromide (1.30 g, 97%) as plates: mp 201-202 °C; ^1H NMR, δ 0.91 (3, s, 18-H), 1.15 (3, s, 19-H), 3.47-3.59 (1, m, 3-H), 3.88-3.98 (2, m, acetal), 4.00-4.10 (1, m, 11-H), 4.10-4.28 (2, m, acetal), 4.51 (1, dd, J = 9.9 and 4.2 Hz, 16-H), 5.39 (1, d, J = 5.7 Hz, 6-H); ^{13}C NMR δ 141.2, 120.9, 116.2, 71.6, 68.7, 66.5, 66.2, 56.9, 55.0, 47.7, 45.6, 42.7, 41.9, 39.1, 38.2, 35.3, 31.9, 31.7, 30.9, 19.1, 15.4; IR (KBr) 3380, 2970, 2920, 2890, 1470, 1210, 1110, 1038 cm^{-1}.

3β,11α-Dihydroxy-17-ethylenedioxyandrosta-5,15-diene

The dihydroxy bromide (2.41 g, 5.64 mmol) and potassium t-butoxide (5.0 g, 45 mmol) were dissolved in dry dimethylsulfoxide (30 mL) under argon. The mixture was stirred at 50 °C for 3 h and partitioned into water (20 mL) and ether (100 mL). The organic phase was separated, and the aqueous layer was extracted with ether (4 x 20 mL) until no product was detected by TLC. Work-up gave a yellowish solid which was recrystallized from THF-ether to give the diene (1.69 g, 87%) as a white solid: mp 175-177 °C; ^1H NMR δ 0.91 (3, s, 18-H), 1.18 (3, s, 19-H), 3.45-3.60 (1, m, 3-H), 3.79-4.02 (4, m, acetal), 4.10-4.22 (1, m, 11-H), 5.42 (1, d, J = 5.7 Hz, 6-H), 5.71 (1, dd, J = 6.0 and 3.0 Hz, 16-H), 6.09 (1, d, J = 6.0 Hz, 15-H); ^{13}C NMR δ 141.6, 135.6, 132.5, 120.9, 118.9, 71.6, 68.7, 65.3, 64.2, 58.0, 55.6, 49.1, 42.7, 41.4, 39.0, 38.4, 31.7, 31.4, 30.0, 19.3, 16.6; IR (KBr) 3350, 2910, 1465, 1340, 1200, 1050, 740 cm^{-1}.

3β,11α-Dihydroxyandrosta-5,15-dien-17-one

The above acetal (1.69 g, 4.88 mmol) was dissolved in acetone (20 mL), and p-toluenesulfonic acid (0.1 g) and water (10 mL) were added. The mixture was stirred at room temperature for 4 h. The reaction mixture was neutralized with sodium bicarbonate (0.3 g) and concentrated *in vacuo* to remove the acetone. The yellow residue was filtered, air-dried, and then recrystallized from ether to afford the dienone (1.41 g, 96%) as needles: mp 105-108 °C; ^1H NMR δ 1.06 (3, s, 18-H), 1.21 (3, s, 19-H), 3.50-3.60 (1, m, 3-H), 4.22-4.34 (1, m, 11-H), 5.46 (1, d, J = 5.1 Hz, 6-H), 6.07 (1, dd, J = 6.0 and 3.0 Hz, 16-H), 7.49 (1, d, J = 6.0 Hz, 15-H); ^{13}C NMR δ 211.4, 157.8, 142.0, 132.2, 120.3, 71.6, 68.2, 58.5, 56.0, 50.4, 42.6, 40.6, 38.8, 38.6, 31.7, 30.7, 29.6, 20.8, 19.4; IR (KBr) 3350, 2930, 1700, 1375, 1228, 1040, 827 cm^{-1}; high resolution MS, m/z (relative intensity) 302.1884 (M^+, 81), 284.1783 (M^+–H_2O, 59), 131.0502 (85), 91.0549 (100) (Calcd for $C_{19}H_{26}O_3$: 302.1883).

3β-(t-Butyldimethylsilyloxy)-11α-hydroxyandrosta-5,15-dien-17-one (11)

The above dienone (1.45 g, 4.8 mmol) was dissolved in dry THF (70 mL) and DBU (1.5 g, 9.9 mmol) was added under an argon atmosphere. A solution of t-butyldimethylsilyl chloride (1.4 g, 9.3 mmol) in dry THF (15 mL) was added. The mixture was stirred at room temperature for 5 h (monitored by TLC) and diluted with ether (100 mL). The solid resulting from work-up was recrystallized from methanol to give the silylated compound **11** (1.85 g, 93%) as needles: mp 183-185 °C; ^1H NMR δ 0.06 (6, s, $SiMe_2$), 0.89 (9, s, $SiCMe_3$), 1.05 (3, s, 18-H), 1.20 (3, s, 19-H), 3.43-3.55 (1, m, 3-H), 4.22-4.34 (1, m, 11-H), 5.42 (1, d, J = 4.8 Hz, 6-H), 6.06 (1, dd, J = 6.0 and 3.0 Hz, 16-H), 7.49 (1, d, J = 6.0 Hz, 15-H); ^{13}C NMR δ 211.5, 157.8, 142.8, 132.2, 119.8, 72.4, 68.1, 58.6, 56.0, 50.3, 43.2, 40.5, 39.0, 38.7, 32.1, 30.8, 29.7, 25.9, 20.8, 19.5, 18.2, -4.6; IR (KBr) 3430, 2925, 2858, 1710, 1250, 1090, 833 cm^{-1}.

3β-(t-Butyldimethylsilyloxy)androsta-5,15-dien-11,17-dione (12)

The above silylated compound (1.85 g, 4.44 mmol) was dissolved in dry dichloromethane (100 mL), and pyridinium dichromate (PDC, 3.4 g, 9.0 mmol) was added under an atmosphere of argon. The mixture was

stirred at room temperature for 12 h. The reaction mixture was diluted with ether and passed through a short column of silica gel and eluted with ether. Evaporation gave a pale yellow solid which was rechromatographed (10:1 hexane:ethyl acetate) to afford **12** (1.64 g, 89%) as a white solid: mp 180-185 °C; ^{1}H NMR δ 0.06 (6, s, $SiMe_2$), 0.89 (9, s, $SiCMe_3$), 1.02 (3, s, 18-H), 1.22 (3, s, 19-H), 3.42-3.53 (1, m, 3-H), 5.38 (1, d, J = 5.1 Hz, 6-H), 6.18 (1, dd, J = 6.0 and 3.0 Hz, 16-H), 7.58 (1, dd, J = 6.0 Hz and 0.9 Hz, 15-H); ^{13}C NMR δ 209.7, 207.6, 157.2, 143.3, 133.1, 118.6, 72.3, 63.6, 55.2, 50.8, 48.7, 42.7, 37.7, 36.4, 31.8, 31.0, 30.9, 25.9, 21.9, 18.6, 18.2, -4.6: IR (KBr) 2923, 2852, 1720, 1700, 1250, 1180 cm^{-1}. high resolution MS, m/z (relative intensity) 357.1853 (M^+–C_4H_9, 80), 283.1665 (3), 75.0276 (100) (Calcd for $C_{25}H_{38}O_3Si$–C_4H_9: 357.1886).

3β-(t-Butyldimethylsilyloxy)-15β,16β-epoxyandrost-5-en-11,17-dione (15)

The enone **12** (0.6 g, 1.45 mmol) was dissolved in pyridine (12 mL) and ethanol (9 mL). The solution was cooled to –20 °C and sodium hypochlorite solution (chlorox, 5.25%, 4 mL, 3 mmol) was added with vigorous stirring during 5 min. Stirring was continued at that temperature for 45 min. The organic product was extracted with ether (100 mL) and the ethereal solution was washed with water (2 x 10 mL), brine, and dried over anhydrous magnesium sulfate. After the solvent was removed under vacuum at 20 °C, the resulting yellow solid was triturated with hexane (in some cases methanol was better). Filtration gave the epoxide **15** (0.54 g, 87%) as a white powder (no appreciable decomposition was observed after storing in a refrigerator for 4 months): mp 206-208 °C; ^{1}H NMR δ 0.06 (6, s, $SiMe_2$), 0.89 (9, s, $SiCMe_3$), 1.13 (3, s, 18-H), 1.20 (3, s, 19-H), 3.43 (1, d, J = 2.7 Hz, 15-H), 3.42-3.53 (1, m, 3-H), 3.98 (1, d, J = 2.7 Hz, 16-H), 5.40 (1, d, J = 5.4 Hz, 6-H); IR (KBr) 2960, 2925, 1755, 1705, 1100 cm^{-1}.

3β-(t-Butyldimethylsilyloxy)-15β,16β-epoxypregna-5,17(20)(E)-dien-11-one (16)

LDA solution was added to a solution of ethyltriphenylphosphonium bromide in THF at –20 to –15 °C and the mixture was stirred for 30 min. The resulting deep orange ylide solution was added to a solution of the epoxide **15** in THF at -20 °C. The mixture was stirred at –20 °C for 20 min and at 0 °C for 1.5 h. The reaction mixture was diluted with ether, washed with water, dried over anhydrous sodium sulfate (anhydrous magnesium sulfate caused decomposition of the Wittig product). A crude sample of **16** gradually decomposed even during evaporation of the solvent. Attempts at recrystallization with ether caused further decomposition: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.05 (6, s, $SiMe_2$), 0.88 (9, s, $SiCMe_3$), 1.05 (3, s, 18-H), 1.16 (3, s, 19-H), 1.67 (3, d, J = 6.9 Hz, 21-H), 3.30-3.50 (1, m, 3-H), 3.54 (1, d, J = 3.0 Hz, 15-H), 3.71 (1, d, J = 3.0 Hz, 16-H), 5.30-5.43 (1, m, 6-H); 5.74 (1, q, J = 6.9 Hz, 20-H).

3β-(t-Butyldimethylsilyloxy),15β-hydroxy-24-ethylenedioxy-cholesta-5,16-dien-11-one (18)

Under an argon atmosphere, a mixture of flame-dried magnesium (140 mg, 5.76 mmol) and 2-(2-bromoethyl)-2-isopropyl-1,3-dioxolane[4] (0.95 mL, 4.26 mmol) in THF (7 mL) was stirred at 50 °C for 1 h and cooled to room temperature. This solution was added via a teflon tube to a suspension of copper(I) cyanide (dried over P_2O_5 *in vacuo* overnight at 40 °C, 381 mg, 4.26 mmol) in THF (10 mL) at room temperature. The green copper(I) cyanide gradually dissolved and the mixture became dark violet. After stirring the violet solution (**17**) for an hour, it was used as described below.

A solution of LDA (1.4 mL, 1.5 M in cyclohexane) was added to a solution of ethyl triphenylphosphonium bromide (0.80 g, 2.16 mmol) in THF (23 mL) at –20 to –15 °C, and the reaction mixture was stirred for 30 min at that temperature. The resulting deep-orange ylide solution was added *via* cannula to a solution of the epoxyketone **15** (dried over P_2O_5 *in vacuo* overnight, 0.54 g, 1.25 mmol) in THF (6 mL) at –20 °C, the solution was kept for 20 min at –20 °C, and then at 0 °C for 1.5 h to give the unstable Wittig product **16**. The reaction was monitored by TLC (10:3 hexane:ethyl acetate, R_f value of **16** was 0.47, whereas R_f value of **15** was 0.29). The solution containing **16** was added *via* cannula to the violet cuprate solution (**17**) from above, previously cooled to –78 °C. Stirring was continued at this temperature for 1 h, and at –20 °C for another hour. The reaction mixture was quenched with saturated ammonium chloride solution (20 mL). The mixture was filtered through Celite to remove inorganic salts which were washed with ether, and the washings and filtrate were combined. The organic phase was separated, and the aqueous layer was extracted with ether (3 x 50 mL). Work-up gave an orange solid, which, on column chromatography (10:1 hexane:ethyl acetate), afforded the compound **18** (0.461 g, 63% from epoxyketone **15**) as a crystalline white solid: mp 164-165 °C; TLC (10:3 hexane:ethyl acetate) R_f 0.25; ^{1}H NMR δ 0.06 (6, s, $SiCH_3$), 0.89 (9, s, $SiC(CH_3)_3$), 0.91 (3, d, J=7.2 Hz, 26-H or 27-H), 0.92 (3, d, J=6.9 Hz, 27-H or 26-H), 0.99 (3, d, J=6.9 Hz, 21-H), 1.05 (3, s, 18-

H), 1.25 (3, s, 19-H), 3.42-3.53 (1, m, 3-H), 3.94 (4, s, acetal), 4.60-4.62 (1, m, 15-H), 5.37 (1, br, d, J=5.1 Hz, 6-H), 5.64 (1, d, J=2.4 Hz, 16-H); ^{13}C NMR 209.4, 163.9, 142.7, 124.5, 119.6, 113.7, 72.9, 72.5, 65.4, 63.1, 58.1, 54.2, 49.1, 42.7, 37.5, 36.5, 34.5, 32.3, 32.1, 31.9, 31.4, 29.8, 29.5, 26.9, 25.9, 24.2, 21.9, 18.4, 18.2, 17.1, –4.6; IR (KBr) 3450, 2925, 1702, 1093 cm^{-1}; high resolution MS, m/z (relative intensity) 568.3958 (M^+–H_2O, 3), 529.3347 (M^+–C_4H_9, 26), 525.3399 (38), 438.2923 (36), 381.2246 (55), 373.1824 (69), 145.1023 (100), 115.0756 (78) (Calcd for $C_{35}H_{58}O_5Si$–H_2O : 568.3950.

When the reaction of **16** and **17** was carried out at –20 to –15 °C, the product from 1,2-addition was isolated in ca 5% yield: mp 188-190 °C; ^{1}H NMR δ 0.06 (6, s, $SiMe_2$), 0.89 (9, s, $SiCMe_3$), 0.94 (6, d, J=6.6 Hz, $(CH_3)_2CH$), 1.17 (3, s, 18-H), 1.23 (3, s, 19-H), 1.67 (3, d, J=7.2 Hz, 21-H), 3.43-3.52 (1, m, 3-H), 3.96 (4, s, acetal), 4.05 (1, d, J=4.5 Hz, 15-H), 5.29 (1, m, 20-H), 5.34 (1, br, d, J=4.5 Hz, 6-H).

3β-(t-Butyldimethylsilyloxy)-15β-hydroxy-24-ethylenedioxycholest-5-en-11-one (19)

The alkene **18** (0.46 g, 0.78 mmol) was dissolved in ethyl acetate (60 mL) and stirred with 10% platinum on activated carbon (30 mg) and sodium carbonate (1.0 g) under an atmosphere of hydrogen at 0 °C for 4 h. The reaction mixture was filtered through a short column of silica gel. Evaporation of solvent and recrystallization of the residue from hexane gave the compound **19** (0.43 g, 93%) as plates: mp 235-237 C (methanol); ^{1}H NMR δ 0.05 (6, s, $SiMe_2$), 0.88 (9, s, $SiCMe_3$), 0.89-0.94 (9, m, 21-H, 26-H, and 27-H), 0.91 (3, s, 18-H), 1.23 (3, s, 19-H), 3.40-3.52 (1, m, 3-H), 3.93 (4, s, acetal), 4.28-4.33 (1, m, 15-H), 5.32-5.33 (1, m, 6-H); ^{13}C NMR δ 210.6, 142.7, 119.3, 113.9, 72.4, 69.4, 65.4, 65.3, 60.6, 59.5, 59.0, 55.0, 45.2, 42.5, 41.4, 37.0, 36.3, 35.2, 34.4, 32.2, 31.8, 30.4, 28.90, 28.87, 25.9, 18.5, 18.3, 17.2, 17.0, 15.1, –4.5; IR (KBr) 3440, 2960, 2925, 1692, 1092 cm^{-1}; high resolution MS, m/z (relative intensity) 545.3635 (M^+–C_3H_7, 54), 531.3516 (M^+–C_4H_9, 100), 115.0755 (88) (Calcd for $C_{35}H_{60}O_5Si$–C_3H_7 : 545.0794). The hydrogenolysis product (5 mg, 1%) was obtained by column chromatography (10:1 hexane:ethyl acetate): mp 165-168 °C (methanol); ^{1}H NMR δ 0.05 (6, s, $SiMe_2$), 0.73 (3, s, 18-H), 0.88 (9, s, $SiCMe_3$), 0.92 (6, d, J=6.9 Hz, 26-H and 27-H), 0.98 (3, d, J=6.3 Hz, 21-H), 1.19 (3, s, 19-H), 3.40-3.52 (1, m, 3-H), 3.93 (4, s, acetal, 5.32 (1, br d, J=4.5 Hz, 6-H). When sodium carbonate was omitted, the hydrogenolysis product was obtained in 16% yield.

3β-(t-Butyldimethylsilyloxy)-11α,15β-dihydroxy-24-ethylenedioxycholest-5-ene (20)

Ten spheres of sodium metal (0.5 g, 22 mmol) were added with vigorous stirring to a refluxing solution of the ketone **19** (0.26 g, 0.44 mmol) in n-propanol (10 mL) during 1 min. Stirring was continued for 30 min; the reaction mixture was cooled to 0 °C, and after destruction of the excess sodium metal with methanol, it was diluted with ether (120 mL), and washed with water (4 x 3 mL), saturated ammonium chloride, sodium bicarbonate, brine, and then dried over anhydrous magnesium sulfate. After removal of the solvent, the compound **20** (0.26 g, quantitative yield) was obtained by recrystallization from acetone-water as a white solid: mp 204-206 °C; ^{1}H NMR δ 0.05 (6, s, $SiMe_2$), 0.88 (9, s, $SiCMe_3$), 0.91 (3, d, J = 7.5 Hz, 26-H or 27-H), 0.92 (3, d, J = 7.5 Hz, 27-H or 26-H), 0.95 (3, d, J = 6.9 Hz, 21-H), 0.97 (3, s, 18-H), 1.18 (3, s, 19-H), 3.43-3.53 (1, m, 3-H), 3.93 (4, s, acetal), 3.98-4.12 (1, m, 11-H), 4.14-4.22 (1, m, 15-H), 5.32-5.33 (1, br d, 5.4 Hz, 6-H); ^{13}C NMR δ 142.1, 120.5, 114.0, 72.7, 69.9, 68.9, 65.4, 65.3, 60.3, 57.0, 56.0, 52.5, 43.3, 42.5, 41.1, 39.4, 38.4, 35.4, 34.4, 32.2, 31.4, 30.5, 29.0, 27.5, 25.9, 19.0, 18.7, 18.3, 17.2, 17.0, 15.5, –4.6; IR (KBr) 3450, 2920, 1464, 1380, 1250, 1088, 832 cm^{-1}; high resolution MS, m/z (relative intensity) 547.3776 (M^+–C_3H_7, 34), 533.3612 (M^+–C_4H_9, 42), 515.3533 (M^+–C_4H_9–H_2O, 21), 143.1037 (74), 115.0786 (100) (Calcd for $C_{35}H_{62}O_5Si$–C_3H_7 : 547.3820).

3β,11α,15β-trihydroxycholest-5-en-24-one (21)

The acetal **20** (0.26 g, 0.44 mmol) was dissolved in acetone (10 mL), and water (2 mL) and p-toluenesulfonic acid monohydrate (17 mg, 0.09 mmol) were added. The mixture was refluxed for 2h and then diluted with ether (100 mL). Work-up gave an amorphous light-orange solid. Pure compound **21** (0.18 g, 95% yield) was obtained as a white solid by precipitation with ethyl acetate and hexane: mp 106-107 °C; TLC R_f 0.21 (10:4:1 hexane:ethyl acetate:ethanol); ^{1}H NMR δ 0.94 (3, d, J = 6.3 Hz, 21-H), 0.97 (3, s, 18-H), 1.09 (6, d, J = 6.6 Hz, 26-H and 27-H), 1.19 (3, s, 19-H), 3.43-3.60 (1, m, 3-H), 3.97-4.13 (1, m, 11-H), 4.15-4.25 (1, m, 15-H), 5.42 (1, d, J = 5.4 Hz, 6-H); ^{13}C NMR δ 215.2, 141.2, 121.1, 71.8, 69.8, 68.8, 60.2, 56.8, 56.1, 52.5, 42.7, 42.5, 41.2, 40.9, 39.1, 38.2, 37.2, 35.1, 31.8, 31.3, 29.5, 27.5, 18.9, 18.5, 18.33, 18.30, 15.5; IR(KBr) 3400, 2930, 1705, 1468, 1042 cm^{-1}; high resolution MS, m/z (relative intensity)

432.3248 (M^+, 40), 414.3124 (M^+-H_2O, 82), 396.3061 ($M^+-2\ H_2O$, 44), 381.2754 (42), 269.1915 (49), 251.1810 (53), 145.1002 (90), 127.1122 (100), 121.1018 (68) (Calcd for $C_{27}H_{44}O_4$: 432.3241).

3β,11α,15β-Triacetoxycholest-5-en-24-one (22)

The triol **21** (0.30 g, 0.69 mmol) was dissolved in acetic anhydride (2 mL), and pyridine (2 mL) and 4-dimethylaminopyridine (20 mg) were added. The mixture was stirred for a day at room temperature and ether (100 mL) was added. The ethereal solution was washed with water (4 x 5 mL), cold HCl solution (1 M, 2 x 5 mL), saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. The solvent was removed and the resulting solid was chromatographed (10:2 hexane:ethyl acetate) and recrystallized from hexane-ethyl acetate to give the acetate **22** (0.35 g, 90%) as needles: mp 166-168 °C; ^{1}H NMR δ 0.90 (3, d, J = 6.3 Hz, 21-H), 0.97 (3, s, 18-H), 1.07 (6, d, J = 6.9 Hz, 26-H and 27-H), 1.13 (3, s, 19-H), 1.99 (3, s, Ac), 2.01 (3, s, Ac), 2.02 (3, s, Ac), 4.50-4.64 (1, m, 3-H), 5.00-5.06 (1, m, 15-H), 5.20-5.40 (1, m, 11-H), 5.43 (1, d, J = 4.8 Hz, 6-H); ^{13}C NMR δ 214.8, 170.6, 170.5, 170.1, 139.6, 122.4, 73.5, 72.5, 71.3, 58.2, 55.8, 53.0, 46.9, 42.6, 40.9, 39.2, 38.5, 38.2, 38.1, 37.0, 34.8, 31.1, 29.4, 27.9, 27.6, 21.9, 21.4, 21.3, 19.0, 18.4, 18.34, 18.27, 14.4; IR(KBr) 2962, 1730, 1710, 1250, 1027 cm^{-1}.

(24E)- and (24Z)-3β,11α,15β-Triacetoxystigmasta-5,24(28)-dien-28-nitrile (23)

Diethyl cyanomethylphosphonate (0.66 g, 3.7 mmol) was added *via* syringe to a suspension of sodium hydride (60% dispersion in oil, 0.13 g, 3.3 mmol) in dry THF (3 mL) cooled to –78°C under an atmosphere of argon. The mixture was stirred for 30 min and warmed up to room temperature. Stirring was continued for 30 min., during which the suspension became homogeneous and pale orange. The resulting phosphonate anion was added *via* cannula to a solution of **22** (0.26 g, 0.47 mmol) in THF (10 mL). The mixture was stirred at room temperature for 10 min and refluxed for 2.5 h. The reaction was monitored by TLC (10:3 hexane:ethyl acetate) after an aliquot was reacted with a solution of sodium borohydride in methanol (R_f of **23** was 0.21, whereas R_f of the reduced form of **22** was 0.11). The reaction mixture was diluted with ether (150 mL), and washed with water (4 x 4 mL) and saturated ammonium chloride solution (2 x 5 mL). Work-up followed by column chromatography (1:1 hexane:ether) afforded a mixture (0.26 g, 96%) of noncrystalline nitriles **23** (3:1 E:Z-isomers by NMR analysis). The mixture was not separable on TLC: mp 69-72 °C; ^{1}H NMR δ 0.96 (1/4 x 3, d, J = 6.6 Hz, 21-H of Z-isomer), 1.00 (3, s, 18-H), 1.02 (3/4 x 3, d, J = 6.9 Hz, 21-H of E-isomer), 1.06 (3/4 x 6, d, J = 6.6 Hz, 26-H and 27-H of E-isomer), 1.10 (1/4 x 6, d, J = 6.9 Hz, 26-H and 27-H of Z-isomer), 1.14 (3, s, 19-H), 2.01 (3, s, Ac), 2.02 (3, s, Ac), 2.03 (3, s, Ac), 4.52-4.65 (1, m, 3-H), 4.98 (1/4 x 1, s, 28-H of Z-isomer), 5.02-5.07 (1, m, 15-H), 5.09 (3/4 x 1, s, 28-H of E-isomer), 5.24-5.34 (1, m, 11-H), 5.44 (1, d, J = 4.5 Hz, 6-H); IR (KBr) 2960, 2883, 2215, 1725, 1618, 1467, 1375, 1363, 1240, 1025, 958 cm^{-1}.

(24E)- and (24Z)-3β,11α,15β-Trihydroxystigmasta-5,24(28)-dien-29-al

A solution of DIBAL-H (9 mL, 1 M in dichloromethane) was added to a solution of the nitriles **23** (0.26 g, 0.45 mmol) in dry dichloromethane (10 mL) cooled to –78 °C under argon. The mixture was stirred at that *temperature for 6 h and then warmed to room temperature. Saturated ammonium chloride solution (10 mL) was* added, stirring continued for 1 h, then ether (60 mL) was added. The mixture was filtered through Celite which was eluted with ether. The organic layer was separated and the aqueous layer was extracted with ether (3 x 10 mL). Work-up gave a TLC-inseparable mixture (0.16 g, 78%) of the aldehydes which was obtained by precipitation from hexane-ethyl acetate as a white solid (3:1 E:Z-isomers by NMR analysis): mp 145-150 °C; ^{1}H NMR δ 1.00 (3, s, 18-H), 1.01-1.12 (9, m, 21-H, 26-H, and 27-H), 1.20 (3, s, 19-H), 3.48-3.61 (1, m, 3-H), 4.02-4.14 (1, m, 11-H), 4.15-4.20 (1, m, 15-H), 5.42 (1, d, J = 4.5 Hz, 6-H), 5.78 (1/4 x 1, d, J = 8.1 Hz, 28-H of Z-isomer), 5.85 (3/4 x 1, d, J = 7.8 Hz, 28-H of E-isomer), 9.99 (3/4 x 1, d, J = 7.8 Hz, 29-H of E-isomer), 10.10 (1/4 x 1, d, J = 8.1 Hz, 29-H of Z-isomer).

(24E)- and (24Z)-3β,11α,15β,29-Tetrahydroxystigmasta-5,24(28)-diene

A solution of DIBAL-H (3 mL, 1 M in dichloromethane) was added to a solution of the above mixture of aldehydes (53 mg, 0.12 mmol) in dry THF (3 mL) cooled to –78 °C under argon. The mixture was stirred at that temperature for 8 h, then the reaction was quenched with saturated ammonium chloride solution (3 mL) and stirred for 1 h at room temperature. The reaction mixture was partitioned between ethyl acetate and water, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). Work-up gave a mixture (47 mg, 88%) of the tetraols as a white solid. The ratio of E-isomer to Z-isomer was determined to be 3:1 by ^{1}H NMR analysis: mp 112-116 °C; ^{1}H NMR δ 0.99 (3, s, 18-H), 0.99-1.04 (9, m, 21-H, 26-H, and 27-H), 1.20 (3, s, 19-H), 3.48-3.60 (1, m, 3-H), 4.02-4.11 (1, m, 11-H), 4.14-4.22 (3, m, 15-H and 29-H),

5.29 (1/4 x 1, t, J = 7.2 Hz, 28-H of Z-isomer), 5.37 (3/4 x 1, t, J = 6.9 Hz, 28-H of E-isomer), 5.43 (1, d, J = 5.1 Hz, 6-H).

3β,11α,15β,24-Tetrahydroxystigmasta-5,28(29)-diene

A solution of vinylmagnesium bromide (10 mL, 1 M in THF) was added to a solution of the ketone **22** (0.50 g, 0.89 mmol) in THF (12 mL) cooled to –78 °C under argon. The mixture was stirred for 20 min at that temperature and for 20 h at room temperature; then saturated ammonium chloride solution was added and the mixture diluted with ether (200 mL) and washed with water. Work-up gave a mixture of the allyl alcohols (0.38 g, 92%) as an amorphous solid: mp 58-62 °C; ^{1}H NMR δ 0.85-0.95 (9, m, 21-H, 26-H, and 27-H), 0.97 (3, s, 18-H), 1.19 (3, s, 19-H), 3.47-3.56 (1, m, 3-H), 4.00-4.09 (1, m, 11-H), 4.14-4.20 (1, m, 15-H), 4.93-5.20 (2, m, 29-H), 5.41 (1, d, J = 5.1 Hz, 6-H), 5.74-5.85 (1, m, 28-H).

3β,11α,15β,24-Tetraacetoxystigmasta-5,28(29)-diene (24)

The crude tetraol from above was mixed with acetic anhydride (7 mL), pyridine (7 mL), and 4-dimethylaminopyridine (DMAP, 0.3 g). The mixture was stirred for 1.5 days at room temperature and then diluted with ether. Work-up followed by column chromatography (10:3 hexane:ethyl acetate) afforded the tetraacetate **24** (0.48 g, 93%) as a white solid: mp 50-53 °C; ^{1}H NMR δ 0.80-0.92 (9, 21-H, 26-H, and 27-H), 0.97 (3, s, 18-H), 1.13 (3, s, 19-H), 1.99-2.03 (12, s, Ac x 4), 4.50-4.64 (1, m, 3-H), 5.02-5.06 (1, m, 15-H), 5.07-5.24 (2, m, 29-H), 5.26-5.35 (1, m, 11-H), 5.44 (1, d, J=4.5 Hz, 6-H), 5.60-5.78 (1, m, 28-H).

3β,11α,15β,29-Tetraacetoxystigmasta-5,24(28)(E)-diene (25), and 3β,11α,15β,29-Tetrahydroxystigmasta-5,24(28)(E)-diene (26)

The above acetate **24** was dissolved in dry THF (13 mL) and bis(acetonitrile)palladium(II) chloride (0.1 g, 0.39 mmol) was added. The mixture was stirred under argon at room temperature for a day. The reaction mixture was passed through a short column of silica gel and eluted with 10:3 hexane:ethyl acetate. The rearranged acetate **25** was obtained as a glossy solid: ^{1}H NMR δ 0.80-0.92 (9, 21-H, 26-H, and 27-H), 1.02 (3, s, 18-H), 1.14 (3, s, 19-H), 1.99-2.03 (12, s, Ac x 4), 4.56-4.64 (1, m, 3-H), 4.64 (2, d, J = 7.2 Hz, 29-H), 5.01-5.06 (1, m, 15-H), 5.26-5.35 (2, m, 28-H and 11-H), 5.44 (1, d, J = 4.5 Hz, 6-H).

The crude tetraacetate **25** was dissolved in methanol (50 mL) and sodium hydroxide (8 g) was added. The mixture was stirred at room temperature for 2 days; then it was diluted with ether and washed with water. The aqueous phase was extracted with ether, the combined organic layers were washed with ammonium chloride, sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. Removal of the solvent and chromatography (1:1 hexane:ethyl acetate) gave the tetraol **26** (275 mg, 78% from **24**) as a powder: mp 117-118 °C; ^{1}H NMR δ 0.99 (3, s, 18-H), 1.01 (3, d, J = 6.0 Hz, 21-H), 1.02 (6, d, J = 6.9 Hz, 26-H and 27-H), 1.20 (3, s, 19-H), 3.48-3.58 (1, m, 3-H), 4.02-4.11 (1, m, 11-H), 4.16 (3, d + m, J = 6.9 Hz, 29-H and 15-H), 5.37 (1, t, J = 6.9 Hz, 28-H), 5.43 (1, d, J = 5.1 Hz, 6-H); ^{13}C NMR δ 150.4, 141.3, 121.0, 71.8, 69.9, 68.9, 60.3, 59.5, 56.9, 55.8, 52.5, 42.7, 42.5, 41.2, 39.2, 36.2, 36.0, 34.6, 31.8, 31.3, 27.6, 27.5, 26.3, 22.0, 21.9, 18.9, 18.7, 15.5; IR(KBr) 3360, 2960, 2920, 2860, 1468, 1040 cm^{-1}; high resolution MS, m/z (relative intensity) 442.3513 (M^+–H_2O, 23), 424.3391 (M^+–2 H_2O, 31), 346.2517 (41), 81.0743 (100), (Calcd for $C_{29}H_{48}O_4$ –H_2O: 442.3449).

Dehydro-oogoniol (3β,11α,15β,29-Tetrahydroxystigmasta-5,24(28)(E)-dien-7-one) (3a)

A mixture of acetic anhydride (10 mL) and formic acid (97%, 10 mL) was heated at 60 °C for 1.5 h and cooled to –10 °C. The tetraol **26** (50 mg, 0.11 mmol) was added to the above mixed anhydride and pyridine (10 mL) was added dropwise at that temperature. After the cold bath was removed, the mixture was stirred at room temperature for 5 h (in some cases an additional amount of mixed anhydride was added) and then diluted with ether (150 mL). Work-up gave the tetraformate **27** as a glossy solid: ^{1}H NMR δ 1.02 (6, d, J = 6.9 Hz, 26-H and 27-H), 1.02 (3, s, 18-H), 1.16 (3, s, 19-H), 4.67 (2, d, J = 7.2 Hz, 29-H), 4.66-4.80 (1, m, 3-H), 5.16-5.21 (1, m, 15-H), 5.32 (1, t, J = 7.2 Hz, 28-H), 5.40-5.51 (2, m, 6-H and 11-H), 8.016 (1, s, OCHO), 8.024 (1, s, OCHO) 8.04 (1, s, OCHO), 8.07 (1, s, OCHO).

3,5-Dimethylpyrazole (830 mg, 8.63 mmol) was added to a suspension of chromium trioxide, dried over P_2O_5 *in vacuo* at 40 °C, (850 mg, 8.50 mmol) in dry dichloromethane (6 mL) and then the mixture was stirred for 20 min at –20 °C under an atmosphere of argon. To the resulting deep-brown solution was added a solution of the tetraformate **27** in dichloromethane (7 mL). The mixture was stirred at –20 to –10 °C for 12 h, filtered

through a short column of silica gel, and eluted with ether. Evaporation of the solvent followed by column chromatography (10:3 hexane:ethyl acetate) gave the 7-oxotetraformate (34 mg, 0.058 mmol, 54% from **26**) as a glossy solid: ^{1}H NMR δ 0.99 (3, s, 18-H), 1.02 (3, d, J = 7.2 Hz, 26-H and 27-H), 1.39 (3, s, 19-H), 4.67 (2, d, J = 7.2 Hz, 29-H), 4.78-4.90 (1, m, 3-H), 5.33 (1, t, J = 7.2 Hz, 28-H), 5.49-5.60 (1, m, 11-H), 5.70-5.80 (1, m, 15-H), 5.80 (1, s, 6-H), 7.94 (1, s, OCHO) 8.03 (2, s, OCHO), 8.07 (1, s, OCHO). The unreacted tetraformate **27** (9 mg, 15% from **26**) was recovered.

The 7-oxotetraformate (34 mg) was dissolved in methanol (6 mL) and potassium carbonate (0.3 g, 2.17 mmol) was added. The mixture was stirred at room temperature for 1 h, and then cooled to 0 °C, neutralized with a solution of ammonium chloride (0.24 g, 4.48 mmol) in water (3 mL), and extracted with ethyl acetate. After work-up, dehydro-oogoniol **3a** (26 mg, 95%) was obtained as a white powder by precipitation from ethyl acetate–hexane: mp 102-104 °C; ^{1}H NMR δ 0.99 (3, s, 18-H), 1.01 (3, d, J = 6.6 Hz, 21-H), 1.03 (6, d, J = 6.9 Hz, 26-H and 27-H), 1.35 (3, s, 19-H), 3.66-3.75 (1, m, 3-H), 4.09-4.20 (1, m, 11-H), 4.16 (2, d, J = 6.6 Hz, 29-H), 4.67-4.73 (1, m, 15-H), 5.36 (1, t, J = 6.9 Hz, 28-H), 5.82 (1, br s, 6-H); ^{13}C NMR δ 201.9, 167.9, 150.2, 125.6, 121.0, 70.53, 70.46, 68.8, 59.4, 56.2, 55.8, 55.0, 51.8, 43.1, 42.5, 40.4, 39.8, 38.7, 38.0, 36.1, 35.7, 34.5, 31.3, 26.4, 22.0, 21.9, 18.7, 17.3, 14.9; IR(KBr) 3400, 2950, 2925, 2863, 1660, 1465, 1383, 1050 cm^{-1}; high resolution MS, m/z (relative intensity) 456.3269 (M^+–H_2O, 12), 438.3088 (M^+–2 H_2O, 47), 423.2940 (30), 299.1664 (84), 161.0977 (100), (Calcd for $C_{29}H_{46}O_5$ –H_2O: 456.3241).

Dehydro-oogoniol and its Z-isomer (from 23)

The procedures used in synthesis of **3a** from **24** were employed. The tetraols **26** (mixture of E- and Z-isomers) (30 mg, 0.065 mmol) was formylated with pyridine (12 mL) and acetic formic anhydride prepared from acetic anhydride (6 mL) and formic acid (97%, 3 mL). After usual work-up, a mixture of the tetraformates (35 mg, 0.061 mmol, 94%) was obtained as an oil: ^{1}H NMR δ 1.02 (3/4 x 6, d, J = 6.9 Hz, 26-H and 27-H of **27**), 1.02 (3, s, 18-H), 1.16 (3, s, 19-H), 4.67 (3/4 x 2, d J=7.2 Hz, 29-H of E isomer), 4.72 (1/4 x 2, d J=6.9 Hz, 29-H of Z isomer), 4.66-4.82 (1, m, 3-H), 5.15-5.25 (1, m, 15-H), 5.32 (3/4 x 1, t, J = 7.2 Hz, 28-H of **27**), 5.40-5.51 (1, m, 6-H and 11-H), 8.02 (1, s, OCHO), 8.03 (1, s, OCHO), 8.04 (1, s, OCHO), 8.07 (1, s, OCHO).

A solution of the above tetraformates in dichloromethane (3 mL) was oxidized with a complex of chromium trioxide (520 mg, 5.2 mmol) and 3,5-dimethylpyrazole (500 mg, 5.2 mmol) in dry dichloromethane (5 mL). Passage through a short column of silica gel which was eluted with ether and rechromatography (10:3 hexane:ethyl acetate) gave recovered tetraformates (5 mg, 14%) followed by 7-oxotetraformates (24 mg, 0.041 mmol, 67%) as an oil: ^{1}H NMR δ 0.98 (3, s, 18-H), 1.02 (3, d, J = 6.9 Hz, 26-H and 27-H), 1.39 (3, s, 19-H), 4.67 (3/4 x 2, d, J = 7.2 Hz, 29-H of E-isomer), 4.72 (1/4 x 2, d, J = 7.2 Hz, 29-H of Z-isomer), 4.78-4.90 (1, m, 3-H), 5.22 (1/4 x 1, t, J = 7.2 Hz, 28-H of Z-isomer), 5.33 (3/4 x 1, t, J = 7.2 Hz, 28-H of E-isomer), 5.49-5.60 (1, m, 11-H), 5.70-5.80 (2, s + m, 6-H and 15-H), 7.94 (1, s, OCHO), 8.03 (2, s, OCHO), 8.07 (1, s, OCHO).

The 7-oxotetraformates were deformylated with methanol (4 mL) and potassium carbonate (0.2 g, 1.45 mmol). After neutralization with 8% aqueous ammonium chloride solution (2 mL) and usual work-up, a 3:1 mixture (17 mg, 57% from tetraol) of dehydro-oogoniol **3a** and its Z-isomer was obtained as a white powder by precipitation using ethyl acetate and hexane. The crude product was purified by HPLC (Waters Associates M-45 Instrument, 7.8 i.d. x 300 mm μ-Bondapak C-18 column, 4 mL/min at 3000 psi, UV 254 nm, 50:50 methanol:water). The peaks with retention time 58.8 and 55.5 min corresponded to the compound **3a** (75%) and the Z-isomer (25%), respectively. After HPLC, the compound **3a** was obtained as a solvent-free white solid by precipitation from ethyl acetate-hexane. The Z-isomer had the following properties: mp 105-110 °C (ethyl acetate solvate); ^{1}H NMR δ 0.99 (3, s, 18-H), 0.99-1.02 (9, m, 21-H, 26-H, and 27-H), 1.35 (3, s, 19-H), 3.65-3.76 (1, m, 3-H), 4.07-4.21 (1, m, 11-H), 4.14-4.22 (2, m, 29-H), 4.65-4.75 (1, m, 15-H), 5.30 (1, t, J=6.9 Hz, 28-H), 5.82 (1, br s, 6-H).

(3R,6RS)-3-(1-Methylethyl)heptan-1,6-diol (29)

(R)–(+)–limonene (**28**) was converted to the diol **29** as reported in the literature.[18,19]

(2RS,5R)-7-(t-Butyldimethylsilyloxy)-5-(1-methylethyl)heptan-2-ol (30)

Under an argon atmosphere, the diol **29** (2.0 g, 11.5 mmol) and t-butyldimethylsilyl chloride (1.8 g, 11.9 mmol) were dissolved in dry dichloromethane (30 mL), and 4-dimethylaminopyridine (0.3 g, 2.5 mmol) and triethylamine (1.5 g, 14.8 mmol) were added. The mixture was stirred at room temperature for a day (monitored by TLC) and diluted with ether (200 mL). Work-up gave an oil, which was chromatographed (10:3 hexane:ethyl acetate) to afford compound **30** (3.05 g, 92%) as an oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.05 (6, s, $SiMe_2$), 0.89 (6, d, J = 6.9 Hz, $CHMe_2$), 0.90 (9, s, $SiCMe_3$), 1.18 (3, d, J = 6.6 Hz, CH(OH)*Me*), 1.1-1.8 (8, m), 3.67 (2, t, J = 6.6 Hz, CH_2OSi), 3.6-3.9 (1, m, *CH*OH).

(R)-7-(t-Butyldimethylsilyloxy)-5-(1-methylethyl)heptan-2-one (31)

The alcohol **30** (3.20 g, 11.1 mmol) was dissolved in dry dichloromethane (80 mL), and pyridinium dichromate (PDC, 6.7 g, 17.8 mmol) was added under an atmosphere of argon. The mixture was stirred at room temperature for a day, and then passed through a short column of silica gel and eluted with ether. Evaporation of the solvent gave an oily residue, which was chromatographed (10:1 hexane:ethyl acetate) to give the ketone **31** (3.10 g, 98%) as an oil: ^{1}H NMR δ 0.05 (6, s, $SiMe_2$), 0.849 (3, d, J = 6.9 Hz, $CHMe$), 0.853 (3, d, J = 6.9 Hz, $CHMe$), 0.90 (9, s, $SiCMe_3$), 1.19-1.75 (6, m,), 2.14 (3, s, Ac), 2.40-2.47 (2, m, $AcCH_2$), 3.62 (2, t, J = 6.9 Hz, $SiOCH_2$); ^{13}C NMR δ 208.8, 61.6, 41.8, 39.6, 33.2, 29.7, 29.1, 25.8, 24.5, 18.9, 18.6, 18.1, –5.5; IR (liquid film) 2950, 1720, 1255, 1092, 836 cm^{-1}.

(R)-1-Acetoxy-5-(t-butyldimethylsilyloxy)-3-(1-methylethyl)pentane (32)

A solution of the ketone **31** (4.9 g, 17.1 mmol) in dry dichloromethane (150 mL) was added to 3,5-dinitroperoxybenzoic acid[20] (9 g, 39.5 mmol) under an argon atmosphere. The mixture was stirred for a day at room temperature (monitored by TLC) and then diluted with hexane (200 mL). A white solid precipitate was filtered off, and the filtrate was washed with saturated sodium thiosulfate, sodium bicarbonate solution, brine, and then dried over anhydrous magnesium sulfate. Filtration and concentration *in vacuo* gave an oil. Column chromatography (10:1 hexane:ethyl acetate) afforded the ester **32** (4.9 g, 95%) as an oil: ^{1}H NMR δ 0.05 (6, s, $SiMe_2$), 0.85 (6, d, J = 6.9 Hz, $CHMe_2$), 0.89 (9, s, $SiCMe_3$), 1.25-1.75 (6, m,), 2.03 (3, s, Ac), 3.57-3.70 (2, m, CH_2OSi), 4.00-4.16 (2, m, $AcOCH_2$); ^{13}C NMR δ 170.8, 63.4, 61.5, 36.9, 33.6, 29.6, 29.3, 25.8, 20.8, 18.7, 18.1, –5.5; IR (liquid film) 2950, 1742, 1240, 1095, 835 cm^{-1}.

(R)-5-(t-Butyldimethylsilyloxy)-3-(1-methylethyl)pentanol

The ester **32** (4.5 g, 14.9 mmol) was dissolved in methanol (50 mL) and potassium carbonate (15 g, 109 mmol) was added. The mixture was stirred for a day at room temperature, then it was concentrated and extracted with ether. Following work-up, the pure alcohol (3.3 g, 85% yield) was obtained as an oil on column chromatography (10:3 hexane:ethyl acetate): ^{1}H NMR δ 0.06 (6, s, $SiMe_2$), 0.85 (6, d, J = 6.9 Hz, $CHMe_2$), 0.90 (9, s, $SiCMe_3$), 1.2-1.8 (6, m,), 3.57-3.72 (4, m, CH_2OH and CH_2OSi); ^{13}C NMR δ 62.3, 61.4, 36.9, 33.8, 33.5, 30.2, 25.8, 18.8, 18.2, –5.3; IR (liquid film) 3350, 2950, 1255, 1093, 835 cm^{-1}.

(S)-5-(t-butyldimethylsilyloxy)-3-(1-methyl)pentyl Bromide (33)

Triphenylphosphine (4.35 g, 16.6 mmol) and carbon tetrabromide (5.55 g, 16.7 mmol) were dissolved in dry THF (30 mL) under argon, giving a yellow solution which was stirred for 1 h at room temperature, and then cooled to 0 °C. A solution of the above alcohol (2.90 g, 11.1 mmol) in THF (25 mL) was added, the mixture was stirred for 1 h at 0 °C, and then pentane (500 mL) was added. The white precipitate was filtered off and the solvent was evaporated. Pure compound **33** (2.34 g, 65%) was obtained by column chromatography (10:0.2 pentane:ethyl acetate) as an oil: $[\alpha]_D$ –1.2° (c 0.057 g/mL, $CHCl_3$); ^{1}H NMR 0.05 (6, s, $SiMe_2$), 0.853 (3, d, J = 7.2 Hz, $CHMe$), 0.855 (3, d, J = 6.3 Hz, $CHMe$), 0.90 (9, s, $SiCMe_3$), 1.26-1.94 (6, m), 3.34-3.50 (2, m, CH_2Br), 3.62 (2, t, J = 6.6 Hz, CH_2OSi); ^{13}C NMR δ 61.6, 39.3, 34.6, 33.3, 32.5, 29.2, 25.9, 18.9, 18.7, 18.2, –5.3; IR (liquid film) 2952, 2925, 1253, 1098, 835 cm^{-1}.

(24R)-3β,29-Bis(t-butyldimethylsilyloxy)-15β-hydroxystigmasta-5,16-dien-11-one (35)

Under an argon atmosphere, a mixture of flame-dried magnesium (45 mg, 1.85 mmol) and the bromide **33** (0.56 g, 1.73 mmol) in THF (5 mL) was refluxed with stirring for 1.5 h, then cooled to room temperature. This solution was added *via* a teflon tube to a suspension of copper(I) cyanide (dried over P_2O_5 *in vacuo* overnight at 40 °C, 155 mg, 1.73 mmol) in THF (10 mL) at room temperature. The green copper(I) cyanide gradually dissolved, the solution becoming dark violet, and after the mixture was stirred for an hour, the reagent (**34**) was ready for use.

A solution of **16** prepared from epoxyketone **15** (0.37 g, 0.86 mmol) as described earlier was added *via* cannula to the violet cuprate solution (**34**) cooled to –78 °C. Stirring was continued at this temperature for 1 h, and at –20 °C for another hour. The reaction mixture was quenched with saturated ammonium chloride solution (10 mL). The inorganic salts were removed by filtration through Celite, and washed with ether (50 mL). The organic phase was separated, and the aqueous layer was extracted with ether (4 x 40 mL). Work-up gave an orange oil. Column chromatography (10:0.5 pentane:ethyl acetate) afforded the compound **35** (0.362 g, 61% from epoxyketone **15**): mp 114-116 °C (crystalline); ^{1}H NMR 0.04 (6, s, $SiMe_2$), 0.05 (6, s, $SiMe_2$), 0.81 (3, d, J = 6.6 Hz, 26-H or 27-H), 0.83 (3, d, J = 6.0 Hz, 27-H or 26-H), 0.89 (18, s, $SiCMe_3$), 0.97 (3, d, J = 6.6 Hz, 21-H), 1.04 (3, s, 18-H), 1.24 (3, s, 19-H), 3.41-3.52 (1, m, 3-H), 3.56-3.63 (2, m, 29-H), 4.58-4.62 (1, m, 15-H), 5.36 (1, d, J = 4.8 Hz, 6-H), 5.61 (1, d, J = 2.4 Hz, 16-H); ^{13}C NMR δ 209.4, 164.4, 142.7, 124.3, 119.6, 72.9, 72.5, 63.1, 62.2, 58.2, 54.2, 49.1, 42.7, 40.3, 37.5, 36.6, 34.5, 33.5, 32.4, 31.9, 31.4, 29.5, 29.3, 28.8, 26.0, 25.9, 24.3, 21.8, 19.5, 18.6, 18.4, 18.3, 18.2, –4.6, –5.2; IR (KBr) 3460, 1465, 1705, 1255, 1095, 837 cm^{-1}; high resolution MS, m/z (relative intensity) 668.4943 (M^+–H_2O, 14), 629.4370 (M^+–C_4H_9, 75), 611.4261 (M^+–C_4H_9–H_2O, 100), 479.3350 (29), 145.1006 (83) (Calcd for $C_{41}H_{74}O_4Si_2$–H_2O: 668.5022).

(24R)-3β,29-Bis(t-butyldimethylsilyloxy)-15β-hydroxystigmast-5-en-11-one

The alkene **35** (0.20 g, 0.29 mmol) was dissolved in ethyl acetate (30 mL) and the solution stirred with 10% platinum on activated carbon (20 mg) and sodium carbonate (0.4 g) under an atmosphere of hydrogen at room temperature for 5.5 h (monitored by TLC). The reaction mixture was filtered through a short column of silica gel. After evaporation, column chromatography (10:1 hexane:ethyl acetate) gave the reduced compound (0.18 g, 90% yield): mp 143-145 °C (methanol); ^{1}H NMR δ 0.049 (6, s, $SiMe_2$), 0.053 (6, s, $SiMe_2$), 0.81 (3, d, J = 6.9 Hz, 26-H or 27-H), 0.84 (3, d, J = 6.6 Hz, 27-H or 26-H), 0.89 (9, s, $SiCMe_3$), 0.90 (9, s, $SiMe_3$), 0.91 (3, s, 18-H), 1.24 (3, s, 19-H), 3.41-3.53 (1, m, 3-H), 3.56-3.64 (2, m, 29-H), 4.25-4.36 (1, m, 15-H), 5.32-5.33 (1, m, 6-H); ^{13}C NMR δ 210.6, 142.8, 119.3, 72.4, 69.4, 62.3, 60.6, 59.5, 59.1, 55.1, 45.2, 42.5, 41.5, 40.5, 37.0, 36.3, 35.6, 33.7, 33.5, 32.3, 31.8, 29.1, 28.9, 27.1, 26.0, 25.9, 19.6, 18.6, 18.5, 18.4, 18.3, 15.1, –4.5, –5.2; IR (KBr) 3450, 1692, 1462, 1253, 1095, 835 cm^{-1}; high resolution MS, m/z (relative intensity) 631.4579 (M^+–C_4H_9, 100), 613.4455 (M^+–C_4H_9–H_2O, 55) 499.3589 (22), 145.1011 (34). (Calcd for $C_{41}H_{76}O_4Si_2$–C_4H_9: 631.4580).

(24R)-3β,29-Bis(t-butyldimethylsilyloxy)-11α,15β-dihydroxystigmast-5-ene

Eight spheres of sodium metal (0.4 g, 17 mmol) were added with vigorous stirring to a refluxing solution of the above ketone (0.16 g 0.23 mmol) in n-propanol (10 mL) in 1 min. Stirring was continued for 20 min. The reaction mixture was cooled to 0 °C, and after destruction of the excess sodium metal with methanol, diluted with ether (150mL), and washed with water (3 x 3 mL), brine, and then dried over anhydrous magnesium sulfate. Filtration and evaporation gave the 11α alcohol (0.15 g, 93% yield) as an amorphous solid: mp 58-60 °C; ^{1}H NMR δ 0.046 (6, s, $SiMe_2$), 0.054 (6, s, $SiMe_2$), 0.80 (3, d, J = 6.9 Hz, 26-H or 27-H), 0.84 (3, d, J = 6.6 Hz, 27-H or 26-H), 0.887 (9, s, $SiCMe_3$), 0.892 (9, s, $SiCMe_3$), 0.97 (3, s, 18-H), 1.18 (3, s, 19-H), 3.44-3.52 (1, m, 3-H), 3.54-3.64 (2, m, 29-H), 3.95-4.10 (1, m, 11-H), 4.14-4.20 (1, m, 15-H), 5.39 (1, d, J = 4.5 Hz, 6-H).

(24R)-3β,11α,15β,29-Tetrahydroxystigmast-5-ene (36)

The above silyloxy ether (0.16 g, 0.23 mmol) was dissolved in acetone (10 mL), and water (2 mL) and p-toluenesulphonic acid monohydrate (10 mg, 0.05 mmol) were added. The mixture was stirred at room temperature for 7 h, and then diluted with ether (200 mL). Work-up gave a light-orange solid. Pure compound **36** (0.105 g, 98%) yield) was obtained as a white solid by precipitation with ethyl acetate and hexane: mp 117-118 °C; ^{1}H NMR δ 0.83 (3, d, J = 6.9 Hz, 26-H or 27-H), 0.86 (3, d, J = 6.9 Hz, 27-H or 26-H), 0.96 (3, d, J = 6.6 Hz, 21-H), 0.98 (3, s, 18-H), 1.20 (3, s, 19-H), 3.45-3.58 (1, m, 3-H), 3.61-3.75 (2, m, 29-H), 4.00-4.13 (1, m, 11-H), 4.15-4.23 (1, m, 15-H) 5.43 (1, d, J = 5.7 Hz, 6-H); ^{13}C NMR δ 141.4, 121.0, 71.8, 70.0, 68.9, 62.0, 60.3, 56.9, 56.1, 52.6, 42.7, 42.5, 41.2, 40.6, 39.2, 38.3, 35.8, 33.8, 33.6, 31.8, 31.3, 29.2, 27.5, 27.2, 19.6, 18.9, 18.8, 18.4, 15.5; IR (KBr) 3380, 1466, 1042 cm^{-1}; high resolution MS, m/z (relative intensity) 462.3708 (M^+, 25), 444.3598 (M^+–H_2O, 57) 426.3513 (M^+–$2H_2O$, 39), 269.1924 (41), 145.1042 (57), 95.0859 (71), 83.0855 (61), 81.0699 (73), 55.0563 (100). (Calcd for $C_{29}H_{50}O_4$: 462.3711).

Oogoniol (24R)-3β,11α,15β,29-Tetrahydroxystigmast-5-en-7-one) (2a)

The tetraol **36** (20 mg, 0.043 mmol) was added to acetic formic anhydride prepared from acetic anhydride (4 mL) and formic acid (97%, 2 mL). The mixture was cooled to 0 °C, and pyridine (8 mL) was added dropwise at that temperature. The mixture was stirred at room temperature overnight and then diluted with ether (100 mL). Work-up gave the tetraformate (23 mg, 0.040 mmol, 93%) as an oil: ^{1}H NMR δ 0.82 (3, d, J = 6,9 Hz, 26-H or 27-H), 0.85 (3, d, J = 6.6 Hz, 27-H or 26-H), 0.93 (3, d, J = 6.3 Hz, 21-H), 1.01 (3, s, 18-H), 1.16 (3, s, 19-H), 4.10-4.25 (2, m, 29-H), 4.66-4.82 (1, m, 3-H), 5.15-5.22 (1, m, 15-H), 5.40-5.50 (1, m, 6-H and 11-H), 8.017 (1, s, OCHO), 8.024 (1, s, OCHO), 8.03 (1, s, OCHO), 8.05 (1, s, OCHO).

3,5-Dimethylpyrazole (86 mg, 0.89 mmol) was added to a suspension of chromium trioxide (dried over P_2O_5 *in vacuo* at 40 °C, 86 mg, 0.86 mmol) in dry dichloromethane (1.5 mL) and the mixture was stirred for 15 min at –25 to –20 °C under an atmosphere of argon. To the resulting deep-brown solution was added a solution of the above tetraformate in dichloromethane (1.5 mL). The mixture was stirred at –20 to –10 °C for 16 h, filtered through a short column of silica gel and eluted with ether. Evaporation of the solvent followed by column chromatography (10:3 hexane:ethyl acetate) afforded starting material (3 mg, 13%) and the 7-oxotetraformate (16 mg, 0.027 mmol, 68%) as an oil: ^{1}H NMR δ 0.82 (3, d, J = 6.6 Hz, 26-H or 27-H), 0.86 (3, d, J = 6.6 Hz, 27-H or 26-H), 0.93 (3, d, J = 6.3 Hz, 21-H), 0.98 (3, 5, 18-H), 1.39 (3, s, 19-H), 4.05-4.25 (2, m, 29-H), 4.75-4.90 (1, m, 3-H), 5.50-5.60 (1, m, 11-H), 5.70-5.80 (2, m, 15-H and 6-H), 7.94 (1, s, OCHO), 8.03 (2, s, OCHO), 8.07 (1, s, OCHO).

The 7-oxotetraformate was dissolved in methanol (3.5 mL) and potassium carbonate (0.5 g, 3.62 mmol) was added. The mixture was stirred at room temperature for 1 h, and then cooled to 0 °C, neutralized with 8% aqueous ammonium chloride solution (5 mL), and extracted with ethyl acetate. The extract was washed with saturated sodium bicarbonate solution, brine, and dried over anhydrous magnesium sulfate. After removal of the solvent, oogoniol **2a** (10 mg, 77%) was obtained as a white powder by precipitation with ethyl acetate–hexane. An analytical sample was obtained by HPLC (Waters Associates M-45 Instrument) 7.8 (i.d.) x 300 mm μ-Bondapak C-18 column, 4 mL/min at 2500 psi, UV 254 nm, 60:40 methanol:water. A peak with retention time 19.8 min corresponded to the compound **2a**: mp 99-101 °C ^{1}H NMR δ 0.83 (3, d, J = 6.6 Hz, 26=H or 27-H), 0.86 (3, d, J = 6.9 Hz, 27-H or 26-H), 0.95 (3, d, J = 6.6 Hz, 21-H), 0.98 (3, s, 18-H), 1.35 (3, s, 19-H), 3.58-3.75 (3, m, 3-H and 29-H), 4.09-4.19 (1, m, 11-H), 4.66-4.73 (1, m, 15-H), 5.82 (1, br s, 6-H); ^{13}C NMR δ 201.9, 167.8, 125.6, 70.6, 70.5, 68.8, 62.0, 56.2, 55.9, 55.3, 51.9, 43.1, 42.5, 40.6, 40.4, 39.7, 38.8, 38.0, 35.5, 33.8, 33.5, 31.4, 29.2, 27.2, 19.6, 18.9, 18.4, 17.3, 14.9; IR (KBr) 3400, 2950, 2870, 1660, 1470, 1058 cm^{-1}; high resolution MS, m/z (relative intensity) 458.3423 (M^+–H_2O, 79), 440.3300 (M^+–2 H_2O, 50), 283.1717 (68), 161.0947 (100), 55.0563 (50) (Calcd for $C_{29}H_{48}O_5$–H_2O : 458.3397).

Crystallographic analysis of 3β,11α,15β–triacetoxy–5–cholesten–24–one (22)

A single crystal was mounted along the largest dimension and the cell parameters were obtained from 16 strong reflections with $15<2\theta<40°$. Data were collected on a Nicolet R3m/V diffractometer. The intensities of three monitored reflections measured after every 100 reflections decayed by 1.2% during 32 h of X-ray exposure. The data were corrected for absorption (analytical), Lorentz and polarization effects. Details of X-ray data are given in Table 1.

The intensity statistics suggested an acentric space group, and the space group P1 was assumed and subsequently confirmed by a successful refinement. The structure was solved by direct methods using SHELXTLPLUS and the structure was refined using least-squares methods. The oxygen atoms were refined anisotropically and the carbon atoms isotropically. The refinement converged to R=0.0643. Hydrogen atoms were then included in subsequent refinements in ideal positions (C-H 0.96 Å, U=0.08). Refinement led to final values of R and R_w, which are given in Table 1. The final difference map had no feature of chemical significance. The function $(|F_o|-|F_c|)^2$ was minimized during least-squares refinement and in the final cycles, a weighting scheme of the form $w^{-1} = [\sigma^2(F) + 0.00001F^2]$ was employed. No evidence of secondary extinction was found.

TABLE 1. Summary of crystal data, intensity collection, and structural refinement of **22**.

cell constants	8.414(2), 9.880(2), 9.928(3) Å
	73.90(2), 88.77(2), 81.07(2)°
cell volume (Å^3)	783.2(4)
crystal system	triclinic
space group	P1 (No. 1)
molecular formula and weight	$C_{33}H_{50}O_7$, 558.7
Z, F (000)	1,304
color, habit	colorless, acicular
ρcalc., ρmeasd (g cm^{-3})	1.19, 1.22
cryst dimens (mm)	0.18 x 0.21 x 0.38
abs coeff, μ (cm^{-1})	6.21 cm^{-1}
min., max. trans. corr.	0.822, 0.897
radiation	CuKα, λ = 1.54184 Å
monochromator	highly oriented graphite
temp (°C)	21 ± 1
2θ angle (°)	2.0 to 110.0
scan type (2θ)	coupled θ (crystal / 2θ (counter)
scan width	Kα1 – 1.0° to Kα2 + 1.0°
scan speed (°min^{-1})	variable, 2.02 – 4.88
background time/scan time	0.5
total reflections measured	1987, (*h*0→8, *k*–10→10, *l*–10→10)
	(R_{int} = 1.09%)
unique data used (m)	1928 [I>2σ(I)]
no. of parameters (n)	193
$R = (\Sigma \| \|F_O\| - \|F_C\| \| / \Sigma \|F_O\|)$	0.0643
$R_W = [\Sigma_W (\|F_O\| - \|F_C\|)^2 / \Sigma_W \|F_O\|^2]^{1/2}$	0.0726
goodness of fit = $[\Sigma(\|F_O\| - \|F_C\|)^2 / (m-n)]^{1/2}$	5.99
$\Delta\rho_{max}$ (e Å^{-3})	0.34
shift : error (max)	0.002

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